STATIC

Intermittent vs. continuous treatment strategies in CLL

A Randomised Phase III Trial Comparing Intermittent with Continuous Treatment Strategies in Chronic Lymphocytic Leukaemia (CLL)

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24 hour Registration and Randomisation

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3 TRIAL SUMMARY

Trial Title:
STATIC - A Randomised Phase III Trial Comparing Intermittent with Continuous Treatment Strategies in Chronic Lymphocytic Leukaemia (CLL)

Trial Design
STATIC is designed with multiple pathways, the 'Randomisation Pathway' and the 'Clinical Need Cohort', which route a participant enters will be determined by their eligibility.

Randomisation Trial: A prospective, national, multicentre, open-label, randomised, controlled, 2-arm, parallel-group, non-inferiority, phase III trial to assess whether patients with CLL on long-term treatment with with a BTK inhibitor, (including ibrutinib) have similar disease control with an intermittent treatment strategy (experimental arm) compared with standard continuous treatment (control arm).

Clinical Need Cohort: A prospective, national, multicentre, open-label, single-arm, non-randomised cohort to assess the safety and overall survival of patients with CLL receiving long-term continuous treatment with ibrutinib.

Aims and Objectives:
The primary aim is to assess whether patients with CLL on long-term treatment with BTK inhibitor, (including ibrutinib) have similar disease control with an intermittent treatment strategy, known as the 'Pausing Ibrutinib' arm compared with standard continuous treatment, the 'Continuous Ibrutinib' arm.

The primary objective is to assess non-inferiority (NI) of the intermittent treatment strategy in terms of time to treatment strategy failure, defined as the first documented instance of active disease (as defined by the 2018 iwCLL criteria) that does not respond to treatment, or death.

The secondary objectives are to assess the following:

1) Overall survival
2) Toxicity and tolerability
3) Cost effectiveness
4) Quality of life
5) Summative treatment-free interval
6) Response to retreatment in intermittent treatment arm
7) Time to next treatment for CLL
8) Response to next treatment for CLL
9) Rate of resistance mutations
10) Evolution of resistant sub-clones

Hypothesis: Reduced Treatment-emergent Resistance

We hypothesise that an intermittent treatment strategy using ibrutinib, will reduce treatment-emergent resistance and thus be at least non-inferior to continuous treatment with regards to time to treatment strategy failure whilst reducing resource impact for the NHS and improving quality of life.

Number of participants:

800 participants will be randomised into the randomisation trial over a 6 year period with ~45% coming from ibrutinib-based treatment arms of the front-line CLL trial FLAIR and ~55% receiving ibrutinib off-trial (via NHS access) for previously treated for CLL. An additional cohort of ~30 patients from the ibrutinib-based treatment arms of FLAIR will be enrolled to a non-randomised Clinical Need Cohort to receive continuous ibrutinib.

Participant population and participant entry pathway: (Refer to protocol Section 9 for a full list of eligibility criteria).

- To be eligible for randomisation, participants aged at least 18 years with previously treated chronic lymphocytic leukaemia (CLL) will have already been treated in second or subsequent line of therapy with ibrutinib for at least 3 years and be in clinical remission, defined as no palpable lymph nodes, no palpable spleen and absolute lymphocyte count (ALC) $<5x10^9$/L, for at least the last 12 months
- For previously treated CLL participants, the entry pathway is to be randomised to either the 'Pausing Ibrutinib' arm or 'Continuous Ibrutinib' arm
- Front-line CLL participants from the ibrutinib-based treatment arms of the FLAIR trial will have completed 6 years of ibrutinib within FLAIR and the following treatment pathways are available:
    - Randomisation Pathway: Randomised to either the Pausing Ibrutinib or Continuous Ibrutinib arms; participants must be in clinical remission, defined as no palpable lymph nodes, no palpable spleen and absolute lymphocyte count (ALC) $<5x10^9$/L, for at least the last 12 months.
    - Clinical Need Cohort: Continuous Ibrutinib (non-randomised and non-comparative)

Clinical Need Cohort: 'Continuous ibrutinib'

FLAIR participants with progressive disease after completing 6 years of treatment, but prior to entry into STATIC, would not be eligible for randomisation, but can enter the Clinical Need Cohort. The Clinical Need Cohort will enable this group of participants to continue to receive ibrutinib (continuous treatment), either at the recommended starting dose, or the stable reduced dose they were receiving at the end of the FLAIR trial, but will not be randomised.

Randomisation Pathway: overview of pausing / resuming and continuous treatment strategies

To be eligible for randomisation, previously treated participants will have been treated with continuous ibrutinib for at least 3 years and must have been in clinical remission for at least the last 12 months; whereas front-line participants from FLAIR will have been treated for 6 years with ibrutinib in FLAIR and be in clinical remission for at least the last 12 months. Participants will be randomised 1:1 to either intermittent ibrutinib, known as the 'pausing ibrutinib' arm, or continuous ibrutinib treatment.

'Continuous ibrutinib' arm

Participants randomised to continuous treatment will receive ibrutinib (oral) 420mg per day (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities) until strategy failure, defined as active disease as per 2018 iwCLL criteria, death, or the end of the trial.

'Pausing ibrutinib' arm

Participants randomised to the 'pausing ibrutinib' arm (intermittent treatment strategy) will pause ibrutinib treatment immediately following randomisation, and restart when the restart criteria are met. When treatment restarts, participants restart ibrutinib treatment at the standard dose (or their previous stable reduced dose) until the treatment pausing criteria are met. The pausing and resuming criteria are assessed locally every 3 months at standard clinic visits. Participants can pause and restart treatment multiple times until treatment strategy failure (defined as active disease per 2018 iwCLL criteria) whilst on treatment, death, or end of the study.

In order to begin the initial ibrutinib pause in the pausing ibrutinib arm, all criteria below must be met and maintained continuously for preceding 12 months:

- No palpable lymph nodes and
- No palpable spleen, and
- ALC $<5x10^9$/L

Criteria to resume/ restart ibrutinib in 'pausing ibrutinib' arm:
Any one of:

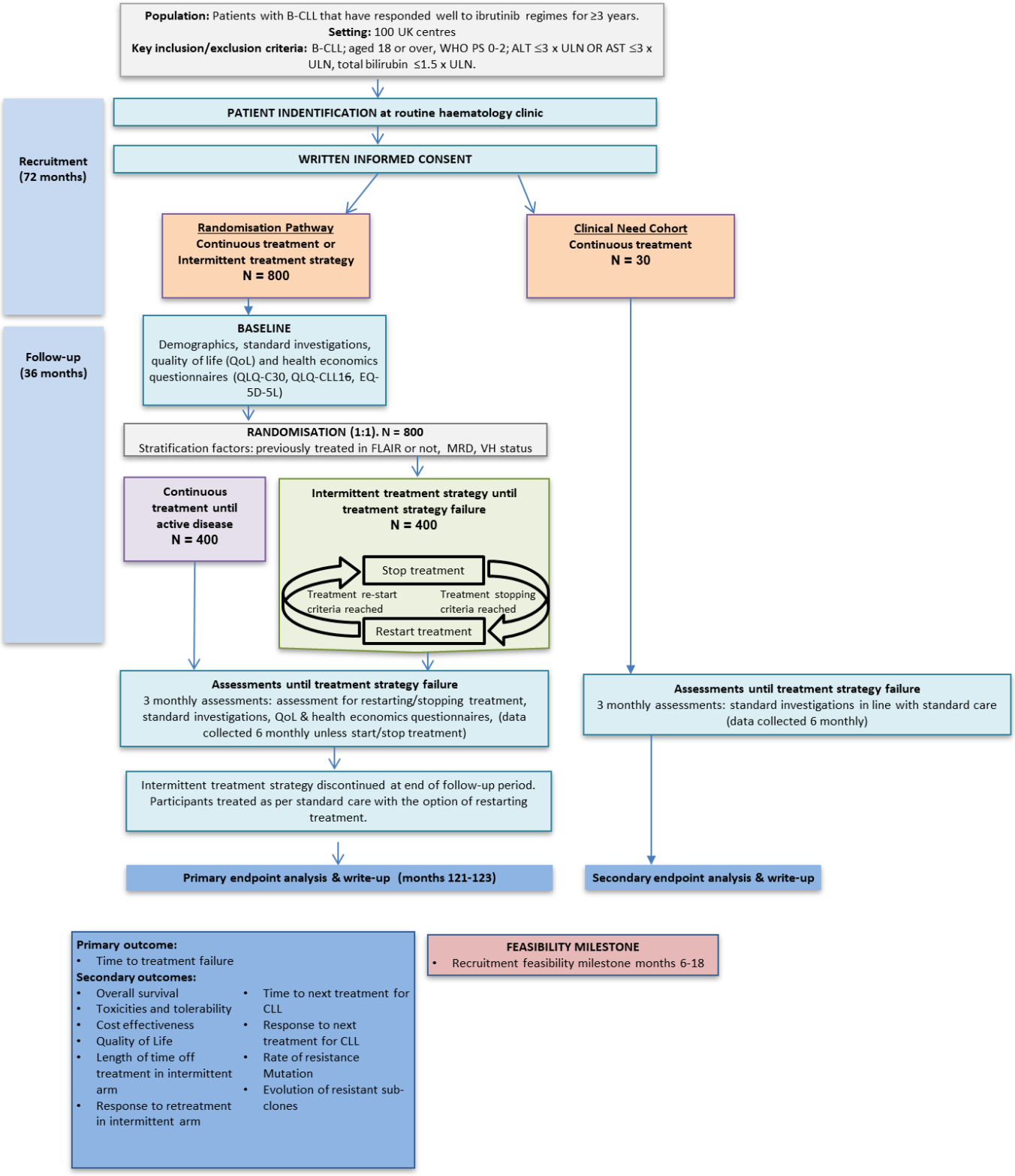
- Palpable lymph nodes (≥2cm), or
- palpable spleen, or
- ALC ≥ 5 $x10^9$/L.

Criteria for subsequent ibrutinib pause(s) (second and subsequent pausing treatment breaks):

- Received at least a further 12 months of ibrutinib, and
- No palpable lymph nodes, and
- No palpable spleen, and
- <5 $x10^9$/L ALC for at least 6 months.

4 FLOW DIAGRAM

A Randomised Phase III Trial Comparing Intermittent with continuous Treatment Strategies in CLL



5 GLOSSARY OF TERMS

AE	Adverse event
ALT	Alanine aminotransferase
AR	Adverse reaction
BCRP	Breast cancer–resistance protein
BTK	Bruton's tyrosine kinase
CHI Number	Community Health Index Number
CI	Chief Investigator
CLL	Chronic Lymphocytic Leukemia
CR	Complete response
CRi	Complete Remission with Incomplete Count Recovery
CRF	Case report form
CTA	Clinical Trials Authorisation
CTRU	Clinical Trials Research Unit
DMEC	Data Monitoring and Ethics Committee
DSUR	Developmental Safety Update Report
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
HMDS	Haematological Malignancy Diagnostic Service
ICD	Informed Consent Document
IMP	Investigational medicinal product
ITT	Intention to treat
LFT	Liver function test
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHRA	Medicines and Healthcare Products Regulatory Agency
MRD	Minimal Residual Disease
NCRI	National Cancer Research Institute
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PIS	Patient Information Sheet
PP	Per Protocol
PR	Partial remission
PS	Performance status
QoL	Quality of life
RDE	Remote Data Entry
REC	Research Ethics Committee
RSI	Reference Safety Information
SD	Stable disease
SAE	Serious adverse event

SAP	Statistical analysis plan
SAR	Serious adverse reaction
SmPC	Summary of Product Characteristics
SPM	Secondary Primary Malignancy
SSOP	Study site operating procedure
SUSAR	Suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TTP	Time to progression
U&E's	Urea & electrolytes
ULN	Upper limit of normal

6 BACKGROUND AND RATIONALE

6.1 Chronic Lymphocytic Leukaemia (CLL)

Chronic Lymphocytic Leukaemia (CLL) is the most common adult leukaemia, affecting 6.6 per 100,000 population (1). CLL is a chronic and currently incurable disease with a highly variable clinical course and can be associated with a range of symptoms including swollen glands, anaemia, fatigue and enlarged liver and spleen. Most patients will eventually require treatment and it is common for patients to receive several lines of therapy during the course of their disease (2).

6.2 Ibrutinib treatment for CLL

Ibrutinib is a small molecule inhibitor of Bruton's tyrosine kinase (BTK) that has dramatically improved the outcome in CLL (3, 4). Ibrutinib is licensed as continuous treatment given daily until disease progression in both previously untreated as well as relapsed, refractory CLL and is also approved for other similar chronic lymphoproliferative disorders, such as mantle cell lymphoma and Waldenstrom's macroglobulinaemia. Ibrutinib is currently commissioned within the NHS (5) for patients who have failed prior therapy for CLL, as well as for newly diagnosed patients with genetically high-risk disease.

6.3 Study Rationale

Ibrutinib is an extremely effective treatment for CLL with median progression-free survival (PFS) estimated to be 4 years in patients with a median of 3 prior lines of CLL therapy (4) and in excess of 10 years in newly diagnosed patients (3).

Ibrutinib is associated with long-term toxicities in a proportion of patients including arthralgia, bruising and bleeding, rashes and hypertension. Potentially serious side effects include cardiac arrhythmias, mostly atrial fibrillation but rarely ventricular tachyarrhythmias, and infections. It is hypothesised that toxicities may be reduced by an intermittent treatment approach.

A major concern with the chronic and continuous administration of ibrutinib is the selection of CLL sub-clones with BTK mutations leading to the development of disease resistance. Such BTK mutations are frequently observed in patients with relapsed/refractory CLL treated with ibrutinib and are also observed, but to a far lesser extent, in previously untreated patients receiving ibrutinib (6, 7). The emergence of these mutations is hypothesized to be reduced by intermittent use of the drug, as has been investigated using a similar strategy in prostate cancer (8).

We hypothesise that an intermittent treatment strategy with ibrutinib will reduce treatment-emergent resistance and thus be at least non-inferior to continuous treatment with regards to time to strategy failure whilst reducing resource impact for the NHS and improving quality of life. Recent work reveals the presence of BTK mutations is associated with drug resistance following continued treatment with ibrutinib in a third of patients with high risk CLL (9).

STATIC is designed with multiple pathways: the randomisation trial and the Clinical Need Cohort. The randomisation trial is designed to address the key question of whether an intermittent treatment

strategy with ibrutinib is at least as effective as the current licensed continuous treatment strategy. The justification for this question is that the trials that led to the approval of ibrutinib were all performed with relatively short follow-up. At the time of the first regulatory approval of ibrutinib in relapsed refractory CLL the pivotal randomised trial had a median follow-up of 9.4 months (10) and at the latest follow-up the median duration of treatment on ibrutinib was only 41 months (11). Similarly in previously untreated CLL the initial report of the RESONATE-2 trial had a median follow-up on ibrutinib of 18.4 months (3) and at the latest follow-up a median duration on treatment of 57.1 months (12). Therefore, the rationale of continuous treatment until active disease has not been studied. In addition, as it is now clear that continuous therapy with ibrutinib selects for CLL sub-clones with resistance mutations, such as the mutation of BTK, that occur in both previously treated and previously untreated CLL, although the rate and timing of mutations varies for front-line vs relapsed/refractory disease (6). Clonal evolution in CLL leads to therapy resistance and shorter remissions with subsequent treatments. Clearly relapse of CLL in patients currently receiving ibrutinib means that this drug, or class of drugs, will no longer be effective. In contrast it would be expected that recurrence of CLL in a patient not on ibrutinib would most likely be responsive to further ibrutinib. In addition to the clonal selection of continuous ibrutinib there are side effects of therapy which can have an impact on the patient's quality of life as well as potentially resulting in compliance issues. Some side effects can be life-threatening (13). Finally, it is becoming clear that when patients stop ibrutinib due to intolerance the disease frequently remains in remission not requiring therapy for potentially considerable periods of time. In the RESONATE-2 trial when patients stopped ibrutinib for intolerance, patients in complete response (CR)/ complete remission with incomplete count recovery (Cri) had a median PFS of 56 months and even those not in CR/CRi had a median PFS of 33 months. This suggests that disease control may persist for a period of time following pausing of ibrutinib treatment, and patients may continue to benefit for a meaningful period of time if they are paused when in good response. Finally the costs associated with continuous therapy until disease progression are not insignificant (14).

The strategy of intermittent treatment with a kinase inhibitor has been studied in chronic myeloid leukaemia (CML), a haematological malignancy treated with continuous oral tyrosine kinase inhibitors (TKI) such as imatinib. TKI treatment breaks in CML have been shown to be a safe and effective approach in this disease with no adverse impact on long-term disease control (15, 16). This precedent demonstrates the efficacy in haematological malignancies treated with an intermittent, as opposed to continuous TKI, which may translate to CLL treatment.

In the FLAIR trial (17) patients who still have detectable CLL after 3 years of ibrutinib-based therapy are scheduled to receive a total of 6 years of ibrutinib and then to stop treatment. It is likely that a proportion of patients will, at the end of 6 years, have a very low level of, or even undetectable, residual disease. There is a strong rationale, as explained above, for patients to consider entry into STATIC, given that patients randomised to intermittent ibrutinib will be carefully monitored and will be able to re-commence ibrutinib if their CLL begins to progress, with the expectation that many would be likely to respond upon restarting therapy.

Given that the efficacy of intermittent treatment is not proven, and continuous treatment with ibrutinib has demonstrated durable disease control in multiple studies, the Clinical Need Cohort affords patients who are concerned about pausing therapy a pathway to continue ibrutinib as it is licensed (continuous treatment) within STATIC.

7 AIMS AND OBJECTIVES

7.1 Aims

The primary aim is to assess whether patients with CLL on prior treatment with a BTK inhibitor, (including ibrutinib for 3 to 6 years) have disease control with an intermittent treatment strategy that is not inferior to disease control with the standard (licensed) continuous treatment.

7.2 Primary objectives

The primary objective is to assess non-inferiority (NI) of the intermittent treatment strategy in terms of time to treatment strategy failure, defined as the first documented instance of active disease (as defined by the 2018 iwCLL criteria) that does not respond to treatment, or death.

7.3 Secondary objectives

The secondary objectives are to assess:

1. Overall survival
2. Toxicity and tolerability
3. Cost effectiveness
4. Quality of life
5. Summative treatment-free Interval
6. Response to retreatment in intermittent treatment arm
7. Time to next treatment for CLL
8. Response to next treatment for CLL
9. Rate of resistance mutation between trial arms
10. Evolution of resistant sub-clones

7.3.1 Hypothesis: Reduced Disease Resistance

We hypothesise that an intermittent treatment strategy using ibrutinib, will reduce treatment-emergent resistance and thus be at least non-inferior to continuous treatment with regards to time to treatment strategy failure whilst reducing resource impact for the NHS and improving quality of life.

7.4 Exploratory objectives

The exploratory objectives are:

- Analysis of the cause of ibrutinib resistance where BTK and/or PLCγ2 mutations are not found
- Identification of predictors for early progression of CLL after pausing ibrutinib
- Study of CLL clonal evolution in patients treated with ibrutinib
- Assessment of response to vaccines and rate of infectious complications

8 DESIGN

8.1 Overall design and plan of the study

The 'Randomisation Pathway' is designed as a prospective, multicentre, open-label, randomised, controlled, 2-arm, parallel-group, non-inferiority study to compare an intermittent treatment strategy (experimental arm) with continuous treatment (control arm) with ibrutinib for patients with CLL who have responded well to treatment with ibrutinib. The primary outcome for this pathway will be time to treatment strategy failure, defined as the first documented instance of active disease as defined by the 2018 iwCLL criteria (Appendix 1) that does not respond to treatment, or death from any cause.

