Clinical Study Protocol	
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A prospective, multi-centre, phase IV clinical trial to assess the safety and efficacy of Acalabrutinib capsules in Indian adult patients with chronic lymphocytic leukaemia and relapsed and refractory mantle cell lymphoma

Sponsor:

AstraZeneca Pharma India Limited

Block N1, 12th Floor, Manyata Embassy Business Park

Rachenahalli, Outer Ring Road, Bangalore-560045.

VERSION HISTORY

Version 1.0 Date 01.09.2020
<<LIST SECTION CHANGED AND A DESCRIPTION OF CHANGE WITH REASON>>

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1: Schedule of Activities (SoA)

Study Phase	**Screening Phase**	**Treatment Phase [a]**		**Follow-up Phase**
Cycle		**Cycles 1-6**	**EOT**	**EOS**
Visit No.	**1**	**2-7 (Day 1 of each cycle)**	**8**	
Study Days	**-6 to 0**	**1-168 (28 days per cycle)**	**170**	**28 days post-EOT**
Screening/Enrolment visit				
Informed consent [$]	X			
Eligibility Criteria	X			
Demographics/ Review medical history	X			
ECOG Performance Status	X	X	X	
General Physical examination [b]	X	Symptom-directed physical examination only		
Concomitant medication recording	Continuous from the time of ICF until 28 days after the last Acalabrutinib dose in the treatment phase.			
Study Drug Administration				
Acalabrutinib dosing		The recommended dose is Acalabrutinib 100 mg capsules BID, starting on Day 1 Cycle 1, until disease progression or unacceptable toxicity. Each cycle of treatment is 28 days.		
Disease Evaluations (Disease characteristics will be performed as per routine clinical practice)				
Baseline Disease Characteristics	X			
Safety Evaluations (baseline and each treatment visit) [*]				
Physical examination [b]	X	Symptom-directed physical examination only		
Vital parameters [c]	X	X	X	
Adverse event monitoring	Continuous from the time of ICF until 28 days after last study dose of Acalabrutinib.			

Study Phase	**Screening Phase**	**Treatment Phase [a]**		**Follow-up Phase**
Cycle		**Cycles 1-6**	**EOT**	**EOS**
Visit No.	**1**	**2-7 (Day 1 of each cycle)**	**8**	
Study Days	**-6 to 0**	**1-168 (28 days per cycle)**	**170**	**28 days post-EOT**
12-lead ECG	X	X	X	
Lymph node biopsy [d]	X			
Next-generation sequencing (NGS)-CLL panel [e]	X			
Haematology [f] & Biochemistry [g]	X	X	X	
Urinalysis [h]	X	X	X	
Pregnancy Test [i]	X	X	X	
Chest X-ray [j]	X	X	X	
Efficacy Evaluations (once in 3 months)				
CT/MRI [k]	X	X	X	
EORTC QLQ-C30 Questionnaire	X	X	X	

[$] Patients must sign the informed consent form before any study-specific procedures are performed.

[*] Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the Informed Consent Form (ICF) may be utilised for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame (-6 to 0 day)

[a] Treatment phase from Day 1 to Day 168. The treatment with Acalabrutinib will be continued until disease progression or unacceptable drug-related toxicity, whichever occurs earlier.

[b] The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical examination, including tumour assessments by palpation, are done thereafter.

[c] Vital signs (blood pressure, heart rate, and temperature) will be assessed after the patient has rested in the sitting position.

[d] Lymph node biopsy will be conducted in patients with lymphadenopathy. However, a report of previous lymph node biopsy performed within 06 months before the study enrolment could be considered if the patient did not receive any medication during that period

Study Phase	Screening Phase	Treatment Phase [a]		Follow-up Phase
Cycle		Cycles 1-6	EOT	EOS
Visit No.	1	2-7 (Day 1 of each cycle)	8	
Study Days	-6 to 0	1-168 (28 days per cycle)	170	28 days post-EOT

[e] Next-generation sequencing will be conducted to understand the genetic profile in Indian settings. Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), trisomy 12 in peripheral blood lymphocytes; TP53 mutation; immunoglobulin variable heavy chain (IGHV) mutational status will be assessed before the start of treatment in CLL/SLL-naïve patients, or CLL/SLL patients who did not have their report. However, MCL patients are Relapsed/Refractory and their previous report data will be used. A six months old report can be considered for both the conditions.

[f] Haematology will include a complete blood cell count [white blood cell count, haemoglobin (Hb), haematocrit, reticulocyte, and platelet count] and differential leukocyte count, including both percent and an absolute number of lymphocytes. Haematology need not be repeated on Cycle 1 Day 1if screening haematology was within 5 days

[g] Biochemistry will include albumin, Total bilirubin, Total protein, Alkaline Phosphatase (ALP), Alanine Aminotransferase (ALT, SGPT), Aspartate Aminotransferase (AST, SGOT), Gamma-glutamyl transferase (GGT), Lactate Dehydrogenase (LDH), Lipase, Amylase, Blood Glucose, Magnesium, Potassium, Bicarbonate, Sodium, Calcium, Chloride, Creatinine (creatinine clearance), Urea or Blood Urea Nitrogen (BUN), Haptoglobin, b2-microglobulin. Serum biochemistry need not be repeated on Cycle 1 Day 1 if screening chemistry was within 5 days.

[h] Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

[i] A urine pregnancy test will be conducted in all females of child bearing potential at the time of screening and during the study (treatment phase)

[j] Chest X-ray will be done as a symptom directed investigation. Patients with signs and symptoms of Pneumonia will be allowed to go for chest X-ray investigation.

[k] CT or MRI scans will be performed prior to the first study medication administration (dosing). CT or MRI scans are applicable for the patients with lymphadenopathy or organomegaly. Patients with abnormalities of blood parameters without any lymphadenopathy or organomegaly will not undergo CT or MRI scans. Patients who will be undergoing CT, should have baseline and every 3-months reports

Note: CMV, HIV, and Hepatitis serology testing will be conducted at the screening.

1.2 Synopsis

Protocol Title: A prospective, multi-centre, phase IV clinical trial to assess the safety and efficacy of Acalabrutinib capsules in Indian adult patients with chronic lymphocytic leukaemia and relapsed and refractory mantle cell lymphoma

Version: 1.0 Date: 01 Sep 2020

Study sites and number of patients planned

No. of total screened patients: Approximately 150

No. of total enrolled patients: Approximately 100

No. of study sites: 10

Total planned study period	
Estimated date of the first patient in	Q4 2020
Estimated date of the last patient in	Q2 2021
Estimated date of last patient last visit	Q4 2021
Estimated date of database lock	Q2 2022
Clinical study report	Q3 2022

Rationale

Chronic lymphocytic leukaemia (CLL) is a malignancy of B cells that predominantly affects an elderly population. It is the most prevalent form of adult leukaemia, with an age-adjusted incidence of 3.3–6.4 per 100,000 person-years and a median age at diagnosis of 70 years (Noone AM, April 2018). The diagnosis of CLL is established using peripheral blood and immune-phenotyping and requires the presence of a minimum of 5 x 10^9/L monoclonal B cells that co-express the surface antigens CD5, CD19, CD20, and CD23. In routine practice, patients with asymptomatic early-stage disease should be monitored without therapy unless they have evidence of disease progression or disease-related symptoms. Treatment of CLL is initiated once there is evidence of progressive or symptomatic/active disease as defined by iwCLL guidelines (Hallek et al., 2018; Hallek et al., 2008). Despite the relatively long life expectancy for early-stage disease, CLL remains an incurable disease.

The incidence of CLL in India is 0.41 per 100,000 person-years; not as common as in the western countries. However, estimates of the incidental cases are 5000 per year with a prevalence of 25000 patients (one-third that of the estimate for the United States)(Lad et al., 2018). In India, CLL accounts for 3-5% of all leukaemia types. CLL is a disease of the elderly and the median age of CLL presentation is >60yrs in India. The high-risk CLL is defined, by a genetic aberration of the TP53 gene [i.e., del(17p) or TP53 mutation]. The incidence of high-risk characteristics (del 17p) increase up to 50% in patients with relapsed and refractory CLL (Gogia, Gupta, Kumar, Sharma, & Soni, 2019). An Indian study showed that high-risk cytogenetic abnormalities like del(17p) and del(11q) were seen in 13.3% patients, which are more common in India than that reported in the West. (Saxena, Kumar, Sazawal, & Mahapatra, 2016)