At randomisation previously treated participants will have been receiving ibrutinib as their second- or subsequent-line of therapy for at least the previous 36 months, whilst front-line participants entering from the FLAIR trial will have received 6 years of treatment with ibrutinib. There is no restriction on maximum duration of treatment for the previously treated cohort prior to enrolment. The recruitment period is 6 years, and each participant will be followed up for at least 3 years after randomisation. Participants will receive treatment during the trials 6 year recruitment period and for the 3 years of follow up, meaning that participants will be on the trial for between 3-9 years, depending upon when they enter the trial. 800 patients will be entered into the Randomisation Pathway with the goal of observing 379 treatment failure or death events.

Participants will be randomised to either an intermittent treatment strategy or to continuous therapy. Treatment allocation (1:1) will be by minimisation with a random element incorporating the following three factors: centre, whether or not the participant was previously treated in FLAIR and minimal residual disease (MRD) level at randomisation.

Participants randomised to the intermittent treatment arm will pause ibrutinib treatment immediately following randomisation, and restart when the restart criteria are met (see Section 13.8.3; the restart criteria do not indicate active disease as per 2018 iwCLL criteria). When the re-start criteria are met participants will receive ibrutinib (oral) 420mg per day (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities) until treatment failure (active disease per 2018 iwCLL criteria) whilst on treatment or death. If these participants demonstrate active disease whilst on the planned treatment pause they will initially resume ibrutinib and the criteria for treatment failure would be met if they present with active disease at the next follow up (in which case the time to treatment failure would be backdated to when active disease was first demonstrated). Those randomised to the continuous treatment arm will receive ibrutinib (oral) 420mg per day (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities) until treatment failure (active disease) as per 2018 iwCLL criteria or death.

The Clinical Need pathway is a prospective, national, multicentre, open-label, single-arm, non-randomised cohort to assess the safety and overall survival of patients receiving continuous ibrutinib treatment. Participants exiting the FLAIR trial who are not eligible for randomised study because they have signs of progressive or returning CLL after completing 6 years of ibrutinib treatment within FLAIR, but prior to entry into STATIC, can join the Clinical Need Cohort. Participants in the Clinical Need Cohort

will receive treatment during the trials 6 year recruitment period and for the 3 years of follow up, meaning that participants will be on the trial for between 3-9 years, depending upon when they enter the trial. Up to 30 patients are expected to enter into the Clinical Need Cohort. Patients will continue receiving continuous ibrutinib, either at the standard dose, or a stable reduced dose.

Front-line participants entering either the Randomisation pathway or the Clinical Need cohort from the FLAIR trial should enter STATIC on completion of treatment in FLAIR, with no break in therapy, with the exception of participants who have completed the 6 years of treatment in FLAIR prior to STATIC opening.

9 ELIGIBILITY

Please note eligibility waivers to inclusion/exclusion criteria are not permitted. Participants must meet all of the inclusion criteria and none of the exclusion criteria.

9.1 Registration Eligibility Criteria

9.1.1 Trial Registration Inclusion Criteria

1. At least 18 years old
2. A diagnosis of chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) (by 2018 iwCLL criteria)
3. World Health Organisation (WHO) performance status (PS) of 0, 1 or 2
4. Biochemical values must be within the following limits within 4 weeks prior to randomisation/or registration for the Clinical Need Cohort and at baseline:
    - Alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN) OR Aspartate aminotransferase (AST) ≤3 x ULN.
    - Total bilirubin ≤1.5 x ULN, unless bilirubin rise is due to Gilbert's syndrome or of non hepatic origin
5. Agree to follow the pregnancy prevention guidelines:
   Women:
    - Women of childbearing potential must agree to use a highly effective form of contraception, this must include a barrier method for participants using hormonal contraceptives, whilst receiving ibrutinib until 3 months after the last dose of ibrutinib*.
    - Agree not donate eggs (ova, oocytes) for the purposes of assisted reproduction

   Men:
    - Males must agree to practice effective barrier contraception whilst receiving ibrutinib until 3 months after the last dose of ibrutinib
    - Agree to not donate sperm during whilst receiving ibrutinib until 3 months after the last dose of ibrutinib

   All participants who are randomised to the pausing Ibrutinib arm will not be required to follow this during treatment breaks, but must restart this once treatment with ibrutinib resumes.
6. Able to provide informed consent

*Participants randomised to the pause/resume arm must adhere to this whilst receiving ibrutinib, but will not be required to follow contraceptive measures during the planned treatment breaks (see section 14.5)

9.1.2 Trial Registration Exclusion Criteria

1. Pregnant females
2. Known intolerance or hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.
3. Receipt of live vaccination within 4 weeks prior to registration and for the duration of the study.

4. History or current evidence of Richter's transformation
5. Major surgery within 4 weeks prior to randomisation/or registration for the Clinical Need Cohort
6. Active infection
7. Concomitant warfarin (or equivalent vitamin K inhibitor)
8. Central nervous system involvement with CLL
9. Cardiac failure; including symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)
10. Respiratory impairment (e.g. bronchiectasis or severe COPD)
11. Other severe, concurrent diseases or mental disorders that could interfere with their ability to participate in the study
12. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the patients will be excluded. During treatment, these participants should be monitored and managed to prevent HBV reactivation.
13. Positive serology for Hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a test for hepatitis C RNA (for example HCV RNA PCR). If positive the patients will be excluded.
14. Persisting severe pancytopenia (neutrophils $<0.5 \times 10^9$/L or platelets $<50 \times 10^9$/L) unless due to direct marrow infiltration by CLL
15. Current treatment with prednisolone of >20mg/day
16. Uncontrolled Active haemolysis
17. History of stroke or intracranial haemorrhage within 6 months prior to enrolment.
18. Requirement for treatment with a strong CYP3A inhibitor or inducer (see Appendix 7)
19. New treatment with two or more antiplatelet drugs, treatment that has been administered at a stable dose for at least 3 months prior to registration is permissible
20. Current treatment with any concomitant ACE inhibitors

9.2 Clinical Need Cohort Registration for Front-line Patients

Participants in the Clinical Need Cohort will need to meet the following additional eligibility criteria:

9.2.1 Clinical Need Cohort Inclusion Criteria

1. Meet all of the Registration Inclusion criteria
2. Currently receiving ibrutinib and nearing the end or having completed 6 years of ibrutinib treatment on FLAIR*
3. Have signs of progressive or returning CLL after completing 6 years of ibrutinib treatment within FLAIR, but prior to entry into STATIC

* Patients should enter STATIC on completion of treatment in FLAIR, with no break in therapy, with the exception of participants who have completed the 6 years of treatment in FLAIR prior to STATIC opening

9.2.2 Clinical Need Cohort Exclusion criteria

1. Meet none of the registration exclusion criteria
2. Active Disease, as per the 2018 iwCLL criteria requiring an alternative therapy.

3. Received treatment other than ibrutinib for CLL since completing FLAIR
4. Be eligible for front-line randomisation (see section 9.3)

9.3 Front-Line: Randomisation Eligibility Criteria

Front-line participants who enter the Randomisation Pathway will need to meet the following additional eligibility criteria:

9.3.1 Front-Line Randomisation Inclusion criteria

1. Meet all of the Registration Inclusion criteria
2. Currently receiving ibrutinib in FLAIR or having completed 6 years of ibrutinib of ibrutinib in FLAIR*
3. In clinical remission all of the following:
    a. no palpable lymph nodes;
    b. no palpable spleen; and
4. lymphocyte count below $5x10^9$/L continuously for at least the 12 months before randomisation

* Patients should enter STATIC on completion of treatment in FLAIR, with no break in therapy, with the exception of participants who have completed the 6 years of treatment in FLAIR prior to STATIC opening

9.3.2 Front-Line Randomisation Exclusion criteria

1. Meet none of the registration exclusion criteria
2. Disease progression (according to 2018 iwCLL criteria)
3. Ibrutinib treatment break for toxicity/patient choice for more than 28 days in last 12 months

9.4 Previously Treated Participants Randomisation Eligibility Criteria

Previously treated participants who enter the Randomisation Pathway will need to meet the following additional eligibility criteria:

9.4.1 Previously Treated Participants Randomisation Inclusion criteria

1. Meet all of the registration inclusion criteria
2. Currently receiving ibrutinib for at least the previous 36 months. There is no restriction on maximum duration of treatment prior to enrolment.
3. In clinical remission fulfilling all of the following:
    a. no palpable lymph nodes;
    b. no palpable spleen; and
4. Lymphocyte count below $5x10^9$/L continuously for at least the 12 months before randomisation

9.4.2 Previously Treated Participants Randomisation Exclusion criteria

1. Meet none of the registration exclusion criteria
2. Disease progression (according to 2018 iwCLL criteria)
3. Ibrutinib treatment break for toxicity/patient choice for more than 28 days in last 12 months
4. Any illness, disease or condition, such as active cancer or secondary primary malignancy (SPM), with a prognosis of less than 5 years

5. Patients with a creatinine clearance of less than 30ml/min (either measured or derived by the Cockcroft Gault formula or alternative locally approved formula).

10 RECRUITMENT PROCESS

10.1 Study setting

The trial will be conducted in 100 NHS Centres in the UK (England, Wales, Scotland and Northern Ireland) the majority of which are already participating in the FLAIR trial. All centres will be experienced in multidisciplinary diagnosis and management of CLL and have an established research infrastructure, including clinical research nurses funded via the NIHR CRN. Centres will be identified via a feasibility assessment to determine those most appropriate to participate in the trial. Research centres will be required to confirm capacity and capability and undertake site initiation training with the Clinical Trials Research Unit (CTRU) prior to the start of recruitment into the trial. Screening and recruitment processes must not be initiated at site until approval to open to recruitment has been formally issued by the CTRU.

800 participants will be recruited over 6 years into the randomisation pathways. Participants treated in an ibrutinib-based arm of the FLAIR trial should be approached by the research team during routine clinic appointments. Additionally, participants with previously treated CLL who have already been treated in second or subsequent line of therapy with ibrutinib for at least 3 years (not in the FLAIR trial) will be identified during routine clinic appointments.

Participants entering the Clinical Need Cohort will be recruited over 6 years. Participants who have been treated with an ibrutinib-based arm of the FLAIR trial may be eligible to enter the STATIC Clinical Need Cohort and will be identified during routine clinic appointments.

Patients from FLAIR entering either the randomisation trial or the Patent Need Cohort must enter STATIC with no break in therapy, with the exception of participants who have completed the 6 years of treatment in FLAIR prior to STATIC opening. Where possible these potential participants should be approached prior to the final routine 3 monthly appointment on FLAIR in order to prevent any break in therapy.

Information about the trial will also be shared with patient support groups as well as the distribution of leaflets via support groups and hospital clinics.

Invitation to participate in the trial and provision of information can be made either in person during routine hospital visits or via telephone/video consultations.

10.2 Responsibility for information provision, informed consent and eligibility assessment

Provision of information about the trial is permitted by any member of the site research team approved to do so by the Principal Investigator (PI) as detailed on the trial Authorised Personnel Log (APL).

For participants who wish to enter the trial, written informed consent must be provided by the participant and obtained by, and the consent form signed by, a medically qualified member of the site research team approved to do so by the PI as detailed on the trial APL.

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any medically qualified person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If the informed consent process is delegated to another clinically qualified member of the trial team they must have received GCP training and be approved by the PI. Full Informed consent must be obtained and the participant must be registered into the trial prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with standard routine care at the participating site.

The right of a participant to refuse participation at any stage without giving reasons must be respected. The participant must remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment, and will be provided with a contact point where they may obtain further information about the trial. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

A record of the consent process (Section 10.4), including the date of consent and all those present (either face-to-face or via video/telephone), will be kept in the participant's notes. The original consent form will be filed in the Investigator Site File, a copy of the consent form will be given to the participant and a copy will be returned to the CTRU at the University of Leeds.

Eligibility according to the trial protocol must be confirmed prior to randomisation by the PI, or an appropriate medically trained delegate as detailed on the APL. Eligibility for the trial will be recorded in the participant's medical records and on the relevant electronic case report form (eCRF).

10.3 Non-registration

Each trial research site will be required to maintain an ongoing log of all participants with confirmed CLL considered for the trial who are not registered either because they are ineligible or because they decline participation.

Anonymised information will be collected including:

- age
- sex
- ethnicity
- reason for ineligibility for trial participation, or
- reason for declining participation, if known

Each individual should only be recorded as a non-registration once. Details of non-registrations will be submitted to the CTRU 3-monthly and on request. Reasons for non-registration will be monitored by the CTRU alongside recruitment progress.

10.4 Full Informed Consent, Trial Registration and Randomisation

10.4.1 Initial Information

Potential participants may be approached with initial information about the trial and the treatment options during routine clinic visits. Information about the trial will also be distributed in the form of leaflets via patient forums, support groups and hospital clinics.

10.4.2 Full Informed Consent

Potential participants will be provided with a full verbal explanation of the trial and the participant information sheet (PIS) and informed consent document (ICD) to consider. The PIS includes detailed information about the rationale, design, personal implications of the trial, data collection and data protection information. Following information provision, potential participants will have as long as they need to consider participation and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to take part in the study.

Potential participants wishing to take part in the trial will be required to provide written informed consent. This may take place in person during a hospital appointment with the clinician seeking consent, or remotely via telephone or video consultation with the consent form subsequently sent by post.

10.4.3 Registration

All participants regardless of whether they enter the Randomisation Pathway or Clinical Need Cohort need to be registered centrally using the CTRU automated 24-hour web-based system.

Once they have given consent, participants will be formally assessed for eligibility in line with Section 9. Participants must sign the consent form for the pathway which they are entering, either the Previously Treated Trial Consent or the STATIC FLAIR Trial Consent, eligible participants can then be registered.

All participants will be allocated a trial number at the time of registration which will be used to identify the participant throughout the trial and which pathway they have entered.

The following information will be required at registration:

- Username and password (registered email address)
- Name of trial research site and site code
- Participant details, including initials, date of birth and NHS or CHI number
- Confirmation of full written informed trial consent
- Confirmation of full written informed consent for samples to be sent to the UK CLL Biobank for participants entering the randomisation pathways only
- Confirmation of eligibility for registration

24 hour trial registration:

https://lictr.leeds.ac.uk/webrand/

Following trial registration, consent forms must be sent via the CTRU's Secure File Transfer Service or other CTRU-approved method. Please contact the trial team for details.

Confirmation of trial registration will be emailed automatically to the research team. The local hospital will provide each participant with a Trial ID Card which they should carry with them at all times and present to medical staff should they be admitted to hospital during their time on the trial. Eligibility must be confirmed on the relevant eCRF before treatment can start.

Following trial registration, any further tests required to confirm eligibility in line with Sections 9 and 13 will be performed.

If the participant is entering the Clinical Need Cohort, there is no randomisation step. Once the participant has been registered into the Clinical Need Cohort the research team should notify the participant's General Practitioner (GP) of their participation using the approved template letter provided by the CTRU. A copy of the letter should be filed in the Investigator Site File. After registration baseline assessments for the Clinical Need Cohort can be completed, refer to Sections 13.6 and the schedule of investigations in Appendix 4, in order for the participant to be confirmed as eligible in line with Section 9.

10.4.4 Randomisation

After participants have been registered, those entering the Randomisation Pathway will need to undergo Randomisation Baseline Assessments (refer to Sections 13.7 and the schedule of investigations in Appendix 4), to be confirmed as eligible in line with Section 9. Participants can then be randomised centrally using the CTRU automated 24-hour web-based system. Refer to Section 10.5 for details about how to randomise.

When recording patient eligibility for any pathway it must be a medically qualified doctor (named on the Authorised Personnel Log for the study) that decides if a potential participant is eligible and this should be clearly documented in the medical notes and signed by the doctor making the decision, prior to starting treatment. A statement should be included in the notes, similar to 'This patient meets all of the inclusion criteria and none of the exclusion criteria and is therefore eligible for entry into the STATIC trial'. The statement in the notes can be made by any healthcare professional (e.g. a research nurse) if it is made clear that a medically qualified doctor made the decision.

10.4.5 Consent to the UK CLL Biobank

Participants who are eligible to take part in the Randomisation Pathway will also be eligible to have a number of biological samples sent to the UK CLL Biobank. Participation within the UK CLL Biobank will be discussed with participants at the same time as discussing their participation in the rest of the trial.

Participants who enter the Clinical Need Pathway will not have biological samples sent to the UK CLL Biobank, and therefore will not be required to provide consent for the UK CLL Biobank.

At the same time as discussing the Randomisation Pathway, participants who wish to have biological samples to be sent to the UK CLL Biobank, will be provided with verbal and written details (the UK CLL Biobank Patient Information Sheet) about the CLL Biobank. As with the Randomisation Pathway consent, following information provision, participants will be given as long as they need to consider participation (normally a minimum of 24 hours) and will be given the opportunity to discuss the study with their family and other healthcare professionals before they are asked whether they would be willing to have samples sent to the UK CLL Biobank.

As for the Randomisation Pathway, a record of consent, detailing the date of consent and all those present will be kept in the participants notes. The original UK CLL Biobank Consent Form will be filed within the Investigator Site File, a copy of the consent form will be given to the participant, a copy will be returned to the UK CLL Biobank at University of Liverpool and a copy will be returned to the CTRU at the University of Leeds.

10.5 Randomisation process

Direct line for 24hr randomisation
https://lictr.leeds.ac.uk/WebRand/

Confirmation of randomisation, including details of allocation will be emailed automatically to the research team and pharmacy department.

The research team should notify the participant's General Practitioner (GP) of the participant's randomised allocation using the approved template letter provided by the CTRU. A copy of the letter should be filed in the Investigator Site File.

The following information will be required at randomisation:

- Participant trial number
- Participant details; date of birth, Sex
- Confirmation of randomisation eligibility
- Stratification factors (see list below)
- Confirmation that pre-randomisation QoL and Health Economics questionnaires have been completed prior to randomisation for participants.
- Confirmation of the participants preferred method of completing the QoL and Health Economics questionnaires, either paper or electronic
- Email address of participants who elect to complete electronic questionnaires

A computer generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well balanced for certain patient characteristics dependent on the randomisation.

10.5.1 Stratification Factors

In addition to the list above the following information will be required at randomisation

- Previously treated on FLAIR (FLAIR/Not FLAIR),
- Minimal residual disease (MRD) level at entry (>10%, 10%- 1%, <1%)
- Centre

10.6 Loss of capacity following informed consent

Where valid informed consent is obtained from the participant, and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Participants who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the PI and participant's carer/family with the participant's best interests foremost in the decision making process on an ongoing basis. Ongoing collection of safety and follow-up data (where possible) will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's analysis and fulfil regulatory requirements specifically for pharmacovigilance purposes.

10.7 Collection and Use of Full Participant Name

Full participant name will be present on Informed Consent Documents, which will be either securely emailed or posted to the CTRU, separately from any other trial data or forms. This information will be stored securely at the CTRU separate to all other STATIC trial data.