The Scientific Expert Committee (SEC) of Oncology and Haematology, nominated by Central Drugs Standard Control Organisation (CDSCO), met on 12-Feb-2020. The committee provided recommendations to obtain marketing authorization for Acalabrutinib in the treatment of patients with CLL/SLL, and patients with MCL who have received at least one prior therapy. The marketing authorization was provided with a condition to conduct a phase IV clinical trial as per the requirements in the latest New Drug and Clinical Trial Rules (2019) in India. The phase IV trial will be a part of the marketing authorization condition, which will be issued for the additional indication of CLL for Acalabrutinib in India.

In line with the SEC recommendation and to comply with the marketing authorization condition, the current phase IV study plans to assess the safety and efficacy of Acalabrutinib in Indian patients. The data obtained from the study will help to understand the safety and efficacy profile of Acalabrutinib in Indian patients with CLL/SLL, and patients with MCL who have received at

least one prior therapy. The study will add information to currently available safety and efficacy data on Acalabrutinib.

Objectives and Endpoints

Primary objective	**Outcome measures**
To investigate the safety of Acalabrutinib among patients with treatment naïve and R/R CLL/ SLL, and relapsed & refractory MCL in Indian patients	Adverse Events (AEs), Serious Adverse Events (SAEs), and AEs of Special Interest (AESI) including Arrhythmias (Atrial Fibrillation), Anaemia, Hypertension, Bleeding, Infections, Reasons for discontinuation and second primary malignancies
Secondary objectives	**Secondary Outcome measures**
To assess the efficacy of Acalabrutinib in patients of CLL/SLL and relapsed & refractory MCL in Indian patients	Objective response to treatment.
Patient-reported outcome (PRO)	Health related quality of life (EORTC QLQ-C30 Questionnaire)

Overall design

The study is a phase IV, open-label, single-arm, multi-centre, prospective study to be conducted in India. The study will evaluate the safety and efficacy of Acalabrutinib in Indian adult patients with CLL/SLL and patients with MCL who have received at least one prior therapy. The Investigator will be trained on the locally approved Prescribing Information (PI) before the enrolment of the first patient at their site to ensure compliance and proper dosing of the study drug. Patients will be monitored throughout the study period for AEs /SAEs/AESI of Acalabrutinib.

Patients with CLL/SLL and MCL who are eligible to receive Acalabrutinib treatment as per locally approved PI and ratified by an independent clinical judgment of treating physician will be evaluated for inclusion into the current phase IV trial. To enrol approximately 100 patients (90 patients of TN & R/R CLL and 10 R/R MCL patients) into the study, it is expected that approximately 150 patients will need to be screened.

The study will be initiated after approval by the Ethics Committee. Patients will undergo the following phases: Screening/Enrolment Phase, Treatment Phase, and Follow-up Phase.

The decision of patients to participate in this study must not, in any way, impact the standard of care they are receiving or any benefits to which they are otherwise entitled. Prior to data collection, all patients must sign an Informed Consent Form (ICF), allowing for data collection and source data verification to be performed in accordance with local requirements and Sponsor policy.

Two cohorts of patients will be included in the current study (a) patients with CLL/SLL who are treatment naïve or have received at least one prior therapy (N= 90) and (b) patients with MCL

who have received at least one prior therapy (N= 10). Potential patients will undergo screening phase within 07 days prior to the first dose. Patients who meet the protocol-defined inclusion/exclusion criteria will be prospectively enrolled in the study.

Acalabrutinib capsules 100 mg are administered twice daily (BID) for 06 cycles, starting from Cycle 1, Day 1, and continuing up to Cycle 6, Day 28; or until study drug discontinuation due to either disease progression or, unacceptable toxicity, or other reasons, whichever occurs earlier.

Acalabrutinib will be provided by the Sponsor to patients in the Treatment Phase. The Sponsor shall also conduct laboratory investigations for safety and efficacy evaluations, including haematology, biochemistry, radiology, and electrocardiography (ECG), as mentioned in the SoA table.