Full participant name will be requested with samples sent to Leeds HMDS central laboratory, along with NHS number/CHI number, initials, date of birth, sex, and trial number to ensure accurate identification for routinely returning results to sites electronically and by post. Samples sent to UK CLL Biobank and will not require participant name but will include NHS number/CHI number, trial number, sex, initials and date of birth to ensure robust tracking and identification processes.

11 TRIAL MEDICINAL PRODUCT MANAGEMENT

Please refer to the STATIC Pharmacy and IMP Study Site Operating Procedure (Pharmacy IMP SSOP) for full details of the trial IMP management requirements including IMP ordering, destruction, accountability and disposal records.

11.1 Investigational medicinal products

Within the trial, the following are classed as Investigational Medicinal Products (IMPs):

11.1.1 Ibrutinib

Trade name: IMBRUVICA
Composition of trial supplied IMP: 140 mg film-coated capsules
Composition of "off the shelf" NHS Stock: 140mg, 280mg and 420mg film-coated tablets

Supply:

Randomisation Trial

- For previously treated CLL participants receiving ibrutinib tablets as standard of care through routine commissioning, the supply of ibrutinib will be from ''off the shelf'' NHS stock. Please refer to the most recent Summary of Product Characteristics (SmPC) for the brand being used.
- For participants receiving ibrutinib front-line who have previously participated in the FLAIR trial, ibrutinib capsules will be provided for these patients free of charge by Janssen Pharmaceutica NV. Please refer to the most recent SmPC.

Clinical Need Cohort

- For participants receiving ibrutinib in the Clinical Need Cohort, who have previously participated in the FLAIR trial, ibrutinib capsules will be provided free of charge by Janssen Pharmaceutica NV. Please refer to the most recent SmPC.

11.2 IMP preparation and storage

Preparation and storage of IMPs is in line with the manufacturers' recommendations. For further details refer to the SmPC and trial supplied Pharmacy and IMP Management SSOP.

11.3 IMP labelling

Ibrutinib supplies from Janssen will contain a study-specific label, in line with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006). The pharmacy will be responsible for completing individual participant details on each label.

Pharmacy will be responsible for labelling 'off the shelf' ibrutinib, in accordance with the requirements of the Medicines for Human Use (Marketing Authorisations Etc.) Regulations 1994. The pharmacy will be responsible for producing these labels.

Please refer to the STATIC Pharmacy and IMP Management SSOP for full details of the trial IMP management requirements, including record keeping.

11.4 IMP accountability

Full accountability of trial-supplied ibrutinib stock must be recorded on the trial-specific accountability logs found within the Pharmacy Site File.

For 'off the shelf' stock of ibrutinib, the batch number and expiry date will be recorded on the trial-specific dispensing logs found within the Pharmacy Site File.

11.5 Product quality complaints

A product quality complaint (PQC) is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Study site personnel must report all PQCs to the CTRU and the relevant pharmaceutical company, within 24 hours of becoming aware of the event as detailed in the Pharmacy and IMP Management SSOP. Whenever possible, the associated product should be retained in accordance with the label instructions pending further guidance from the relevant pharmaceutical company. A sample of the suspected product should be retained for further investigation, if requested.

12 TRIAL TREATMENT DETAILS

12.1 IMP administration

Ibrutinib will only be given to eligible participants under the supervision of the PI or identified sub-investigators as delegated on the APL. The responsibility for the prescription and provision of trial treatment ultimately remains with the PI.

Toxicity will be assessed every 3 months and doses adjusted in accordance with the guidelines given in the SmPC.

With the exception of IMPs (listed in Section 11.1), all other medications, including prophylactic or concomitant medication and supportive therapy, will be administered according to routine clinical practice at each site. Refer to Section 12.3 for details of excluded concomitant medications for IMPs.

12.1.1 Ibrutinib

140 mg film coated capsules, 140mg, 280mg and 420mg film-coated tablets of ibrutinib should be taken orally once daily with approximately 240mls of water at approximately the same time each day. The capsules/tablets should be swallowed whole with water and should not be opened, broken, or chewed.

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If the dose is more than 6 hours late, the dose should not be taken and the participant should take the next dose at the scheduled time the following day.

12.2 Treatment compliance

Treatment compliance with ibrutinib will be recorded using a Participant Diary Card that will be given to participants prior to their first course of treatment. The participant will be asked to bring this card with them at every visit – diary cards must be returned to the research team at site to allow treatment compliance to be reviewed.

In addition front-line participants, who have been previously treated on FLAIR, who are receiving trial supplied ibrutinib should be instructed to return any unused capsules to the research team at each follow-up visit and the research team will return this to the hospital pharmacy. Returned capsules will be destroyed per the Pharmacy and IMP SSOP. Pharmacies do not need authorisation from the CTRU to destroy returned capsules.

Previously treated participants receiving “off the shelf” Hospital supply, in the randomisation pathway should follow local Hospital policies for unused tablets.

Non-compliance with trial medication should be reported to the CTRU. Repeated non-compliance with trial medications may result in a discussion between the Chief Investigator (CI) and research site, with a view to the participant being withdrawn from study treatment if no longer able to meet protocol requirements.

12.3 Concomitant medication

12.3.1 Supportive care

Local supportive care protocols, including for anti-infection prophylaxis and anti-emetics, should be followed. If participants are identified as having emergent hypertension this should be managed in line NICE hypertension guidance, see Appendix 5, with the exception of the excluded concomitant medications listed in section 12.3.2 (*ACE inhibitors, as recommended in the NICE guidance, should not be given concurrently with ibrutinib based regimens in the study, also note the cautionary advice in relation to diltiazem and verapamil which should be used with caution whilst receiving ibrutinib*).

For participants who are randomised to the pausing ibrutinib arm, stopping of supportive medications should be completed in line with local policy whilst on treatment breaks.

12.3.2 Excluded concomitant medications

A full list of CYP3A inhibiting and inducing drugs, ACE inhibitors and other cautionary medications is provided in Appendix 7.

Table 1 Guidance on the use of CYP3A inhibiting/inducing drugs & other cautionary medications/foods

Name	Examples	Advice
Strong CYP3A inhibitors	Ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, telithromycin, and voriconazole	Avoid whilst on ibrutinib treatment. Strongly recommend alternative with less potent enzyme inhibition but if required should be discussed with CI/Co-I before use and monitor patient closely for treatment-related toxicities. For ibrutinib either interruption of ibrutinib or reduction to 140mg daily initiated. Resume treatment dose that was used before administration of the inhibitor 2-3 days after discontinuing the inhibitor.
Moderate CYP3A inhibitors	Erythromycin, ciprofloxacin, dronedarone, fluconazole, verapamil, and diltiazem	Avoid and consider alternatives but can be used with caution whilst on ibrutinib treatment. If required should be discussed with CI/Co-I before use and monitor patient closely for treatment-related toxicities. For ibrutinib either interruption treatment or reduce dose to 140mg daily. Resume treatment dose that was used before administration of the inhibitor 2-3 days after discontinuing the inhibitor.
Weak CYP3A inhibitors	Azithromycin, fluvoxamine	Monitor participant closely for toxicity and follow dose modification guidance as needed.

Strong CYP3A inducers	Carbamazepine, phenytoin, St. John's wort, and rifampicin	Should be avoided as may decrease plasma concentration of ibrutinib, consider alternative treatments with less enzyme induction.
Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, nafcillin	
Weak CYP3A inducers	Prednisolone, pioglitazone	
P-gp, BCRP and OATP1B1 substrates	Digoxin, methotrexate, rosuvastatin, dabigatran, everolimus, sirolimus	In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp). The dihydrodiol metabolite and other metabolites are P-gp substrates. Ibrutinib is a mild P-gp and BCRP inhibitor in vitro. As no clinical data are available on this interaction, it cannot be excluded that ibrutinib could inhibit intestinal P-gp and BCRP after a therapeutic dose and so other substrates should be avoided. Contact CI/Co-I before administering P-gp, OATP1B1 or BCRP substrates to participants treated with ibrutinib.
ACE inhibitors	Common examples include (but not limited to): Ramipril, Perindopril, Lisinopril, Enalapril.	Avoid whilst on ibrutinib treatment. For participants requiring antihypertensive therapy an alternative therapy should be given.
Food	Grapefruit, Seville oranges (including marmalade), and starfruit	Avoid whilst on ibrutinib treatment
Supplements	Fish Oil and Vitamin E	Avoid whilst on ibrutinib treatment

12.3.3 Dose modifications

Participants should be monitored for toxicity. Dose modifications are permitted and should be in accordance with the SmPC. The management of toxicities should be in accordance with the SmPC and local practise.

12.3.4 Anticoagulants and anti-platelet drugs

Warfarin, or other vitamin K antagonists, should not be given concomitantly whilst the participant is receiving ibrutinib. For participants requiring anticoagulant therapy low molecular weight heparin, apixaban, rivaroxaban or edoxaban should be considered instead. Dabigatran should be avoided. Participants with new requirement for anticoagulant therapy during the trial whilst treated with ibrutinib should contact the CI/Co-I for advice.

Anti-platelet drugs can be used with ibrutinib but can be associated with increased bruising and bleeding. Therefore, patients on these agents should be monitored for any significant change in

bruising or bleeding. Dual antiplatelet therapy at baseline is permissible if this has been administered at a stable dose for at least 3 months prior to registration. If a patient develops a need for dual antiplatelet therapy during the trial this should be discussed with the CI/Co-I beforehand.

12.3.5 Surgery whilst receiving ibrutinib

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be stopped for at least 7 days prior to the intervention and not be restarted for at least 7 days after the procedure. Ibrutinib should be 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 stopped 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 participant is on ibrutinib, it is not necessary to withhold ibrutinib for these procedures.

For investigational procedures (e.g. colonoscopy, endoscopy) consideration should be given as to whether a biopsy or other instrumentation is likely to be taken and the extent of the biopsy. If a biopsy or other instrumentation is possible ibrutinib should be stopped 3 or 7 days before the procedure and not be restarted for at least 3 or 7 days after, depending on the extent of the biopsy.

For emergency procedures, ibrutinib should be withheld after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

Participants must be provided with the advice card, provided by the CTRU, which details the circumstances where ibrutinib should be withheld for surgery. It is recommended that sites reissue the advice card annually due to the prolonged treatment period. Please remind participants of the requirement to stop ibrutinib before any surgical procedures at each clinic appointment. The increased risk of bleeding whilst taking ibrutinib should be communicated to other hospital departments as per local practice.

Where the participant has had a minor or major procedure without stopping ibrutinib a Protocol Violations eCRF should be completed.

12.4 Early discontinuation of treatment strategy

In line with standard clinical care, cessation or alteration of treatment regimens at any time will be at the discretion of treating clinicians or the participants themselves.

If participants cease trial therapy for more than 4 weeks, the CI should be consulted and the participants may need to discontinue trial treatment; this does not apply to planned treatment breaks associated with the pausing ibrutinib arm.

If trial treatment is discontinued early (e.g. due to toxicity, clinician/participant choice, delay of 4 weeks), the participant should be treated off study at the discretion of the investigator.

12.5 Treatment post-relapse/treatment failure

Participants randomised to the pausing ibrutinib arm who demonstrate active disease will initially resume ibrutinib treatment. Participants who present with non-responsiveness to the reintroduction of ibrutinib as evidenced by continued active disease as per the 2018 iwCLL criteria, will meet the criteria of treatment failure and this should prompt the discontinuation of ibrutinib and consideration of subsequent therapy off-study at the discretion of the local investigator.

Participants randomised to the continuous ibrutinib arm who demonstrate active disease (see Appendix 1) at any time during the trial will meet the criteria of treatment failure and should be treated off-study at the discretion of the treating clinician.

Participants in the Clinical Need Cohort should continue to receive ibrutinib at the treating clinician's discretion until this is no longer providing benefit. Non-responsiveness to continued ibrutinib, as evidenced by symptomatic active disease, should prompt the discontinuation of ibrutinib and the participant should be treated off-study at the discretion of the treating clinician.

13 ASSESSMENTS, SAMPLES, DATA COLLECTION AND FOLLOW UP

13.1 Local policies for COVID-19 (and / or similar)

In light of the COVID-19 pandemic (and / or similar pandemics or epidemics), sites may have implemented policies concerning the treatment and assessment of patients with CLL, for example in order to minimise hospital/clinic visits. Full blood counts are an essential component of the treatment in STATIC. If it is necessary for some of the 3-monthly follow-up appointments to be conducted remotely blood tests should be performed nearer the patient's home, for example by the GP, in order to minimise hospital/clinic visits. If implementation of these policies whilst treating STATIC participants results in a deviation from the protocol, sites should refer to Section 13.15 and follow the usual process for the reporting of protocol violations, if required.

Face-to-face clinic visits with a relevant medical professional will remain mandatory if there is evidence of a patient progressing, for example if they report noticing lymphadenopathy, in order to ensure the safety and wellbeing of participants. Furthermore, participants on the intermittent treatment pathway who are due to pause ibrutinib should continue to undergo face-to-face review to ensure there is no clinical evidence of disease before pausing treatment.

13.2 Submission of trial data

Informed Consent Documents will be collected via paper case report forms (CRF). QoL, Healthcare Resource Use questionnaires will be available as paper CRF's and electronic case report forms (eCRFs). All other data collection will be via Remote Data Entry (RDE) on eCRFs managed by the CTRU at the University of Leeds. Access to the live STATIC database will be provided by the CTRU following sites being authorised to open to recruitment; guidance on RDE and completing eCRFs will be provided.

The CTRU will provide an electronic copy of the paper case report forms (CRFs) required for Informed Consent Documents and QoL and Healthcare Resource Use questionnaires. Data will be completed on printed CRFs by staff at research sites and sent to the CTRU, usually via secure file transfer or standard post.

Paper QoL and Healthcare Resource Use questionnaires can be completed either in the clinic or, if a clinic visit is not possible, posted to the participant for completion at home. If they are completed by the participant in clinic, they should be sealed in an envelope before handing back to the site research team who will return them to the CTRU via post. If they have been posted to the participant for completion at home, an addressed envelope should be provided so that the questionnaires can be posted directly back to the STATIC team at the CTRU. Questionnaires completed by the participant must not be copied or retained by the site.

Electronic QoL and Healthcare Resource Use questionnaires are also available as eCRFs, and a link to the eplatform can be shared with the participant for completion. Electronic versions of questionnaires completed by the participant must not be copied or retained by the site.

Data must only be completed by personnel authorised to do so by the PI, as recorded on the trial-specific Authorised Personnel Log. Where additional documentation is required by the CTRU, e.g. hospital reports, letters etc., it is the responsibility of staff at research sites to redact all personal identifiable data prior to sending to the CTRU. Such records should only include trial number, initials and date of birth to identify the participant. The exception to this is the participant Informed Consent Document, where the participant name and signature must not be redacted. The Informed Consent Document should be returned to the CTRU via secure file transfer, where this is not possible it must be sent via post. If signed Informed Consent Documents are posted to the CTRU, they must be sent in a separate envelopes and not accompanied by clinical data or questionnaires.

Participating hospitals will be expected to maintain a file of essential trial documentation (Investigator Site File), digital versions of the site files including all essential trial documents will be provided by the CTRU.

13.3 Schedule of investigations

A tabulated summary of all local and central assessments is provided in Appendix 4.

13.4 Samples for central analysis

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 2018 Data Protection Act and General Data Protection Regulation (GDPR). Biological samples collected from participants 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.

13.5 Registration

Please note that assessments performed specifically for the trial must not be performed until after consent has been received. Where a test has been performed as part of local care and is within the required time-frame it does not have to be repeated but cannot be used for trial purposes until the participant has given consent.

All participants regardless of whether they enter the Randomisation Pathway or Clinical Need Cohort need to be registered. Refer to Section 10.4.3.

13.6 Clinical Need Cohort

For participants entering the Clinical Need Cohort, there is no randomisation step. Initial assessments to confirm eligibility and perform a baseline for the day-today clinical care should be performed within the timeframes specified in 13.6.1. It is expected that all assessments will be performed as part of standard clinical care.

Potential participants must attend for a face-to-face clinic appointment in order for a medically qualified doctor to assess eligibility for STATIC (even whilst policies are in place to minimise hospital visits during the COVID-19 pandemic or similar epidemic/ pandemic).

Any assessments performed specifically for the purposes of the trial must only be performed after full written informed consent has been obtained and the participant has been registered into the trial.

Cardiac monitoring should be conducted, in line with standard of care. If abnormal cardiac function is identified during screening, and, in the opinion of the PI, meets the following exclusion criterion, then the participant should be excluded from the trial:

Symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)

13.6.1 Eligibility and Baseline Local Investigations

Mandatory Investigation to Confirm Eligibility?	**Type of Investigation**	**Comments**
Yes	Complete Medical History	Including detailed history of CLL (including duration of treatment with ibrutinib or other BTK inhibitor (date of commencement of ibrutinib, dose, any significant periods of treatment since starting, prolonged (of a month or more) planned and unplanned periods of treatment breaks, history of treatment and how long the potential participant has been in clinical remission (minimum of preceding 12 months), other ongoing medical conditions that require treatment, concomitant medications, IGVH mutation status (if known) **Within 2 weeks prior to registration**
Yes	Pregnancy test	Serum or urine HCG in women of child bearing potential **within 2 weeks** prior to registration
No	Complete Physical Examination, Vital Signs and Clinical Assessment of Disease	Within **within 2 weeks** to registration To confirm potential participant remains in clinical remission: - No palpable lymph nodes ; - no palpable spleen; - B-CLL in accordance with 2018 iwCLL criteria In addition: Systolic and diastolic blood pressure, pulse rate, height, weight

Yes	Local Haematology and Biochemistry	To confirm potential participant remains in clinical remission: - ALC lymphocyte count below $5x10^9$/L Within **4 weeks** prior to registration
Yes	WHO performance status	Within 4 weeks prior to registration Refer to Appendix 2.
No	Local Haematology and Biochemistry	FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes, reticulocyte count) Within **2 weeks** prior to registration
No	Local Haematology and Biochemistry	U&E's (calcium (adjusted), urea, urate, serum creatinine, calculated creatinine clearance) Within **4 weeks** prior to registration
Yes	Local Haematology and Biochemistry	LFT's (bilirubin, alkaline phosphatase, ALT or AST) Within 4 weeks prior to registration
Yes	Hepatitis B and C	Serology for Hepatitis B and C (HBsAg, HBcAb & HCAb) (Within **12 weeks** prior to registration)
Yes	Cardiac Assessment (conducted as per SoC)	Cardiac assessments should be performed as per SoC (if formal assessments, such as an ECHO, are conducted within any time frame the results will be acceptable)
No	Blood pressure	Take/ document blood pressure and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Participants with hypertension (either prior to the trial or emergent on treatment) should be managed according to NICE Guidelines (NG136; published August 2019)*, see Appendix 5, to keep the blood pressure below 140/90mmHg. Blood pressure should be reported on the relevant eCRF according to the (CTCAE) V5.0 grades, see Appendix 3. *with the exception of the excluded concomitant medications listed in section 12.3.2

13.6.2 Local investigations whilst on study

These assessments should be conducted in line with standard of care every 3 months during routine follow up visits, and data collected for the trial 6 monthly.

- Physical examination, including clinical assessment of disease and B-CLL in accordance with 2018 iwCLL criteria

- Local haematology and biochemistry test including:
  - FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes, reticulocyte count)
  - U&E's (calcium (adjusted), urea, urate, serum creatinine, calculated creatinine clearance)
  - bilirubin, alkaline phosphatase, ALT or AST
- Blood pressure (monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Participants with hypertension (either prior to the trial or emergent on treatment) should be managed according to NICE Guidelines (NG136; published August 2019)*, see Appendix 5, to keep the blood pressure below 140/90mmHg.

  *with the expception of the excluded concomitant medications listed in section 12.3.2

13.7 Randomisation Pathway: Eligibility and Baseline Assessments

For participants entering the Randomisation Pathway, initial assessments aiming to confirm eligibility and provide a baseline for the day-to-day clinical care of participants should be performed within 4 weeks prior to randomisation, unless otherwise stated below. If randomisation does not occur within 4 weeks of confirming eligibility then the tests will have to be repeated. It is expected that all assessments will be performed as part of standard clinical care.

Potential participants must attend for a face-to-face clinic appointment in order for a medically qualified doctor to assess eligibility for STATIC (even whilst policies are in place to minimise hospital visits during the COVID-19 pandemic or similar epidemic/ pandemic).

Any assessments performed specifically for the purposes of the trial must only be performed after full written informed consent has been obtained and the participant has been registered into the trial.

Cardiac monitoring should be conducted, in line with standard of care. If abnormal cardiac function is identified during screening, and, in the opinion of the PI, meets the following exclusion criterion, then the participant should be excluded from the trial:

> *Symptomatic cardiac failure not controlled by therapy, or unstable angina not adequately controlled by current therapy (in patients with a significant cardiac history the left ventricular function should be assessed and patients with severe impairment should be excluded)*

13.7.1 Baseline Local Investigations

Mandatory Investigation to Confirm Eligibility?	Type of Investigation	Comments
Yes	Complete Medical History	Including detailed history of CLL (including duration of treatment with ibrutinib or other BTK inhibitor (date of commencement of ibrutinib, dose, any significant periods of treatment since starting, prolonged (of a month or more) planned and unplanned periods of treatment breaks, history of

		treatment and how long the potential participant has been in clinical remission (minimum of preceding 12 months), other ongoing medical conditions that require treatment, concomitant medications, IGVH mutation status (if known), and details of any previous COVID-19 vaccinations Within **4 weeks** prior to being randomised
Yes	Pregnancy test	Serum or urine HCG in women of child bearing potential within **2 weeks** prior to being randomised
Yes	Complete Physical Examination, Vital Signs and Clinical Assessment of Disease	Within **2 weeks** prior to randomisation To confirm potential participant remains in clinical remission: - No palpable lymph nodes ; - no palpable spleen; - B-CLL in accordance with 2018 iwCLL criteria In addition: pulse rate, height, weight
Yes	Local Haematology and Biochemistry	To confirm potential participant remains in clinical remission: - ALC lymphocyte count below $5x10^9$/L Within **4 weeks** prior to being randomised
Yes	WHO performance status	Within **4 weeks** prior to being randomised Refer to Appendix 2.
No	Local Haematology and Biochemistry	FBC (Hb, platelets, WBC count, ANC neutrophils, ALC lymphocytes, reticulocyte count) Within **2 weeks** prior to being randomised
Yes *(for previously treated partcipants only)*	Local Haematology and Biochemistry	U&E's -calculated creatinine clearance Within **4 weeks** prior to being randomised
No	Local Haematology and Biochemistry	U&E's- calcium (adjusted), urea, urate, serum creatinine All tests within **2 weeks** prior to being randomised
Yes	Local Haematology and Biochemistry	LFT's (bilirubin, alkaline phosphatase, ALT or AST) Within **4 weeks** prior to being randomised

Yes	Hepatitis B and C	Serology for Hepatitis B and C (HBsAg, HBcAb & HCAb) (Within **12 weeks** prior to randomisation)
Yes	Cardiac Assessment (conducted as per SoC)	Cardiac assessments should be performed as per SoC (if formal assessments, such as an ECHO, are conducted within any time frame the results will be acceptable)
No	Blood pressure	Take/ document blood pressure and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Participants with hypertension (either prior to the trial or emergent on treatment) should be managed according to NICE Guidelines (NG136; published August 2019)*, see Appendix 5, to keep the blood pressure below 140/90mmHg. Blood pressure should be reported on the relevant eCRF according to the (CTCAE) V5.0 grades, see Appendix 3. *with the exception of the excluded concomitant medications listed in section 12.3.2

13.7.2 Baseline Central Investigations

The following samples are required from both randomisation arms (pausing ibrutinib and continuous ibrutinib arm) at baseline (these must be collected following registration, prior to randomisation):

- 20ml blood in EDTA to HMDS central laboratory for MRD flow cytometry, B-cell sorting, molecular BTK mutation analysis and for DNA/RNA storage
- 50ml anti-coagulated blood sent to UK CLL Biobank central laboratory
- Saliva Sample sent to the UK CLL Biobank central laboratory

13.7.3 Baseline QoL and Health Economic questionnaires

The following questionnaires should be completed in clinic after registration, before treatment is started:

- QoL Questionnaires (EORTC QLQ-C30, QLQ-CLL and EQ-5D-5L)
- Healthcare resource use questionnaire

13.8 Randomisation Pathway: Assessments while on study

Participants randomised to the continuous treatment pathway will receive ibrutinib (oral) 420mg per day (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities other stable reduced dose) until active disease leads to the requirement to change to an alternative therapy in the opinion of the local Investigator (strategy failure) or death.

Participants randomised to the intermittent treatment strategy will pause treatment immediately following randomisation, and restart when the restart criteria are met. When treatment restarts, participants restart treatment with ibrutinib at the standard dose (or other reduced dose, if that dose has been stable for the past 6 months and there are no unresolved toxicities) until the treatment stop criteria are met.

The pausing and resuming criteria will be assessed locally every 3 months, at standard clinic visits. Participants can pause and restart treatment multiple times until active disease whilst on treatment leads to the requirement to change to an alternative therapy, death, or the end of the trial. Participants who demonstrate active disease whilst on the treatment pause will initially resume ibrutinib treatment, and the criteria for treatment failure will only be met if active disease is present at the subsequent follow up.

Refer to Section 13.8.3 for pausing and re-starting criteria.

Participants randomised to either pathway will be assessed as per standard of care clinic visits every 3 months, and data collected for the trial 6 monthly.

13.8.1 Randomisation Pathway Local Investigations

Mandatory Time-Points	**Type of test**	**Comments**
Every 3 months	Physical Examination, Vital Signs and Clinical Assessment of Disease	Including B-CLL symtoms in accordance with 2018 iwCLL criteria and assessment of lymph nodes, spleen and ALC to confirm if participant meets re-starting or pausing criteria (see section 13.8.3 and 13.8.4)
Every 3 months	Local Haematology and Biochemistry	ALC to confirm potential participant remains in clinical remission: - ALC lymphocyte count below $5x10^9/L$ Within 4 weeks prior to being randomised
Every 3 months	Local Haematology and Biochemistry	FBC (Hb, platelets, WBC count, ANC neutrophils, reticulocyte count)
Every 3 months	Local Haematology and Biochemistry	U&E's (calcium (adjusted), urea, urate, serum creatinine, calculated creatinine clearance)

Every 3 months	Local Haematology and Biochemistry	LFT's (bilirubin, alkaline phosphatase, ALT or AST)
Every 3 months	Blood pressure	Take/ document blood pressure and monitor participants as appropriate to ensure blood pressure is below 140/90mmHg. Participants with hypertension (either prior to the trial or emergent on treatment) should be managed according to NICE Guidelines (NG136; published August 2019)*, see Appendix 5, to keep the blood pressure below 140/90mmHg. Blood pressure should be reported on the relevant eCRF according to the (CTCAE) V5.0 grades, see Appendix 3. *with the exception of the excluded concomitant medications listed in section 12.3.2
Every 3 months	Adverse Events Assessed	Adverse events assessed by CTCAE (V5.0) grades (see Section 14.4 for reporting requirements)
Every 3 months	Treatment Compliance Assessed	Review of participant diary cards
Every 3 months	Medical History and Concomitant Medication	Review of other ongoing medical conditions that require treatment and concomitant medications

- NB. Management of pregnancy risk in women of child bearing age should be followed as per local guidance.
- Management and monitoring of hypertension should be managed in line with NICE hypertension guidance, see Appendix 5, with the exception of the excluded concomitant medications listed in section 12.3.2.

13.8.2 Randomisation Pathway: Central investigations while on study

The following samples are required from both randomisation arms (pausing ibrutinib and continuous ibrutinib arm):

- 20ml in EDTA blood sent to HMDS at:
    a. 24 months
    b. 48 months
- 50ml anti-coagulated blood sent to UK CLL Biobank at:
    a. 12 months
    b. 36 months
    c. 60 months
    d. 72 months

13.8.3 Intermittent Treatment Strategy: Pausing and Re-Starting Criteria

Initial pausing ibrutinib criteria (defined within the eligibility criteria; all to be met and maintained continuously for preceding 12 months):

- No palpable lymph nodes (<2cm), and

- No palpable spleen and
- Absolute lymphocyte count (ALC) <5x10^9/L.

Ibrutinib treatment restarting criteria:
Any one of:
- Palpable lymph nodes (≥2cm), or
- palpable spleen, or
- ALC ≥5x10^9/L

Ibrutinib treatment pausing criteria (second and subsequent pausing treatment breaks):
- Received at least a further 12 months of ibrutinib, and
- No palpable lymph nodes, and
- No palpable spleen, and
- ALC <5x10^9/L for at least 6 months

13.8.4 Intermittent Treatment Strategy: Central Samples at Restart Criteria

The following samples are required for participants who meet the restarting criteria:
- 20ml blood in EDTA to HMDS central laboratory
- 50ml anti-coagulated blood sent to UK CLL Biobank

13.8.5 Randomisation Pathway: QoL and Health Economic questionnaires

The following questionnaires should be completed in clinic after 3, 6, 12, 18, 24, 30, 36 and 48 months of trial treatment:

- Questionnaires (EORTC QLQ-C30, QLQ-CLLand EQ-5D-5L)
- Healthcare resource use questionnaire

13.9 Follow up after early treatment discontinuation (prior to treatment failure)

QoL and Health Economic questionnaires should continue to be completed at the timepoints detailed in Appendix 4.

If a participant explicitly states they do not wish to attend further visits or contribute further data to the study the CTRU should be informed using the Withdrawal eCRF (see Section 13.13).

13.10 Active Disease

13.10.1 Definition of Active Disease

Participants will be evaluated for progression until the criteria of active disease is met, leading to the requirement to change to an alternative therapy (treatment failure). For participants randomised to the intermittent treatment arm the criteria of active disease must be met whilst the participant is on treatment.

Active disease, defined by the 2018 iwCLL criteria, is characterised by at least one of the following:

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia. Cut-off levels of Hb <10 g/dL or platelet counts <100 × 10^9/L are generally regarded as indication for treatment. However, in some patients, platelet counts <100 × 10^9/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
- Massive (i.e., ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
- Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts <30 × 10^9/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g., infections, steroid administration) should be excluded.
- Autoimmune complications including anaemia or thrombocytopenia poorly responsive to corticosteroids.
- Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
    a. Unintentional weight loss ≥10% within the previous 6 months.
    b. Significant fatigue (i.e., ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
    c. Fevers ≥100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
    d. Night sweats for ≥1 month without evidence of infection.

Hypogammaglobulinemia, or monoclonal or oligoclonal paraproteinemia does not by itself constitute a basis for initiating therapy. However, it is recommended to assess the change in these protein abnormalities, if patients are treated.

13.10.2 Local investigations

Type of Investigation	Comments
Clinical Assessment of Disease	Assess for B-symptoms Assess lymph nodes and spleen
Full Blood Count	Assess ALC lymphocyte count Assess haemoglobin, neutrophils and platelets

13.10.3 Central investigations

At treatment failure in the Randomisation Pathway for either arm (continuous or intermittent treatment arms) the following samples should be sent:

- 20ml blood in EDTA to HMDS central laboratory
- 50ml anti-coagulated blood sent to UK CLL Biobank

13.11 Post-progression follow-up

Following treatment failure all participants will be followed up annually for 3 years, until death, or until the end of the study. For those participants who have consented, long-term follow-up survival data will collected from routine NHS data.

However, for those who have consented, the QoL and Health Economics questionnaires should be completed at all the timepoints detailed in Appendix 4 even if the participant has progressed before reaching this point in treatment.

13.12 Deaths

All deaths must be recorded on the Notification of Death eCRF within 24 hours of notification to the site trial research team.

All deaths should be assessed to determine whether they meet the criteria of a serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR). Definitions and reporting requirements for SAEs, SARs and SUSARs can be found in Section 14.

13.13 Long term follow up

For participants who have consented long term survival data will be collected by the CTRU via one off data download of routine data from NHS digital or other central UK NHS bodies. This data will be collected 6 years after the main trial has ended.

13.14 Participant withdrawal

The PI or delegate should ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial, be that from further treatment and/or follow-up data collection, are defined and documented using the Withdrawal eCRF in order that the correct processes are followed by the CTRU and site following the withdrawal of consent.

Where the participant withdraws consent for further data collection, data collected prior to withdrawal of consent will be included in the analysis. It should be made clear to any participant specifically withdrawing consent for further data collection in a CTIMP that data pertaining to safety will continue to be collected for regulatory reporting purposes and will be included in any safety analysis. In addition it is suggested that the participant is made aware of the fact that if any significant new information becomes available in regard to the treatment they have received in the trial it may be necessary to contact them in the future.

If it is the decision of the PI to withdraw the participant from further involvement in the trial then this should also be documented on the Withdrawal eCRF.

13.15 Participant transfer

If a participant is being transferred to a different site, the Participant Transfer eCRF must be completed.

13.15.1 Transfer to another site participating in STATIC

Copies of any paper CRFs, Informed Consent Documents and any other relevant correspondence are sent to the new hospital, with originals kept at the original site. Data from before the date of transfer is questioned with the original site, data after the transfer date is questioned with the new site. Both sites must ensure that the participant transfer is recorded on the participant log in the Investigator Site File and the Pharmacy Site File

13.15.2 Transfer to a site that is NOT participating in STATIC

- All trial treatment will cease. Any further treatment for CLL received by the participant will be off-study.
- If the participant agrees to be followed up at the new site, it is the responsibility of the original site to gather follow up data from the new site in order to complete the eCRFs. The original site will keep all trial documentation and ensure that the participant transfer is recorded on the participant log in the Investigator Site File and the Pharmacy Site File.
- If the participant does not want to be followed up at the new site, a Participant Withdrawal eCRF must be completed by the original site.

13.16 Protocol violations

A protocol violation can be defined as: any accidental or unintentional change to, or non-compliance with the protocol that **does** increase risk or decrease benefit, or has a significant effect on the participant's rights, safety, or welfare, or on the integrity of the data.

Examples of a violation include, but are not restricted to:

- Failure to obtain valid informed consent prior to performing any other trial investigation or procedure
- Breaches of eligibility criteria
- Drug administration errors relating to the IMP (e.g. overdose, underdose, not performing specified suitability for treatment tests, not modifying dose in line with required modifications)
- Non-adherence to the protocol in relation to prohibited concomitant therapy whilst receiving trial treatment.
- Concomitant medication

During the COVID-19 pandemic, sites may have local policies in place to limit hospital visits or to allow for temporary limitations on resources/facilities. If a protocol violation has occurred due to COVID-19-related reasons, sites are still required to follow the guidance in this section and to report the violation as per normal processes.

Protocol violations should be reported immediately to the CTRU using the Protocol Violations eCRF. Protocol violations will be monitored and escalated to the Trial Management Group (TMG) for review of medical significance. Medically significant protocol violations will be considered as to whether they meet the criteria for Serious Breaches of GCP (Section 21.1).

The following events do not need to be reported as a protocol violation as long as the local investigator deems it not medically significant and the event does not result in an SAE/SUSAR:

- A rescheduled study visit

- Participant refusal to complete scheduled research activities
- Limited dosing errors by participant, i.e. 14 missed doses over 2 weeks, that did not result in an SAE and that were deemed not medically significant by site. (NB: Where 15 or more doses are missed the event must be reported as a protocol violation).

13.17 Definition of end of trial

The end of the trial is defined as the date of the collection of the last participant's last data item. Participants will be followed up until death or until the final analysis as described in Section 19 (whichever is sooner).

13.18 Site and Trial Closure

The CTRU will notify sites of procedures for site closure following the trial final analysis.

14 PHARMACOVIGILANCE PROCEDURES

14.1 General definitions

The standard definitions are derived from the document 2011/C 172/01 'Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ("CT-3")' (based on the Clinical Trials Directive 2001/20/EC) and from the CIOMS Working Group VII definitions.

Term	Definition
Adverse Event (AE)	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. *An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.*
Adverse Event of Special Interest (AESI)	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to ibrutinib, for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an adverse event might require further investigation in order to characterise and understand it. Depending on the nature of the adverse event, rapid communication by the trial sponsor to other parties (e.g. regulators) might also be warranted.
Adverse Reaction (AR)	All untoward and unintended responses to an IMP related to any dose administered. *This definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.* *This definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means there are facts (evidence) or arguments to suggest a causal relationship.*
Serious Adverse Event (SAE)	Any untoward medical occurrence or effect that at any dose: • Results in death, • Is life-threatening, • Requires hospitalisation or prolongation of existing hospitalisation, • Results in persistent or significant disability or incapacity, • Results in a congenital anomaly or birth defect, • Jeopardises the subject or may require an intervention to prevent one of the above characteristics/consequences – herein referred to as 'Other important medical events' *These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.*

	Medical and scientific judgement must be exercised in deciding whether an event is "serious" in accordance with these criteria.
Serious Adverse Reaction (SAR)	Reference is made to the criterion of "Seriousness" above in relation to SAE and the definition of AR. *Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.*
Suspected Unexpected Serious Adverse Reaction (SUSAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable Reference Safety Information (Section 14.2). *The term "severity" is used here to describe the intensity of a specific event. This has to be distinguished from the term "serious".* *Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.*

14.2 Reference Safety Information

The Reference Safety Information (RSI) is the identified section of the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) used for assessing the causality and expectedness of an adverse reaction.

The RSI in this trial is defined as:

- Section 4.8 of the trial-supplied SmPC for ibrutinib tablets
- Section 4.8 of the trial-supplied SmPC for ibrutinib capsules

The versions of the above SmPCs are to be used for the purposes of pharmacovigilance reporting (in the case of this trial, for determining causality of an event) will be supplied to sites by the CTRU i.e. it is not necessarily the most recent available version online.

14.3 Operational definition – Serious Adverse Events (SAEs)

14.3.1 Events not classed as SAEs

The following events will not be recorded as SAEs within this trial:

- Hospitalisation for:
    - *Routine treatment or monitoring of the studied indication not associated with any deterioration in condition*
    - *Treatment which was elective and pre-planned, for a pre-existing condition not associated with any deterioration in condition*
    - *Admission to hospital or other institution for general care, not associated with any deterioration in condition*
    - *Treatment on an emergency, out-patient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission*
    - *Active Disease (this should be reported on the Active Disease eCRF)*
- Deaths attributable to CLL beyond 60 days of the last administration of trial IMP. These should be reported on the Death eCRF.

14.4 Recording and reporting AEs, SAEs, and SUSARs

Due to the nature of CLL and its treatment, participants are likely to experience several adverse events throughout the course of the disease.

Events will be reported on the eCRF using Medical Dictionary for Regulatory Activities (MedDRA) term(s) where possible and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0 (NCI-CTCAE). A copy is provided in the Investigator Site File and may be obtained at:
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf

MedDRA coding of events will be performed centrally at the CTRU.

Should an event fulfil any of the Serious Adverse Event criteria described in Section 14.1, a serious adverse event eCRF should also be completed.

14.4.1 AEs and ARs

AEs may be spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures, and should be reviewed at each cycle of protocol treatment. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE, whether or not it is considered related to the IMP, if it meets the criteria of an AE or causes a change in the action taken.

When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

All adverse events, both related and unrelated to CLL treatment will be collected on the relevant eCRF from trial registration until 60 days after the last dose of protocol treatment.

14.4.2 AEs of Special Interest (AESIs)

Both SAEs and AE of Special Interest should be collected and reported to Janssen (via CTRU) within one working day. AESIs in this study are:

Major Hemorrhage
defined as:

- Any treatment-emergent hemorrhagic AE of Grade 3 or higher.*
- Any treatment-emergent SAE of bleeding of any grade.
- Any treatment-emergent CNS hemorrhage/hematoma of any grade.

*All hemorrhagic AEs requiring a transfusion of red blood cells should be reported as a Grade 3 or higher AEs per NCI-CTCAE Version 4.03.

14.4.3 Special Situations

The following special situations should be collected and reported to Janssen (via the CTRU) within one working day, with or without an associated (SAE):

- exposure to ibrutinib during pregnancy (paternal, maternal)
- suspected transmission of any infectious agent via administration of ibrutinib
- Overdose of ibrutinib
- Exposure to ibrutinib whilst breastfeeding
- Suspected abuse/misuse of ibrutinib
- Inadvertent or accidental exposure to ibrutinib
- Any failure of expected pharmacological action (i.e., lack of effect) from ibrutinib
- Medication dispensing error (includes potential, intercepted or actual) involving ibrutinib (with or without patient exposure to the Janssen Product(s) e.g., name confusion)
- Unexpected therapeutic or clinical benefit from ibrutinib

14.4.4 SAEs and SARs

All SAEs must be recorded on the electronic Serious Adverse Event Report eCRF within 24 hours of the research staff becoming aware of the event, from registration until 30 days post the last dose of study drug.

All SARs occurring for the duration of the trial must be recorded on the electronic Serious Adverse Event Report eCRF within 24 hours of the research staff becoming aware of the event. SARs will be reported from the date of first study dose and for the duration of the trial.

Each SAE/SAR will be described by:
- symptoms / diagnosis
- case description
- duration (start and end dates; times, if applicable)
- seriousness criteria
- action taken in relation to IMPs
- outcome
- causality, in the opinion of the investigator*

**Assessment of causality must be made by a clinician. If a clinician is unavailable, initial reports without causality assessment should be submitted to the CTRU without a clinician's assessment within 24 hours, but must be followed up by medical assessment as soon as possible thereafter.*

When determining the expectedness of an event, please refer to the Reference Safety Information (RSI) (see Section 14.2)

The CTRU will be responsible for determining expectedness for each event in line with the RSI.

Please ensure that each SAE/SAR event is reported separately and not combined on one SAE/SUSAR form.

Changes in SAE outcome, seriousness criteria, causality, or significant / medically relevant changes to the event (key data) should be reported within 24 hours of becoming aware. Other follow up information should be added to the SAE/SUSAR eCRF when the event has reached a final outcome.

Events will be followed up until the event has resolved or a final outcome has been reached. Investigators must report all SAEs to their host institution in line with their local arrangements.

Refer to the Pharmacovigilance SSOP for SAE and SAR reporting.

14.4.5 SUSARs

All SARs assigned by the CTRU as being unexpected (in line with the RSI) will be classified as SUSARs and will be forwarded to the CI/TMG delegates for review and subject to expedited reporting to the relevant regulatory authority.

Following the assessment of unexpectedness, the CTRU will request the site research team complete any additional information on the electronic Serious Adverse Event Report eCRF within 24 hours. The CTRU will inform the relevant regulatory authority, the Research Ethics Committee (REC) and the Sponsor of SUSARs within the required expedited reporting timescales. SUSARs will be sent to relevant pharmaceutical companies at the same time as submission to the relevant regulatory authority. **SUSARs are reportable from the date of first study dose and for the duration of the trial**.

Changes in SUSAR outcome, seriousness criteria, causality, or significant / medically relevant changes to the event (key data) should be reported within 24 hours of becoming aware. Other follow up information should be added to the SAE/SUSAR eCRF when the event has reached a final outcome. Events will be followed up until the event has resolved or a final outcome has been reached. Investigators must report all SUSARs to their host institution in line with their local arrangements.

Refer to the Pharmacovigilance SSOP for SAE and SAR reporting.

Contact details for queries relating to SAEs / SUSARs
Email: ctru_pharmavig@leeds.ac.uk

14.5 Pregnancies or suspected pregnancies

Pregnancy in participants on trial treatment must be prevented as effectively as possible. As participants could be on treatment for up to 9 years, it is important to provide regular pregnancy counselling about highly effective contraceptive measures and document these discussions in the medical notes. All guidance regarding contraception, pregnancy and breast-feeding outlined in the relevant SmPCs and Appendix 6 must be followed. Highly effective contraceptive measures must be used by both female participants of child bearing potential and male participants (see Appendix 6 for details of appropriate contraception). Female participants of child bearing potential must use highly effective contraceptive measures throughout the study and for 3 months after stopping treatment. Male participants must use appropriate contraception throughout the study and for 3 months after stopping treatment.

Participants who are randomised to the pausing ibrutinib arm will not be required to follow contraceptive measures whilst on treatment breaks, but must continue to follow contraceptive measures for 3 months after stopping treatment for each treatment break. Contraceptive measures

must restart once treatment with ibrutinib resumes. Participants who become pregnant during a treatment break will come off trial treatment.

All protocol therapy must be stopped immediately if a pregnancy in a female participant occurs or is suspected, including during a treatment break in the pausing ibrutinib arm. Participants must be instructed to return any unused portion of the medication to the investigator. Participants withdrawn from treatment will still attend for follow-up assessments unless unwilling to do so and case report forms will continue to be collected.

Female participants should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling. If a pregnancy occurs in a male participant's partner, the partner should be advised to consult her GP or gynaecologist as soon as possible.

Breast-feeding must be discontinued during treatment with ibrutinib.

The local PI shall be responsible for any decision regarding the continued participation in the study of participants who, after an initial positive pregnancy diagnosis, are confirmed as no longer being pregnant.

14.5.1 Recording and reporting pregnancies/suspected pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a female participant must be reported throughout the study and for 3 months after stopping treatment. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a male participant's partner must be reported throughout the study and for 3 months after stopping treatment. Pregnancies must be reported using the electronic Pregnancy eCRF within 24 hours of the research staff becoming aware of the event.

Because the effect of ibrutinib on sperm is unknown, pregnancies in partners of male participants exposed to ibrutinib will be reported within 24 hours of the knowledge of the event using the Serious Adverse Event eCRF. Depending on local legislation, this may require prior consent of the partner.

Contact details for queries relating to pregnancies/suspected pregnancies
Email: ctru-pharmavig@leeds.ac.uk

The CTRU will report the pregnancy or suspected pregnancy to relevant pharmaceutical companies as required on the same working day that Sponsor is made aware and will follow the pregnancy up to outcome.

Pregnant participants must be followed until the end of their pregnancy and the CTRU must be notified of the outcome of the pregnancy (including false-positive pregnancy tests) within 24 hours of this information being known. If a pregnancy occurs in a male participant's partner, details of the pregnancy will still be collected where possible and the outcome of the pregnancy must be notified to the CTRU.

The outcome of any pregnancy which qualifies as a SAE (i.e. spontaneous or therapeutic abortion, foetal and neonatal death, or congenital abnormalities – including those detected in an aborted foetus), birth defects, or the death of an infant which occurs in connection with in utero exposure to the study drugs must be reported to the CTRU as a SAE in accordance with Section 14.4.

14.6 Pharmacovigilance responsibilities

14.6.1 Local Principal Investigator

- Checking for AEs/ARs, SAEs and AEoSI during treatment/follow up's;
- Ensuring that AEs and ARs are recorded and reported to the CTRU in line with the requirements of the protocol.
- Using medical judgement in assigning seriousness and causality to SAEs/SUSARs, using the RSI approved for the trial;
- To ensure that the trial team are using the correct version of the safety reference documents;
- To ensure all SAEs, SARs (including SUSARs) and AEoSIs are recorded and reported to the CTRU within 24 hours of becoming aware and to provide further key follow up information within 24 hours. To ensure that reported events are chased with the CTRU if a confirmation of receipt is not received within 2 days of reporting.
- To report SAEs to local committees in line with local arrangements.
- In the case of pregnancy, to ensure that treatment is stopped immediately (in female participants) and the pregnancy is reported to the CTRU within 24 hours of becoming aware.

14.6.2 Clinical Trials Research Unit, University of Leeds (CTRU)

- Identifying at the beginning of the study the information in the SmPC (or IB) that will be used as the RSI for pharmacovigilance reporting.
- Central data collection and verification of AEs, ARs, SAEs, SARs, SUSARs and AEoSIs according to the trial protocol onto a MACRO database according to MedDRA.
- Using the RSI to assign expectedness of all SAEs
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit ratio.
- Notifying the local investigator of any event reported from their site that is assessed by the Chief Investigator (or delegate) as unexpected.
- Reporting safety information to the independent oversight committees identified for the trial Data Monitoring & Ethics Committee (DMEC) and / or Trial Steering Committee (TSC).
- Expedited reporting of SUSARs to the Competent Authority (Medicines and Healthcare Products Regulatory Agency (MHRA) in UK), REC and Sponsor within required timelines.
- Notifying Investigators of SUSARs that occur within the trial.
- Notifying PIs at sites, the Sponsor, REC and MHRA/relevant regulatory authority of findings that could adversely affect the health of participants, impact on the conduct of the trial, or alter the authority's authorisation of the trial.
- Reporting events to collaborating pharmaceutical company in accordance with the trial contracts
- Checking for updates to the RSI (annually as a minimum) and communicating changes to the CI for reassessment of the risk benefit ratio.
- Notifying PIs of updates to the RSI.

- Communicating changes associated with a change in the risk benefit ratio to sites via a substantial amendment.
- Preparing standard tables and other relevant information for the Developmental Safety Update Report (DSUR) in collaboration with the CI and ensuring timely submission to the MHRA, REC and relevant pharmaceutical companies. The DSUR will be prepared annually.
- Providing periodic safety reports to the DMEC
- Monitoring site's compliance with safety reporting procedures and timelines.

14.6.3 Chief Investigator (or delegated member of the TMG)

- Using medical judgement to assign causality of SAEs where it has not been possible to obtain local assessment
- To review all SAEs and SARs
- To review all events assessed as SUSARs
- Preparing the clinical sections, and final sign-off of the DSUR

14.6.4 Pharmaceutical companies

- Inform the CTRU/CI of any new information, which becomes available during the course of the study, which may affect the overall safety profile of the study drug.

14.6.5 Data Monitoring and Ethics Committee (DMEC)

- In accordance with the trial the DMEC charter, periodically reviewing safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.
- Reviewing results from interim analyses for early efficacy (one for each of the randomisations).

14.6.6 Trial Steering Committee (TSC)

- In accordance with the trial Terms of Reference for the TSC, provide advice on all appropriate aspects of the trial, including trial progress, adherence to the protocol, and participant safety and liaising with the DMEC regarding safety issues.

14.7 Safety Monitoring Plan

Refer to Appendix 10.

15 QUALITY OF LIFE AND HEALTH ECONOMICS

15.1 Quality of Life studies

Quality of life will be assessed in participants in the randomisation pathway, who are able to read and complete the quality of life questionnaires using validated instruments completed at appropriate and specified timepoints throughout the trial. The QLQ-CLL (latest version validated at the time of trial opening), a CLL specific module, EORTC QLQ-C30, and EQ-5D-5L will be used to assess quality of life during the trial. The EORTC QLQ-C30 is a multi-dimensional tool for participants with cancer that addresses aspects of participants' functioning and symptoms as well as their overall quality of life. The EORTC-QLQ-CLL aims to specifically address the health-related quality of life of CLL patients. EQ-5D-5L is a generic multidimensional to measure a patient's general health.

QoL and health economics questionnaires can be completed on paper CRFs or electronically, in line with the participants preference. These can be completed at clinic visits or if a clinic visit is not possible, the participant can complete this at home, at the time-points detailed in Section 13 and Appendix 4.

Participants completing paper questionnaires during clinic visits will be given an envelope to seal their questionnaires in before returning to their clinical team in order to preserve the confidentiality of their answers. The clinical team should post the paper questionnaires (within the sealed envelope) to the CTRU. If questionnaires have been posted to the participant for completion at home, an addressed envelope should be provided so that the questionnaires can be posted directly back to the STATIC team at the CTRU. The clinical team should not read, review or photocopy the questionnaires.

Participants will continue to be asked to complete questionnaires at all timepoints specified (Section 13 and Appendix 4) regardless of whether previous questionnaires have been completed, unless they express a wish to withdraw consent for this part of the study.

15.2 Health Economics

Data to enable the economic evaluation will come from responses to EQ-5D-5L, EORTC QLQ-C30 and health care resource use measures. We will supplement this with a Hospital Episode Statistics data request.

16 CRITERIA OF RESPONSE

Active disease and response to treatment will be assessed according to 2018 iwCLL criteria (Appendix 1).

The local clinician will provide an assessment of response in line with the response criteria as required by the schedule of investigations (see Appendix 4).

17 ENDPOINTS

17.1 Primary Endpoint

The primary endpoint will be evaluated in the Randomisation Pathway only.

- Time to Treatment Strategy Failure

17.2 Secondary Endpoints

All secondary endpoints will be evaluated for participants in the Randomisation Pathway, given the relevant consent. For the Clinical Need Cohort, only the following will be assessed: overall survival, toxicity and tolerability, time to next treatment and response to next treatment.

- Overall Survival
- Toxicity and Tolerability
- Cost Effectiveness of the Intermittent Treatment Strategy
- Quality of Life
- Summative treatment-free Interval
- Response to re-treatment in the intermittent arm
- Time to next treatment for CLL
- Response to next treatment for CLL
- Rate of Resistance Mutation between Trial-Arms
- Evolution of Resistant Sub-Clones

17.3 Exploratory Endpoints

All exploratory endpoints will be evaluated for participants in the Randomisation Pathway, given the relevant consent. For the Clinical Need Cohort, only the following will be assessed: Assessment of response to vaccines and on infectious complications.

- Analysis of the cause of ibrutinib resistance where BTK mutations are not found
- Identification of predictors for early progression of CLL after pausing ibrutinib
- Study of CLL clonal evolution in patients treated with ibrutinib
- Assessment of response to vaccines and on infectious complications

17.4 Derivation of Endpoints

17.4.1 Time to Treatment Strategy Failure

Time to treatment strategy failure is defined as the time from randomisation to time of treatment strategy failure. Treatment strategy failure is defined as the first documented instance of active disease that does not respond to treatment, or death from any cause. If a participant reaches active disease whilst on a break and they continue to meet this criteria whilst on subsequent ibrutinib treatment, then the time of the event is when they first met the criteria for active disease. Individuals who are lost to follow-up, withdraw from all follow-up or continuing with their treatment strategy at the time of analysis will be censored at the date of last assessment. Participants who transfer to an alternate BTK inhibitor without experiencing active disease will be censored at their last assessment pre-transfer.

17.4.2 Overall Survival

Overall survival is defined as the time from randomisation to the time of death from any cause. Individuals who are lost to follow-up or still alive at the time of analysis will be censored at their last known date to be alive.

For the Clinical Need Cohort, this will be time from registration to the time of death from any cause.

17.4.3 Toxicity and Tolerability

Toxicity and tolerability will be reported based on the adverse events, as graded by CTCAE V5.0 and determined by routine clinical assessments at each centre. SAEs will be reported according to MedDRA System Organ Class.

For the Clinical Need Cohort this endpoint will be defined as above.

17.4.4 The Cost Effectiveness of the Intermittent Treatment Strategy

Cost-effectiveness is defined as a cost per incremental QALY below £20,000 and/or a positive incremental net monetary benefit. The cost-effectiveness of treatment options will be evaluated with respect to this criteria. Details of all analyses will be detailed in a separate health economics analysis plan.

17.4.5 Quality of life

Quality of Life will be assessed using the patient-reported outcome measures: EORTC-QLQ-C30, EORTC-QLQ-CLL and EQ-5D-5L. This will be assessed at clinic visits or via questionnaires, completed at baseline and then at the time-points detailed in Section 13 and Appendix 4.

17.4.6 Summative treatment-free Interval

This is defined as the time to treatment strategy failure, excluding any time spent on treatment. This is equivalent to the total time spent on trial minus the total time spent on treatment. Alternatively the sum of all treatment-free intervals. For example, for a participant on the intermittent strategy, this is their time on trial minus any time spent on treatment due to hitting the restart criteria, whereas for a patient in the continuous strategy, this is the time spent off treatment (for example, due to toxicity breaks) whilst on trial. If a participant does not experience treatment failure or death during the trial they will be considered censored at the time of analysis.

17.4.7 Response to Re-Treatment in Intermittent Arm

Objective response rate is defined as a categorical outcome consisting of whether a participant had partial remission (PR), stable disease (SD) or progressive disease (PD) according to the response criteria defined by the standard 2018 iwCLL criteria (Appendix 1) between 9 and 12 months after restarting ibrutinib. To avoid mandating bone marrow biopsies, CR and CRi will not be an outcome, where they are reported due to local practice they will be included as PR.

17.4.8 Time to Next Treatment for CLL

Time to next treatment is defined as the time from randomisation to the start date of the next line of treatment. Participants who have died post cessation of ibrutinib but before taking up a new treatment

will be censored. Participants not known to have received another treatment for CLL at the time of the analysis will be censored at the last date they were known to be alive or dead without confirmed progression. Additionally if the participant switches to an alternative irreversible BTK inhibitor such as acalabrutinib or zanubrutinib, this will not be considered a new line of treatment, for this endpoint. These participants will be considered censored from the time of their switch.

For the Clinical Need Cohort, this will be time from registration to the start date of the next line of treatment.

17.4.9 Response to Next Treatment for CLL

It is hypothesised that patients who had less ibrutinib treatment before progression may have a better response to subsequent treatment, having been less exposed to long periods of prior treatment. Objective response rate is defined as a categorical outcome consisting of whether a participant had PR, SD or PD according to the response criteria defined by the standard 2018 iwCLL criteria (Appendix 1). The best response achieved by a participant at any timepoint will be used to assess the overall response. Again the outcomes CR and CRi will be not considered to avoid needing a bone marrow biopsy, if these are reported they will be summarised and included in any analysis as PR.

For the Clinical Need Cohort this endpoint will be defined similarly.

17.4.10 Resistance Mutation

The proportion of participants in each arm with a detectable BTK mutation (C481S and variant mutations or an alternative described resistance mutation such as the mutation of PLC-γ2) will be assessed at baseline, 24 months and 48 months for all randomised participants, and at 12, 36 months for those participants in whom a BTK mutation is detected.

17.4.11 Evolution of Resistant Sub-Clones

The proportion of BTK mutated CLL over time. This will be assessed at baseline and at the timepoints laid out in 13.8.2 by HMDS. If resistant subclones are present, biobank samples will be used to identify the onset of these subclones.

17.4.12 Analysis of the cause of ibrutinib resistance where BTK mutations are not found

A BTK mutation or alternative resistance mutation is not observed in a significant proportion of participants who develop acquired resistance to ibrutinib. At present the mechanism for such resistance is not clear and the samples taken in this trial will be used to study the mechanism of resistance in these cases.

17.4.13 Identification of predictors for early progression of CLL after pausing ibrutinib

It is likely that some participants on the intermittent treatment strategy will remain in remission off treatment for a prolonged even indefinite period of time whereas others will progress rapidly after pausing ibrutinib. The level of minimal residual disease is expected to strongly influence the time off treatment. It may also be expected to be influenced by other disease specific factors such as IGHV mutation status. There may also be additional factors that influence treatment interval. All of these will be studied in the trial from samples collected at baseline.

17.4.14 Study of CLL clonal evolution in patients treated with ibrutinib

It is well recognised that the CLL cells from patients can develop mutations of multiple genes some of which drive resistance and others merely demonstrate clonal evolution. Such clonal evolution within the CLL population is a key driver of resistance to therapies in general and the analysis of this would be expected to shed light on why some patients remain responsive to therapies such as ibrutinib whereas others don't. We intend to study this clonal evolution within the STATIC trial.

17.4.15 Assessment of response to vaccines and on infectious complications

The rates of infections, in particular of COVID-19 infections, will be assessed in the trial. This will be correlated by vaccination status (unvaccinated, 1 dose of a vaccine, 2 doses etc.). The number of participants who have received at least one dose of a vaccine will be summarised by vaccine.

The serological response to COVID-19 vaccinations will be assessed and the seroconversion rates will be compared between the two arms to assess whether a temporary cessation of ibrutinib improves vaccine response.

18 STATISTICAL CONSIDERATIONS

18.1 Sample Size

As the primary endpoint will be evaluated for the Randomisation Pathway the sample size and recruitment rate calculations are based on participants entering this pathway.

In relapsed/refractory patients, the median PFS on ibrutinib is almost 4 years [7]. In treatment naive patients, the median PFS is estimated to be approximately 10 years [6]. We expect to be able to recruit ~45% of participants from FLAIR and ~55% from relapsed/refractory patients. We assume that PFS will be strongly related to the primary endpoint: time to treatment strategy failure. Assuming exponential distributions leading to a hyperexponential distribution, these medians combine to produce an overall median PFS of 5.84 years. We use PFS here as a surrogate for time-to-treatment strategy failure.

With a one-sided alpha of 2.5%, 80% power and allowing for 5% dropout, to detect a non-inferiority hazard ratio (HR) upper bound of 1.33 would require 379 events (using the continuous treatment arm as the reference). Accounting for those participants who will be lost-to-follow-up 800 patients (approximately 140/year) are planned to be randomised over a 6 year period, with the required number of events expected at approximately 3 years after the close of recruitment.

The highest HR point estimate that would lead to a result of non-inferiority is 1.08, based on a 95% confidence interval of (0.89, 1.33). This corresponds to the intermittent treatment strategy having an 8% extra risk of relapsing, or equivalently a 2.7% decrease in 5-year PFS probabilities (55.2% to 52.5%), with a range of a 9.3% decrease to a 3.3% increase. This reduction in PFS agreed to be clinically acceptable with the National Cancer Research Institute (NCRI) CLL subgroup, because of expected reduction in toxicity, increase in QoL, and the substantial potential for health care resource savings. In addition, there are good salvage therapies on progression, such as venetoclax which is approved for patients failing ibrutinib in the NHS, so a small impact on PFS would not be likely to translate to a difference in overall survival (OS).

We believe it is very likely that the intermittent strategy will actually be superior to continuous treatment in terms of PFS, because the treatment breaks may well delay the time to emergence of drug resistance (18, 19) as well as reducing long-term toxicities (20). If the experimental strategy is actually 5% better, the power increases to 90%.

Considering the number of FLAIR participants taking ibrutinib who are reaching the end of the study, 30 patients are expected to enter the Clinical Need Cohort. This may result in a larger proportion of relapsed/refractory patients being required to reach the Randomisation pathway sample size. However, feasibility and sensitivity analysis has suggested that this remains achievable sample size target that may also shorten the duration of the trial.

18.2 Recruitment Rate

To reach the required 800 participants the trial will recruit for a total of 6 years. This requires on average approximately 12 participants per month to be recruited.

18.2.1 Recruitment Feasibility Milestone

To ensure the feasibility of recruitment to the trial, the trial has been designed with a recruitment feasibility milestone incorporated.

A red/ amber/ green decision criteria for continuation will be assessed between months 6 and 18. Recruitment is expected to increase gradually over a 12 month period to a steady-state rate. Our expected recruitment rate is 12 patients per month at the steady-state level, which corresponds to a rate of 0.12 patients/centre/month given that we anticipate running the trial in approximately 100 centres.

The red/ amber/ green decision criteria will be used based on 95% and 80% confidence intervals for this expected recruitment rate over months 6-18.

Applying this criteria:

- If 114 patients were recruited between months 6-18 (>0.107 patients/centre/month), the trial would be deemed to be feasible (green)
- Recruitment of 105-113 patients (0.100-0.107 patients/centre/month) would put us in the amber category
- Lower recruitment would demonstrate that recruitment was infeasible (red)

If recruitment was in the amber target we would explore the reasons for this and take actions, if deemed appropriate. This could include improvements to patient materials, amending eligibility criteria or opening additional centres. If recruitment was in the red category a rescue plan will be put in place following review by the trial independent DMEC and TSC.

19 STATISTICAL ANALYSIS

19.1 General considerations

Statistical analysis is the responsibility of the CTRU statisticians, with the exception of the analysis for cost-effectiveness, which will be undertaken by the Health Economists at the University of Leeds. A full statistical analysis plan will be written before any analysis is undertaken.

For analyses carried out by the CTRU, the analysis plan will be written in accordance with current the CTRU standard operating procedures and will be finalised and agreed by the following people: the trial statistician and supervising statistician, the Chief Investigator and the CTRU Scientific and Project Delivery Leads. Any changes to the finalised analysis plan, and reasons for changes, will be documented.

The analysis population used will depend on the pathway and is detailed below. The intention to treat (ITT) population will include participants according to their randomisation allocation, regardless of eligibility and whether they prematurely discontinued treatment or did not comply with the regimen. The per-protocol (PP) population will exclude individuals who did not uptake their trial treatment or strategy, as well as those who are found to be ineligible following randomisation or any other major protocol violations, as determined by the CI. The safety population will consist of all participants who receive at least one dose of the study treatment on study. The populations for each pathway will be fully defined within the statistical analysis plan (SAP).

19.2 Frequency of analysis

19.2.1 Interim analyses

An independent data monitoring and ethics committee (DMEC) will be assembled to monitor the data during the trial and will review annual safety data and strategy characteristics (e.g. time spent on treatment breaks) by stratification factor with the intention of detecting major difference in intermittent strategy efficacy. In this event, consideration will be given to the transfer of all high MRD level participants to the Clinical Need Cohort. A planned interim analysis, expected to take place upon half the number of required events occurring in the primary endpoint (190), will be presented to the DMEC. The content of these reports will be fully detailed within the statistical analysis plan (SAP).

The DMEC, in the light of the reports they review and of any advice or evidence they wish to request, will if necessary report to the Trial Steering Committee if there are concerns regarding the safety of the trial treatment.

19.2.2 Final analyses

The final analysis will take place upon the trial reaching its specified stopping point, 379 treatment failure events. This is estimated to be approximately 3 years after the close of recruitment.

19.3 Primary Endpoint Analysis

The primary endpoint will be assessed on both the PP and the ITT population in the Randomisation Pathway, as recommended (21). In order to reject the null hypothesis that the intermittent strategy is

inferior, we require demonstration of non-inferiority in both the PP and ITT populations. If the results of the analyses are discrepant this will be reported to highlight the inconclusiveness result.

19.3.1 Time to Treatment Strategy Failure

Cox regression analysis will be used to analyse the time to strategy failure accounting for stratification factors (excluding centre), and Kaplan-Meier curves will be presented. The proportional hazards assumptions will be assessed by plotting the hazards over time (i.e., the log cumulative hazard plot). Participants not known to have experienced treatment failure or death at the time of the analysis will be censored at the last date they were known to be alive and not suffering active disease. This comparison will be made against a 2.35% significance level, adjusted to maintain an overall one-sided 2.5% significance level with the included interim analysis of this endpoint. Comparisons will be made against a hazard ratio non-inferiority margin of 1.33, considering the continuous treatment strategy as the reference.

A formal interim analysis on the primary endpoint will be presented to the DMEC when half the number of events (190) have been reported across both treatment arms, with an O'Brien Fleming adjustment used to maintain the overall type I error rate. This is anticipated to be after 5 years of recruitment.

If the upper 95% CI for the observed interim HR is less than the lower bound of our NI margin CI, the trial will be stopped for futility and all participants who are having a treatment break will be able to go back onto therapy. If the lower limit of the 99.5% CI for the HR is higher than the upper bound of our NI margin CI, the trial will be able to report early evidence of non-inferiority. This confidence level corresponds to a significance level of 0.25% for a one-sided test. This value has been calculated using the alpha spending approach with the O'Brien Fleming approximation (22).

19.4 Secondary endpoint analysis

In the Clinical Need Cohort, analysis will only be performed for the overall survival, response to next treatment for CLL and time to next treatment, and the toxicity and tolerability endpoints. Clinical Need Cohort outcomes will not be compared with randomised pathway. Unless stated otherwise all secondary endpoints will use the ITT population in the Randomised Pathway. All analyses will be conducted with a 2.5% significance level unless stated otherwise.

19.4.1 Overall Survival

In the Randomisation Pathway, Cox regression analysis will be used to analyse overall survival accounting for the stratification factors (excluding centre), and Kaplan-Meier curves will be presented. Participants not known to have died at the time of the analysis will be censored at the last date they were known to be alive. The aim of this secondary endpoint will be to show the non-inferiority of the intermittent strategy in comparison to the continuous strategy. This will be assessed in both the ITT and PP populations and will need to show non-inferiority in both to conclude non-inferiority in this endpoint. This comparison is not powered.

There will be no formal comparison of OS in the Clinical Need Cohort with the OS survival in the randomisation pathway.

19.4.2 Toxicity and Tolerability

Safety analyses will summarise the AR, SAE, SAR and SUSAR rates per participant, by treatment arm, overall and also in the Clinical Need Cohort. Suspected relationship to the protocol treatment will be presented along with other causality, outcome and event duration. ARs will be presented by CTCAE toxicity grade (V5). Individual AR/SAE line listings will be reported by treatment arm and MedDRA System Organ class (where applicable). Treatment related mortality rates will be presented by treatment received. This analysis will be over the safety population.

19.4.3 The Cost Effectiveness of the Intermittent Treatment Strategy

An economic evaluation of continuous versus intermittent treatment will be conducted following the NICE reference case with the primary outcome being incremental cost per quality-adjusted life year (QALY) gained. The perspective will be that of the health care and personal social service provider. Utility values will be generated during the trial using the EQ-5D-5L (23) and EORTC-8D (24). Currently, NICE advise the use of a published (EQ-5D-5L to EQ-5D-3L) mapping algorithm to generate the utility index from the EQ-5D-5L (25, 26). However, a new valuation study is on-going (27) and we will use the new UK valuation tariff when this is available, providing the results are valid and robust. QALYs will be generated using and area under the curve approach between adjacent EQ-5D-5L completions (or death). These will be based on the EORTC-8D in a supplementary analysis.

Costs will be based on patient-completed resource use questionnaires (for primary, community and social care) and NHS digital data (for secondary care). The questionnaires will be completed at baseline and every subsequent follow-up. Therapy use will be captured in the CRFs. Unit costs will be taken from resources such as NHS reference costs, Personal Social Services Research Unit (PSSRU) report, electronic market information tool (eMIT) and British National Formulary (BNF). We will use the prevailing drug list prices at the time of analysis.

In the trial analysis, regression models will be used to adjust for baseline imbalance and account for cost-QALY correlations. Where appropriate, we will mirror the statistical team approach to incorporating control variables and adjust for the specified stratification factors (excluding centre). We will assess the type and degree of missing data and evaluate whether the assumption of missing at random (MAR) holds (28). If that is the case, multiple imputation will be used to impute missing data. Should MAR not hold we will explore the impact of alternative assumptions (29). We will report incremental cost-effectiveness ratios (ICERs) (30) at trial end however the primary end-point will be based on lifetime expected costs and outcomes generated from a decision analytic model.

A decision-analytic model being developed in FLAIR will allow the extrapolation of costs and consequences of the treatment strategies over a lifetime horizon. The FLAIR decision model is a Markov model with health states based around CLL response criteria. The final model will be agreed with patient and clinician collaboration. Parameter values will be derived from the proposed trial and other relevant datasets (such as FLAIR and ARCTIC (ISRCTN16544962)) and reviews of the literature. Survival will be extrapolated using parametric survival curves selected using guidance from the NICE Decision Support Unit (31). Incremental cost effectiveness ratios (ICERs) will be generated over a lifetime horizon in reference to the £20,000-£30,000 per QALY willingness to pay threshold. We will conduct extensive deterministic sensitivity analyses and capture total parameter uncertainty using a

probabilistic sensitivity analyses. Results will be represented as cost-effectiveness acceptability curves (32) and net monetary benefit distributions.

As part of the interim analysis, we will use the decision model to explore the cost-effectiveness of treatment breaks and generate value of information estimates to inform study continuation decisions (33). Costs and benefits post 12 months will be discounted at a rate of 3.5% per annum as per NICE guidance. NICE is currently updating the guidance for technology appraisals and we will review the planned methods stated here taking into consideration the updated guidance when published.

A full health economics analysis plan (HEAP) will be written before any analysis is undertaken.

19.4.4 Quality of life (EQ-5D-5L, QLQ-C30, QLQ-CLL)

Mean Quality of Life (QoL) scores and 95% CIs adjusted for the baseline score will be calculated for all domains of the EORTC QLQ-C30 and CLL specific module, EORTC QLQ-CLL, for each treatment group at each assessment time-point and overall. Additionally, a mixed-model based analysis will be carried out accounting for the baseline QoL, stratification factors, time, patient, and treatment strategy. The aim of this analysis is to show the superiority of the intermittent treatment strategy, in line with the hypothesis of reduced side effects and increased QoL.

19.4.5 Summative Treatment-free Interval

This is defined as the time to treatment strategy failure, excluding any time spent on treatment. This is equivalent to the total time spent on trial minus the total time spent on treatment. Alternatively the sum of all treatment-free intervals. In addition, the median summative time on treatment annually post randomisation will be estimated using the Kaplan-Meier method. By design this endpoint should confirm compliance with the intermittent strategy by showing superiority in the intermittent strategy when compared to the continuous strategy with respect to more time spent off treatment.

19.4.6 Response to Re-Treatment in Intermittent Arm

The responses of PR, SD and PD will be summarised for the first, second, third etc. treatment breaks with an exact 95% CI.

19.4.7 Time to next treatment for CLL

Time from randomisation to next treatment after the cessation of trial treatment will be analysed using Cox regression analysis accounting for the stratification factors (excluding centre), and Kaplan-Meier curves will be presented. This analysis will seek to show the superiority of the intermittent strategy in this endpoint.

This endpoint, measuring time from registration, will also be summarised with Cox's regression and a Kaplan-Meier curves for the participants in the Clinical Need Cohort, stratified by MRD level, available from FLAIR.

19.4.8 Response to next treatment for CLL

Response to next for CLL will be compared between the arms for those participants receiving further treatment using a logistic regression model assessing achievement of partial or complete (PR or CR+CRi), adjusted for the stratification factors (excluding centre). To avoid mandating bone marrows,

only an assessment for PR is required, but if bone marrows are performed, these will be summarised as PR. The proportion of participants with each class of response will be summarised by treatment arm. This is evaluated with the goal of showing the superiority of intermittent strategy.

This endpoint will also be summarised only for the participants in the Clinical Need Cohort, accounting for MRD level.

19.4.9 Rate of Resistance Mutation between Trial Arms

The presence of BTK mutations (and other mutations, such as PLC-γ2 mutations) will be analysed at screening, 2 years, 4 years and when a participant progresses. The proportion of participants with such resistance mutations will be reported at screening (without a description of which arm the participant is randomised to) with a 95% confidence interval. In addition the rate of resistance mutation observed will be compared between the two randomised arms at 2 and 4 years post-randomisation. This comparison will be made using a 95% confidence interval for the difference in rates.

The proportion of participants with resistance mutations, with 95% confidence intervals, will be provided to the independent DMEC at these time-points. If there is a significant difference assessed by a 95% confidence interval, they will consider whether this should lead to the early reporting of the endpoint.

19.4.10 Evolution of Resistant Sub-Clones

In participants where a BTK mutation (or alternative resistance mutation) is observed the proportion of the CLL cells with the mutation will be studied and compared between the two treatment strategies. Annual samples will be studied to follow the variant allele frequency (VAF) of the mutant cells over time and by treatment strategy. This will be reported with 95% confidence intervals.

The effect of the treatment strategies will be assessed with a 95% confidence interval for the difference between the two groups. It might be expected that the VAF will increase in the continuous treatment arm but remain stable or even decrease in the intermittent treatment strategy. If a significant difference is detected then the DMEC will consider the early reporting of this endpoint.

19.5 Exploratory endpoint analysis

The methods for analysis of exploratory endpoints will be detailed within a separate SAP.

19.6 Subgroup Analysis

Exploratory subgroup analyses will be conducted to assess the heterogeneity of the treatment effect among the subgroups of interest for the primary endpoint and the secondary endpoint: overall survival. These analyses will be dependent on the number of participants seen with each event of interest. A primary subgroup analysis will be IGVH mutation status and VH risk. The specific subgroups will be detailed in the SAP, but will include the stratification factors (excluding centre).

Subgroup analyses may, by chance, generate false positive or negative results. Those carried out will be interpreted with caution and treated as hypothesis generating.

20 TRIAL MONITORING

20.1 Trial monitoring

A Trial Monitoring Plan will be developed and agreed by the TMG based on the trial risk assessment. There will be a degree of site monitoring and a risk-based monitoring approach will be used to determine when and where site visits should be carried out in order to direct monitoring resources most effectively.

20.2 Data monitoring

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. With the exception of questionnaires, missing data items will not be chased from participants; for participants who have opted to complete paper questionnaires missing questionnaires may be chased from sites, whilst participants who are completing ePROMS maybe contacted directly by the CTRU via email to request their completion. The CTRU/Sponsor will reserve the right to intermittently conduct source data verification exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification may involve direct access to participant notes at the participating hospital sites and the collection of copies of consent forms and other relevant investigation reports. Remote monitoring methods (including virtual/telephone review of source data) may also be used to verify source data and will be approved by the CTRU.

20.3 Data monitoring and ethics committee

An independent DMEC will review the safety and ethics of the study. The DMEC will review cumulative safety data by arm on an ongoing basis along with individual SAE/SAR listings. Detailed reports will be prepared by the CTRU for the DMEC meetings which will take place at approximately yearly intervals. The committee will also review the formal interim analyses detailed in Section 19.2.

Any interim reports provided to the DMEC will be provided by the CTRU Statistician and will be transferred securely as they contain research-sensitive data.

20.4 Clinical governance issues

To ensure responsibility and accountability for the overall quality of care received by participants during the study period, clinical governance issues pertaining to all aspects of routine management will be brought to the attention of the DMEC, TSC, Sponsor and, where applicable, to individual NHS Trusts.

21 QUALITY ASSURANCE & ETHICAL CONSIDERATIONS

21.1 Serious breaches of GCP or trial protocol

The CTRU and Sponsor have systems in place to ensure that serious breaches of GCP or the trial protocol are picked up and reported. Investigators are required to promptly notify the CTRU of any potential serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) that they become aware of. A "serious breach" is a breach which is likely to effect to a significant degree –

(a) The safety or physical or mental integrity of the participants of the trial; or

(b) The scientific value of the trial

In the event of doubt or for further information, sites should contact the CTRU trial and data management team.

21.2 Data Protection and patient confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the Data Protection Act 2018 and operationally this will include:

- Consent from participants to record personal details including name, date of birth, email, NHS number/ CHI number;
- Appropriate storage, restricted access and disposal arrangements for participant personal and clinical details;
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation;
- Consent from participants for the data collected for the trial to be used to evaluate safety and develop new research;
- Participant name will be collected on the trial Informed Consent Document at the time of trial entry, but all other data collection forms that are transferred to or from the CTRU will be coded with a trial number and will include two participant identifiers, usually the participant's initials and date of birth;
- Where central monitoring of source documents by the CTRU (or copies of source documents) is required (such as scans or local blood results), the participant's name must be obliterated by site before sending and labelled with only trial number, participant's initials and date of birth;
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to the CTRU.
- Participant name will be included on samples being sent to the central laboratories at Leeds HMDS to ensure correct identification and for feeding results back to the treating clinician at site at key timepoints. These samples will also include initials, date of birth, sex, and trial number. Samples sent to UK CLL Biobank and will not require participant name but will include NHS number/CHI number, trial number, sex, initials and date of birth to ensure robust tracking and identification processes.

If a participant withdraws consent for further trial treatment and / or further collection of data, their data and samples will remain on file and will be included in the final study analysis.

21.3 Indemnity

This trial is sponsored by The University of Leeds. The University of Leeds is able to provide insurance to cover for liabilities and prospective liabilities arising from negligent harm. Clinical negligence indemnification will rest with the participating NHS Trust or Trusts under standard NHS arrangements.

21.4 Quality assurance

The trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research, and through adherence to the CTRU Standard Operating Procedures (SOPs).

21.5 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 Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996. Informed written consent will be obtained from the participants prior to registration into the trial. The right of a participant to refuse participation without giving reasons must be respected. The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment. The trial will be submitted to and approved by a Research Ethics Committee (REC), Health Research Authority and the appropriate local R&D department for each participating centre prior to entering participants into the trial. The CTRU will provide the REC with a copy of the final protocol, participant information sheets, Informed Consent Document and all other relevant trial documentation.

21.6 Archiving

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 25 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at the participating centres. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made. If a participant withdraws consent for their data to be used, it will be confidentially destroyed.

22 STUDY ORGANISATIONAL STRUCTURE

22.1 Individuals and individual organisations

Chief Investigator (CI) - The Chief Investigator is involved in the design, conduct, coordination and management of the trial. The CI will have overall responsibility for the design and set-up of the trial, the investigational medicinal product supply and pharmacovigilance within the trial.

Trial Sponsor – The Sponsor is responsible for the overall conduct of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU), University of Leeds - The CTRU will have responsibility for initiation and management of the trial as delegated by the Sponsor in accordance with relevant GCP standards and CTRU SOPs. The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2006 including: randomisation design and service, database development and provision, protocol development, eCRF/CRF design, trial design, source data verification, monitoring schedule and statistical analysis for the trial. In addition the CTRU will support REC, HRA and MHRA submissions and clinical set-up, support centres in assessment of capacity and capability, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

Janssen

Janssen will have responsibility for the supply of investigational medicinal product ibrutinib for patients receiving ibrutinib front-line who have previously participated in the FLAIR trial and enter the randomisation trial of STATIC (estimated to be approximately 45% of the ibrutinib supply).

The other approximately 55% of supply of ibrutinib for the randomisation trial will be from NHS 'off the shelf' stock and will be for previously treated CLL participants receiving ibrutinib as standard of care through routine commissioning.

Janssen will also provide the supply of ibrutinib for the anticipated 30 front–line patients who have previously participated in the FLAIR trial and who enter the Clinical Need Cohort.

Laboratories: Leeds HMDS and UK CLL Biobank

The central laboratories are responsible for processing samples in accordance with the participant's consent to provide data relating to trial endpoints. The laboratories are also responsible for handling and storing participant samples and data in accordance with relevant regulations and participant consent.

22.2 Oversight / Trial monitoring groups

Trial Management Group - The TMG, comprising the Chief Investigator, CTRU team and co-investigators will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation of results. Specifically the TMG will be responsible for (i) protocol

completion, (ii) eCRF/CRF development, (iii) obtaining approval from the REC and Health Research Authority (iv) submitting a CTA application and obtaining approval from the MHRA, (v) completing cost estimates and project initiation, (vi) appointing and facilitating the TSC and DMEC, (vii) reporting of serious adverse events to relevant parties, (viii) monitoring of screening, recruitment, treatment and follow-up procedures, (ix) auditing consent procedures, data collection, trial end-point validation and database development.

Data Monitoring and Ethics Committee (DMEC) - The DMEC will include independent membership and will review the safety and ethics of the trial by reviewing interim data throughout the trial. The Committee will meet or communicate via teleconference approximately annually. After each annual review, the DMEC will make their recommendations to the TSC about the continuation of the trial.

Trial Steering Committee - The Trial Steering Committee will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an Independent Chair, not less than two other independent members, and at least one patient representative. The Chief Investigator, Co-Chief Investigator and other members of the TMG will attend the TSC meetings and present and report progress. The Sponsor will also be invited to attend. The committee will meet annually as a minimum.

22.3 Patient and Public Involvement (PPI)

A patient representative was involved in the grant applications, trial design and protocol development. A CLL patient advisory group have reviewed and provided input to the protocol, PIS and recruitment documents. There will also be at least one PPI representative on the TSC and TMG.

22.4 Funding

Funding for this study has been provided by the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) Programme and Janssen.

N.B The exploratory endpoints and Clinical Need Cohort are funded by Janssen.

23 PUBLICATION POLICY

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior to the start of recruitment.

The success of the trial depends upon the collaboration of all contributors. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- *conception and design, or acquisition of data, or analysis and interpretation of data;*
- *drafting the article or revising it critically for important intellectual content;*
- *final approval of the version to be published;*
- *that all these conditions must be met (www.icmje.org).*

In light of this, the Chief Investigator, and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

Publications will be sent to Janssen for courtesy review only ahead of submission with full independence and autonomy retained by the investigators and trial management group.

To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial or a primary endpoint being reached, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee and the Chief Investigator. In addition, individual collaborators must not publish data concerning their participants that is directly relevant to the questions posed in the trial until the main results of the trial have been published and following written consent from the Sponsor.

A summary of the study results and trial updates will also be shared with participants via the trial sites, patient forums, seminars and digital platforms , once the results have been published.

24 APPENDICES

APPENDIX 1: 2018 iwCLL Response Criteria for CLL

Active Disease

Active disease is characterised by at least one of the following:

- Evidence of progressive marrow failure as manifested by the development of, or worsening of, anaemia and/or thrombocytopenia. Cutoff levels of Hb <10 g/dL or platelet counts <100 × 10^9/L are generally regarded as indication for treatment. However, in some patients, platelet counts <100 × 10^9/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
- Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
- Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts obtained at intervals of 2 weeks over an observation period of 2 to 3 months; patients with initial blood lymphocyte counts <30 × 10^9/L may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (eg, infections, steroid administration) should be excluded.
- Autoimmune complications including anaemia or thrombocytopenia poorly responsive to corticosteroids.
- Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
    - Unintentional weight loss ≥10% within the previous 6 months.
    - Significant fatigue (ie, ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
    - Fevers ≥100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
    - Night sweats for ≥1 month without evidence of infection.

Definition of response, relapse, and refractory disease

Assessment of response should include a careful physical examination and evaluation of the blood and bone marrow (Tables 3 and 4). The timing of response assessment for therapies with a defined treatment duration (such as chemoimmunotherapeutic approaches) should be at least 2 months after completion of therapy. To define the response to therapy, 2 groups of parameters need to be assessed and documented: parameters of group A assess the lymphoid tumour load and constitutional symptoms; parameters of group B assess the hematopoietic system (Table 4).

Table 4.

Response definition after treatment of CLL patients

Group	Parameter	CR	PR	PD	SD
A	Lymph nodes	None ≥1.5 cm	Decrease ≥50% (from baseline)*	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% (from baseline)	Increase ≥50% from baseline or from response	Change of −49% to +49%
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	Normal	Decrease ≥50% from baseline	Increase ≥50% over baseline	Change of −49% to +49%
B	Platelet count	≥100 × 10^9/L	≥100 × 10^9/L or increase ≥50% over baseline	Decrease of ≥50% from baseline secondary to CLL	Change of −49 to +49%
	Haemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11 g/dL or increase ≥50% over baseline	Decrease of ≥2 g/dL from baseline secondary to CLL	Increase <11.0 g/dL or <50% over baseline, or decrease <2 g/dL
	Marrow	Normocellular, no CLL cells, no B-lymphoid nodules	Presence of CLL cells, or of B-lymphoid nodules, or not done	Increase of CLL cells by ≥50% on successive biopsies	No change in marrow infiltrate

For a detailed description of the response parameters, see section 5.

*****Sum of the products of 6 or fewer lymph nodes (as evaluated by CT scans and physical examination in clinical trials or by physical examination in general practice).

†Spleen size is considered normal if <13 cm. There is not firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation in clinical trials and be recorded according to the definition used in a study protocol.CR, complete remission (all of the criteria have to be met); PD, progressive disease (at least 1 of the criteria of group A or group B has to be met); PR, partial remission (for a PR, at least 2 of the parameters of group A *and* 1 parameter of group B need to improve if previously abnormal; if only 1 parameter of both groups A and B is abnormal before therapy, only 1 needs to improve); SD, stable disease (all of the criteria have to be met; constitutional symptoms alone do not define PD).

For continued therapies or treatment strategies that contain a maintenance phase, the assessment of response should be performed at least 2 months after patients achieve their maximum response or at a time point that is predefined in the protocol; in this case, it is not necessary to interrupt therapy for response assessment. Maximum response can be defined as a treatment phase in which no additional improvement is seen during at least 2 months of therapy. In clinical trials, any response (eg, CR, partial remission) should be sustained for at least 2 months before using this response in the assessment. In

addition, where appropriate, a further assessment of response (ie, marrow assessment) may be performed at least 2 months after the patient has cleared MRD from the peripheral blood.

5.1. Complete remission

CR requires all of the following criteria (Table 4).

5.1.1. Peripheral blood lymphocytes (evaluated by blood and differential count) $<4 \times 10^9$/L.

5.1.2. Absence of significant lymphadenopathy by physical examination. In clinical trials, a CT scan of the neck, abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should be <1.5 cm in longest diameter. Once this is determined, further imaging should not be required until disease progression is apparent by clinical examination or on blood testing.

5.1.3. No splenomegaly or hepatomegaly by physical examination. In clinical trials, a CT scan of the abdomen should be performed at response assessment and should show no evidence for lymphadenopathy and splenomegaly. We propose to use a recent consensus response cut-off for splenomegaly of 13 cm in craniocaudal length.[96,97] However, the persistence of splenomegaly may not correlate with outcome.[96] The quantitative determination of hepatomegaly seems more difficult; changes such as focal or disseminated hepatic nodules support liver involvement.

5.1.4. Absence of disease-related constitutional symptoms.

5.1.5. Blood counts need to show the following values:

5.1.5.1. Neutrophils $\geq 1.5 \times 10^9$/L.

5.1.5.2. Platelets $\geq 100 \times 10^9$/L.

5.1.5.3. Haemoglobin ≥11.0 g/dL (without red blood cell transfusions).

5.1.6. MRD assessment.

In clinical trials aimed at maximizing the depth of remission, the presence of MRD after therapy should be assessed (see section 5.9). The sensitivity of the method used to evaluate for MRD should be reported, as should the tissue studied (blood or marrow). The proportion of patients achieving undetectable MRD should be reported with the total number of patients treated with the specific therapy as the denominator (not as a proportion of responders or those in CR).

5.1.7. For patients in clinical trials (Table 3). A bone marrow aspirate and biopsy should be performed if clinical and laboratory results listed in sections 5.1.1 to 5.1.5 demonstrate that a CR may have been achieved. To define a CR, the cytological or pathological evaluation of the bone marrow smear or biopsy must be at least normocellular for age, without evidence for typical CLL lymphocytes by morphological criteria. This evaluation is not based on a flow cytometry–based MRD assessment (see section 9).

In a clinical trial, the time point of marrow biopsy should be defined by the protocol. For example, in patients receiving chemo(immuno)therapy, the time point of marrow biopsy is typically 2 months posttherapy.

When performing marrow biopsies in clinical trials, lymphoid nodules can be found that may reflect residual disease.[98,99] These nodules may be recorded as "nodular partial remission." Immunohistochemistry may be performed to define whether the nodules comprise primarily T cells, B cells other than CLL cells, or CLL cells. If nodules are not composed of CLL cells, a CR can be documented provided all other criteria are met. If the marrow is hypocellular, a repeat determination should be performed 4 weeks or later, when peripheral blood counts have recovered; however, this interval should not exceed 6 months after the last treatment. In cases in which a marrow biopsy was obtained at baseline, a comparison of pre- vs posttherapy biopsies should be performed. In general practice, the use of a marrow biopsy for evaluating a CR is at the discretion of the physician.
In clinical trials aimed at maximizing the response rate, the quality of the response should be assessed in the marrow for MRD by highly sensitive molecular-based assays or immunophenotyping (see section 5.9).

5.1.8. Some patients fulfil all the criteria for a CR (including the marrow examinations described in section 5.1.7), but have a persistent anaemia, thrombocytopenia, or neutropenia apparently unrelated to CLL, but related to drug toxicity. These patients should be considered as a different category of remission, CR with incomplete marrow recovery (CRi). For the definition of this category, the marrow evaluation (see section 5.1.7) should be performed with scrutiny and not show any clonal disease infiltrate. In clinical trials, patients having CR with incomplete marrow recovery should be monitored prospectively to determine whether their outcome differs from that of patients with detectable residual disease or with noncytopenic CR.

5.2. Partial remission

To define a partial remission, at least 2 parameters of group A *and* 1 parameter of group B need to improve, if previously abnormal (Table 4; sections 5.2.1 to 5.2.5). If only 1 parameter of both groups A and B was abnormal before therapy, only 1 needs to improve. Constitutional symptoms persisting for >1 month should be recorded.

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

5.2.2. Reduction in lymphadenopathy compared with baseline (by cross-sectional imaging scans in clinical trials or by palpation in general practice) as defined by:

5.2.2.1. A decrease in lymph node size by 50% or more in

- the sum of the products of the same enlarged lymph nodes selected at baseline as assessed by imaging (an established number in clinical trials of lymph nodes has been up to 6).
- and the sum of longest diameters of the same enlarged lymph nodes selected at baseline as assessed by physical examination (an established number in clinical trials of lymph nodes has been a maximum of 6).

5.2.2.2. No increase in any lymph node and no new enlarged lymph node (diameter ≥1.5 cm). For small lymph nodes (longest diameter <1.5 cm), an increase <25% is not considered significant.

5.2.3. A regression ≥50% of the extent of enlargement of the spleen below the costal margin defined by palpation, or normalization in size. When assessed by CT, scan spleen size must have regressed by ≥50% in length beyond normal.96 A persistence of splenomegaly posttherapy may have limited influence on outcome in CLL.96

5.2.4. A regression of ≥50% of the extent of enlargement of the liver below the costal margin defined by palpation, or normalization in size. Given the impact of numerous medical conditions, liver size by physical examination or CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.

5.2.5. The blood count should show 1 of the following results:

5.2.5.1. Platelet counts >100 × 10^9/L or 50% improvement over baseline.

5.2.5.2. Hb >11.0 g/dL or 50% improvement over baseline without red blood cell transfusions or erythropoietin support.

5.3. Progressive disease

Progressive disease (PD) during or after therapy is characterized by at least 1 of the following, when compared with nadir values (Table 4):

5.3.1. Lymphadenopathy. Progression of lymphadenopathy is often discovered by physical examination and should be recorded at regular intervals. In CLL, the use of imaging (CT scans) usually does not add much information for the detection of progression or relapse.100 Disease progression occurs if 1 of the following events is observed.

- Appearance of any new lesion such as enlarged lymph nodes (≥1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. Transient increases of lymph node size during treatment with novel inhibitors may occur and should not be counted as PD.
- An increase by ≥50% in greatest determined diameter of any previous site (≥1.5 cm).

5.3.2. An increase in the spleen size by ≥50% or the de novo appearance of splenomegaly. In the setting of splenomegaly, the splenic length must increase by ≥50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to ≥16 cm). If no prior splenomegaly was observed at baseline or if splenomegaly has resolved with treatment, the spleen must increase by at least 2 cm from baseline.96

5.3.3. An increase in the liver size of ≥50% of the extent enlargement of the liver below the costal margin defined by palpation, or the de novo appearance of hepatomegaly. Given the impact of numerous medical conditions, liver size by physical examination or by CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.

5.3.4. An increase in the number of blood lymphocytes by 50% or more with at least 5 × 10^9/L B lymphocytes. Certain therapies (eg, kinase inhibitors) may cause lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count by itself does not uniformly indicate an increased tumour burden, but may reflect redistribution of leukaemia cells from lymphoid tissues to the blood. This should be predefined in the protocol of clinical trials for therapies in which redistribution of disease occurs. In such cases, increased lymphocytosis alone is not a sign of treatment failure or PD.101

5.3.5. Transformation to a more aggressive histology (Richter syndrome or Richter transformation). The diagnosis of Richter transformation should be established by lymph node or other tissue biopsy.
5.3.6. Occurrence of cytopenia (neutropenia, anaemia, or thrombocytopenia) directly attributable to CLL and unrelated to autoimmune cytopenias.

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

Table 5.
Grading scale for haematological toxicity in CLL studies

Grade*	Decrease in platelets† or Hb‡ (nadir) from baseline value, %	Absolute neutrophil count (nadir)§ × 10^9/L
0	No change to 10	≥2
1	11-24	≥1 and <2
2	25-49	≥1 and <1
3	50-74	≥0.5 and <1
4	≥75	<0.5

*Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from baseline will be recorded as grade 5.
†Platelet counts must be below normal levels for grades 1-4. If, at any level of decrease the platelet count is <20 × 10^9/L, this will be considered grade 4 toxicity unless a severe or life-threatening decrease in the initial platelet count (eg, 20 × 10^9/L) was present at baseline, in which case the patient is not evaluable for toxicity referable to platelet counts.
‡Hb levels must be below normal levels for grades 1-4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
§If the absolute neutrophil count (ANC) reaches <1 × 10^9/L, it should be judged to be grade 3 toxicity. Other decreases in the white blood cell count or in circulating granulocytes are not to be considered because a decrease in the white blood cell count is a desired therapeutic end point. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was <1 × 10^9/L before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of G-CSF is irrelevant for the grading of toxicity, but should be documented.

5.3.6.2. Posttreatment. The progression of any cytopenia (unrelated to autoimmune cytopenia), as documented by a decrease of Hb levels ≥2 g/dL or <10 g/dL, or by a decrease of platelet counts ≥50% or <100 × 10^9/L, which occurs at least 3 months after treatment, defines disease progression, if the marrow biopsy is consistent with the cytopenia resulting from increased marrow infiltration of clonal CLL cells and is not considered a treatment related toxicity.

5.4. Stable disease

Patients who have not achieved a CR or a partial remission, and who have not exhibited PD, will be considered to have stable disease (which is equivalent to a nonresponse).

5.5. Treatment failure

Responses that should be considered clinically beneficial include CR and PR; all others (eg, stable disease, nonresponse, PD, death from any cause) should be rated as a treatment failure.

5.6. Time to next treatment, progression-free survival, event-free survival, and overall survival

Progression-free survival is defined as the interval between the first treatment day (in phase 3 trials: day of randomization for intent-to-treat analysis) to the first sign of disease progression or death from any cause. Event-free survival is defined as the interval between the first treatment day (in phase 3 trials: day of randomization for intent-to-treat analysis) to the first sign of disease progression or start of a new treatment or death (whichever occurs first). Overall survival is defined as the interval between the first treatment day (in phase 3 trials: day of randomization for intent-to-treat analysis) to death. Time to next treatment is defined as interval between the first treatment day until the patient starts an alternative therapy for progressive CLL.

Note that the response duration may be assessed during therapy for continuous treatment, in particular with oral agents, as well as after the end of treatment, in particular with chemo(immuno) therapy. Study protocols should provide detailed specifications of the planned time points for the assessment of the treatment response under continuous therapy. Response durations <6 months are not considered clinically relevant (see refractory disease, section 5.8).

5.7. Relapse

Relapse is defined as evidence of disease progression (see section 5.3) in a patient who has previously achieved the above criteria of a CR or partial remission (sections 5.1-5.2) for ≥6 months.

5.8. Refractory disease

Refractory disease is defined as treatment failure (as defined in section 5.5) or as progression within 6 months from the last dose of therapy.

5.9. Minimal residual disease

The complete eradication of the leukaemia is a desired end point. Use of sensitive multicolour flow cytometry, PCR, or next-generation sequencing can detect MRD in many patients who achieved a complete clinical response. Prospective clinical trials have provided substantial evidence that therapies that are able to eradicate MRD usually result in an improved clinical outcome.97,102-106 The techniques for assessing MRD have undergone a critical evaluation and have become well standardized.107,108 Six-colour flow cytometry (MRD flow), allele-specific oligonucleotide PCR, or high-throughput sequencing using the ClonoSEQ assay are reliably sensitive down to a level of <1 CLL cell in 10 000 leukocytes.108 Refinement and harmonization of these technologies has established that a typical flow cytometry–based assay comprises a core panel of 6 markers (ie, CD19, CD20, CD5, CD43, CD79b, and CD81).108 As such, patients will be defined as having undetectable MRD (MRD-neg) remission if they have blood or marrow with <1 CLL cell per 10 000 leukocytes. The blood generally can be used for making this assessment because the marrow will have detectable CLL when it is also found in the peripheral blood. However, there are therapies that preferentially clear the blood but not the

marrow (such as monoclonal antibodies); therefore, it may be important to confirm that the marrow aspirate also is MRD-neg when the blood is found to be MRD-neg. Clinical trials aimed at maximizing the depth of remissions should include at least 1 test to assess for MRD, because the lack of leukaemia persistence using these sensitive tests has a strong, positive prognostic impact. The report should be clear as to whether blood and/or marrow have been assessed and should report the proportion of MRD-neg patients on an intent-to-treat basis using the total number of patients in that treatment arm as the denominator (not those assessed or those who responded to treatment).

Hallek et al, iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL, Blood, *131:25: 2745–2760* (34)

APPENDIX 2: ECOG Status

Table 1: ECOG Performance Status

Grade	ECOG
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.
5	Dead

Oken et al, American Journal of Clinical Oncology; 1982: 5: 649-55 (35)

APPENDIX 3: Common Terminology Criteria For Adverse Events (CTCAE)

Events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V5.0 (NCI-CTCAE). A copy is provided in the Investigator Site File and may be obtained at:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Published: November 27, 2017

APPENDIX 4: Schedule of Investigations

(eligibility assessments will also provide baseline)	**Pre-Registration** (within 4wks prior to randomisation/or registration for the Clinical Need Cohort unless stated otherwise) For all participants	**Post registration/ Baseline** For randomisation arms only (within 4wks of randomisation unless stated otherwise)	**3 monthly visit**		**At Restart Criteria (intermittent treatment strategy only)**	**At Treatment Failure**	**Post Active Disease follow up 3 years Annually**	**6 years after the end of the trial** Only for participants who have consented
			Randomisation arms	Clinical Need Cohort				
Trial Written Informed Consent	✓ Consent to be taken prior to all assessments							
Biobank Written informed Consent (Randomisation trial only)		✓ Consent to be taken prior to all assessments (for Randomisation participants only)						
Local investigations								
Pregnancy test (serum or urine HCG) [3]	✓ Within 2 wks prior to randomisation/or registration for the Clinical Need Cohort	✓ Within 2 wks prior to randomisation					The CTRU will collect survival data from routine NHS data	
Demographic data	✓							
Complete Medical History	✓ Within 4 wks prior to randomisation/or within 2 weeks prior to registration for the Clinical Need Cohort	✓	✓					
Ongoing medical conditions	Monitor throughout study and report on relevant treatment eCRFs							
Review of Concomitant medication		Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)						
Review of adverse events		Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)						
Review of treatment compliance			✓	✓				
Clinical assessment of disease	✓ Within 2 wks prior to randomisation/or	✓ Within 14 days prior to randomisation	✓	✓		✓		

	registration for the Clinical Need Cohort							
FBC	✓ Within 2 wks prior to randomisation/or registration for the Clinical Need Cohort ✓ ALC within 4wks prior to randomisation/or registration for the Clinical Need Cohort	✓** Within 2 weeks prior to randomisation ✓ ALC within 4wks prior to randomisation	✓	✓		✓		
LFTs	✓	✓	✓	✓				
U&Es	✓	✓**	✓	✓				
Calculated Creatinine Clearance[6]	✓ Within 2 wks prior to randomisation	✓ Within 2 wks prior to randomisation	✓	✓				
WHO performance status	✓	✓		✓				
Cardiac assessments[7]	✓[1] No time frame given	✓[1] No time frame given						
Physical examination and Vitals	✓	✓ Within 14 days prior to randomisation	✓	✓				
Blood pressure		✓** No time frame given	✓	✓				
CLL-related B symptoms	✓ Within 2 wks prior to randomisation/or registration for the Clinical Need Cohort	✓	✓	✓				
Serology for Hepatitis B and C (HBsAg, HBcAb & HCAb)	✓ Within 12 weeks randomisation/or registration for the Clinical Need Cohort	✓ Within 12 weeks prior to randomisation						
Blood pressure	✓	✓	✓	✓				
Review of pausing and re-start criteria		✓ For participants on the intermitant strategy only	✓ For participants on the intermitant strategy only					
Central investigations								

20ml in EDTA blood sample for HMDS		✓	✓ Months 24/48		✓	✓ randomisation arms only		
50ml in EDTA blood sample for UK CLL Biobank		✓	✓ Months 12/36/60/72		✓	✓ randomisation arms only		
Saliva sample for UK CLL Biobank		✓						
Questionnaires[4]								
QoL Questionnaires (EORTC QLQ-C30, QLQ-CLL and EQ-5D-5L) (Randomisation trial only)		✓ prior to starting treatment	✓ At 3, 6, 12, 18, 24, 30, 36 and 48 months of trial treatment				✓8 (for randomised participants only these must be completed at all the timepoints even if the participant has progressed before reaching this point in treatment)	

*Assessments completed to confirm eligibility for randomisation and provide a baseline for the day-to-day clinical care of participants should be performed within 4 weeks prior to randomisation, unless otherwise stated. Assessments completed for registration can be used to avoid repetition if they fall within the required timeframe, if this is not the case then they will need to be repeated.

** Not mandatory

1 Cardiac assessments should be performed as per SoC (if formal assessments, such as an ECHO, are conducted within any time frame the results will be acceptable

2Within 4 weeks prior to starting treatment. For participants with a history of hypertension (defined as on treatment for hypertension) and / or cardiac disease.

3 Females of childbearing potential (FCBP) must have a negative pregnancy test performed by a healthcare professional.

4To be completed in clinic after registration, before treatment is started and 3 months after randomisation, then every 6 months until 48m post treatment

5Using CTCAE v5.0 grades (see section 14.4 for reporting requirements)

6 either measured or derived by the Cockcroft Gault formula or alternative locally approved formula).

7As per standard of care

8Note that participants who stop trial treatment should complete QoL at the equivalent time points as per section 13.11.2 (unless the participant wishes to withdraw consent for any further data collection as per section 13.15).

APPENDIX 5: NICE Hypertension Guidance

Nice Guideline 136: https://www.nice.org.uk/guidance/ng136/resources/hypertension-in-adults-diagnosis-and-management-pdf-66141722710213 (36)

Nice Guideline 136 Visual Summary: https://www.nice.org.uk/guidance/ng136/resources/visual-summary-pdf-6899919517(37)

APPENDIX 6: Effective Methods of Contraception

(Adapted from ibrutinib SmPC)

''Women of child-bearing potential/Contraception in females

Based on findings in animals, IMBRUVICA may cause foetal harm when administered to pregnant women. ***Women should avoid becoming pregnant while taking IMBRUVICA and for up to 3 months after ending treatment. Therefore, women of child-bearing potential must use highly effective contraceptive measures while taking IMBRUVICA and for three months after stopping treatment****.*

Pregnancy

IMBRUVICA should not be used during pregnancy. There is no data from the use of IMBRUVICA in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 of SPC).

Breast-feeding

It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk to breast-fed children cannot be excluded. ***Breast-feeding should be discontinued during treatment with IMBRUVICA****.''*

Highly effective contraceptive measures are considered to:

For participants treated with ibrutinib it is recommended that hormonal methods of contraception should add a second barrier method (e.g. condom).

- combined (oestrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progesterone-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomised partner [3]
- sexual abstinence [4]

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

APPENDIX 7: Inhibitors or Inducers of CYP3A, ACE Inhibitors and other cautionary medications

Examples of inhibitors and inducers of CYP3A are given below. Note that this is not an exhaustive list. Further information can be found at the following websites: http://www.medicine.iupui.edu/Flockhart/table.htm and https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers. The general categorisation into strong, moderate, and weak CYP3a inhibitors is displayed below:

- A strong inhibitor is one that causes a >5-fold increase in plasma AUC values or >80% decrease in clearance. Strong inhibitors are capitalised in the list below.
- A moderate inhibitor is one that causes a >2-fold increase in plasma AUC values or 50-80% decrease in clearance.
- A weak inhibitor is one that causes a >1.25-fold but <2-fold increase in plasma AUC values or 20-50% decrease in clearance.

In addition to the medications listed in tables 1 and 2 , participants receiving ibrutinib should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

Table 1: Inhibitors or Inducers of CYP3A

INHIBITORS		**INDUCERS**		**SUBSTRATES**
STRONG CYP3A INHIBITORS:	**MODERATE CYP3A INHIBITORS:**	**STRONG CYP3A INDUCERS:**	**MODERATE CYP3A INDUCERS:**	**SUBSTRATES OF P-GP**
boceprevir	aprepitant	avasimibe	bosentan	aliskiren
clarithromycin	amprenavir	carbamazepine	efavirenz	ambrisentan
cobicistat	atazanavir	phenobarbital	etravirine	colchicines
conivaptan	ciprofloxacin	phenytoin	modafinil	dabigatran etexilate
indinavir	crizotinib	rifabutin	nafcillin	digoxin
itraconazole	darunavir/ritonavir	rifampin	oxcarbazepine	everolimus
ketoconazole	dronedarone	St. John's Wort	troglitazone	fexofenadine
lopinavir	erythromycin			lapatinib
mibefradil	diltiazem	**WEAK CYP3A INDUCERS:**		loperamide
nefazodone	fluconazole	amprenavir		maraviroc
nelfinavir	fosamprenavir	aprepitant,		nilotinib
posaconazole	imatinib	armodafinil		ranolazine
ritonavir	verapamil	clobazamechinacea		saxagliptin
saquinavir		glucocorticoids (eg, prednisone)		sirolimus
telaprevir		nevirapine		sitagliptin
telithromycin		pioglitazone		talinolol
troleandomycin		rufinamide		tolvaptan
voriconazole*		vemurafenib		topotecan
WEAK CYP3A INHIBITORS:				
alprazolam	goldenseal			

INHIBITORS		INDUCERS	SUBSTRATES
amiodarone	isoniazid		
amlodipine	nilotinib		
atorvastatin	oral contraceptives		
bicalutamide	pazopanib		
cilostazol	ranitidine		
cimetidine	ranolazine		
cyclosporine	suboxone		
fluvoxamine	tipranavir/ritonavir		
fluoxetine	ticagrelor		
ginkgo	zileuton		

* moderate CYP3A inhibitor per ibrutinib in vitro and clinical studies

Table 2: ACE inhibitors

Listed below are ACE inhibitors as both brand and generic names are shown below, whilst we have tried to make this list as complete as possible, however it is not exhaustive. Please also note that some ACE inhibitor medicines are also part of a combined tablet with a calcium-channel blocker medicine or water tablet' (diuretic) medicine (click on the hyperlinks to find out more).

Source: UK website called ''Patient'' https://patient.info/heart-health/ace-inhibitors

Generic Name	Brand Names / generic names	Weblink
Ramipril	Tritace Triapin (ramipril with felodipine) Altace	https://patient.info/medicine/ramipril-an-ace-inhibitor-tritace-triapin-altace
Lisinopril	Zestril; Zestoretic (lisinopril combined with hydrochlorothiazide)	https://patient.info/medicine/lisinopril-an-ace-inhibitor-zestril
Perindopril	Perindopril arginine; perindopril erbumine; perindopril tert-butylamine; Brand: Coversyl® Arginine; Combination brands: Coversyl® Arginine Plus (perindopril with indapamide)	https://patient.info/medicine/perindopril-an-ace-inhibitor-coversyl
Enalapril	Innovace; Innozide (contains enalapril with hydrochlorothiazide)	https://patient.info/medicine/enalapril-an-ace-inhibitor-innovace-innozide
Fosinopril	Fosinopril sodium	https://patient.info/medicine/fosinopril-an-ace-inhibitor
Imidapril	Tanatril	https://patient.info/medicine/imidapril-for-high-blood-pressure-tanatril
Quinapril	Accupro Accuretic (quinapril in combination with hydrochlorothiazide)	https://patient.info/medicine/quinapril-tablets-accupro
Trandolapril	None	https://patient.info/medicine/trandolapril-an-ace-inhibitor

Captopril	Noyada	https://patient.info/medicine/captopril-an-ace-inhibitor-noyada

APPENDIX 8: Central laboratory addresses

Leeds Haematology Malignancy Diagnostic Service (HMDS)	HMDS Level 03, Bexley Wing St James's University Hospital Leeds LS9 7TF Tel:0113 206 7851
UK CLL Biobank	UK CLL Biobank GCPLab Facility 1st Floor William Henry Duncan Building 6 West Derby Street University of Liverpool Liverpool L7 8TX Tel: 0151 706 4949/4845 Email: ukctbb@liverpool.ac.uk

APPENDIX 9: Management of clinical events

Some management guidelines regarding specific events are outlined below for ease of reference but should be read in conjunction with the trial supplied IB or SmPCs for latest version of Summary of Product Characteristics for ibrutinib.

APPENDIX 10: Safety Monitoring Plan

Risks associated with trial interventions ☐ **LOW ≡** Comparable to the risk of standard medical care ☒ **MODERATE ≡** Somewhat higher than the risk of standard medical care ☐ **HIGH ≡** Markedly higher than the risk of standard medical care	

Justification: *Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):*

Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase, a key molecule in B-cell receptor signalling. It is licenced as monotherapy for untreated CLL and for patients that have previously had at least one prior treatment for CLL.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?	**How will these risks be minimised?**	
Body system/Hazard	**Activity**	**Frequency**
Hypertension Cardiac	Screening and monitoring hypertension in accordance with NICE guidelines NG136 (published August 2019) to keep the blood pressure below 140/90mmHg More details in statement below	Eligibility assessment
Cardiac	Patients with symptomatic cardiac failure not controlled by therapy or unstable angina not adequately controlled by current therapy are excluded from the trial.	Eligibility assessment
Thrombocytopenia Neutropenia	Full blood count/assessment for suitability for treatment. Dose reductions and delays to be implemented in accordance with Section 12.3.3.	Throughout treatment
Haemorrhage Bleeding	Patients on concomitant warfarin or equivalent vitamin K inhibitors are excluded from the trial. Participants who require these after starting ibrutinib will be discussed with the CI/CoI beforehand in accordance with Section 12.3.2.	Eligibility assessment and throughout treatment
	Patients who have had major surgery within 4 weeks prior to randomisation/or registration for the Clinical Need Cohort are excluded from	Eligibility assessment and throughout treatment.

	the trial. When a patient requires surgery during ibrutinib then the drug will be interrupted around the surgery. It will be stopped at least 7 days prior to the procedure and will only be restarted at least 7 days following the operation in accordance with Section 12.3.5.	
Nausea Vomiting Diarrhoea	Participants questioned regarding symptoms during treatment and, where indicated, anti-emetics administered. Dose reductions and delays implemented in accordance with the SmPC.	Throughout treatment
Drug interactions with CYP3A inhibitors and inducers	Use of CYP3A inhibitors and inducers to be given in accordance with Section 12.3.2.	Throughout treatment
Drug interactions with ACE inhibitors	Use of ACE inhibitors to be given in accordance with Section 12.3.2.	Throughout treatment
Compliance with treatment (ibrutinib will be taken by participants at home)	Participants with concurrent diseases or mental disorders that may interfere with their ability to participate in the study are excluded from the trial.	Eligibility assessment
	Participants will be given a diary card to record treatment errors and will return unused tablets/capsules at each study visit.	Throughout treatment
	Participants will be given instructions to take home to provide details of how ibrutinib should be taken.	Before the start of treatment
	Participants will be asked to report any dosing errors immediately to their treating hospital.	Throughout treatment
Infection	PCP prophylaxis, and other anti-infective prophylaxis treatment, should be administered as per local supportive care protocols.	Throughout treatment

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. IDMC, independent data review)

A Data Monitoring and Ethics Committee (DMEC) will be convened for the trial, who will meet on an annual basis and will review interim safety information for the trial as agreed by the committee at their initial meeting. Safety information will be reviewed at least 3 monthly intervals for at least the first year of the trial, and at least 6 monthly for the remainder of the trial. This 3 monthly safety review will continue for at least the first year of I treatment. The DMEC will also review SUSARs and SARs that result in death in real time. The DMEC will, in light of these reports, have the authority to recommend trial closure to the Trial Steering

Committee (TSC) should they have concerns over the safety or ethics of the trial. The TSC have the authority to recommend appropriate action including amendments to or closure of the trial at any time.

Participant data will be entered on to a validated database and monitored for completeness and quality by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. A validation check program will be incorporated into the trial database to verify the data, and discrepancy reports will be generated for resolution by the investigator. Priority validations will be incorporated into the validation programme to ensure that any discrepancies related to participant rights, or the safety of participants, are expedited to sites for resolution.

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