Patient Population

Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Men and Women aged 18yrs or more.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0,1, or 2
3. Able to receive all outpatient treatments, all laboratory monitoring, and all radiologic evaluations.
4. The following laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥750 cells/μL or ≥500 cells/μL in patients with documented bone marrow involvement, and independent of growth factor support 07 days before the assessment
    b. Platelet count ≥50,000 cells/μL or ≥30,000 cells/μL in patients with documented bone marrow involvement, and without transfusion support 07 days before the assessment
    c. Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤2.0 x ULN
    d. Total bilirubin ≤1.5 x ULN
    e. Estimated creatinine clearance of ≥30 mL/min
5. Refractory disease defined as achieving less than partial response with the most recent treatment within 6 months before study entry
6. Provision of signed, written and dated informed consent prior to any study-specific Procedures
7. The patients of either CLL or MCL:
    a. **CLL patients:**
        i. Treatment naïve or ≥1 prior systemic therapy for CLL
        ii. Diagnosis of CD20+ CLL that meets published diagnostic criteria (Hallek et al. 2018)
        iii. An active disease that meets ≥1 of the following iwCLL 2018 criteria for requiring treatment:
            1) 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 an 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.

2) Massive (i.e., ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
3) Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4) Progressive lymphocytosis with an increase of ≥50% over a 2-month period or Lymphocyte Doubling Time (LDT) in <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.
5) Autoimmune complications, including anaemia or thrombocytopenia poorly responsive to corticosteroids.
6) Symptomatic or functional extra-nodal involvement (e.g., skin, kidney, lung, spine).
7) Disease-related symptoms as defined by any of the following:
    a) Unintentional weight loss of ≥10% within the previous 06 months.
    b) Significant fatigue (i.e., ECOG performance scale 02 or worse; cannot work or unable to perform usual activities).
    c) Fever ≥100.5°F or 38.0°C for 02 or more weeks without evidence of infection.
    d) Night sweats for ≥1 month without evidence of infection.

b. MCL Patients:

i. Confirmed MCL with translocation t(11;14) (q13;q32) and/or overexpressed cyclin D1
ii. Measurable nodal disease (one or more lesions measuring ≥2 cm in the longest diameter)
iii. Relapsed after, or were refractory to, 1-5 previous treatments

Exclusion criteria

1. Known prolymphocytic leukaemia, Central Nervous System (CNS) lymphoma or leukaemia; or known history of (or currently suspected) Richter's syndrome
2. Treatment with chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days of the first dose of study drug
3. Prior radio-conjugated or toxin-conjugated antibody therapy

4. Anticoagulation therapy (e.g., warfarin or equivalent vitamin K antagonists) within 07 days of the first dose of study drug.
5. Major surgery ≤30 days before the first dose of study drug
6. History of stroke or intracranial haemorrhage ≤6 months before the first dose of study drug
7. History of bleeding diathesis
8. Prior exposure to a B-cell lymphoma-2 (Bcl-2) inhibitor or B-cell receptor inhibitor like BTKs
9. Active Cytomegalovirus (CMV) infection or serologic status reflecting active Hepatitis B or C infection or known history of infection with Human Immunodeficiency Virus (HIV), or any uncontrolled active systemic infection.
10. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, Congestive Heart Failure, or Myocardial Infarction within 06 months of screening, or any Class 3 or 4 cardiac diseases as defined by the New York Heart Association Functional Classification, or QTcB >480 msec at screening.
11. Requiring treatment with proton-pump inhibitors (e.g., Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Rabeprazole, or Pantoprazole).
12. Breastfeeding or pregnant.
13. Current life-threatening illness, medical condition, or organ/system dysfunction which, in the Investigator's opinion, could have compromised the subject's safety or put the study at risk.
14. Concurrent participation in another therapeutic clinical trial.

Study Drug, dosage, and mode of administration

The recommended dose of Acalabrutinib is 100 mg given per oral (PO) twice daily (BID) (each treatment cycle is 28 days) until disease progression or unacceptable toxicity. Dose escalation or reduction is recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability.

Duration of treatment

The Treatment Phase will be from the start of Cycle 1, Day 1 to end of Cycle 6, Day 28, or until study drug discontinuation due to either disease progression or unacceptable toxicity, or other reasons whichever occurs earlier, as listed in Section 7.1.

Post-trial access

Patients who are observed to receive clinical benefit from Acalabrutinib after completion of treatment phase, may continue to receive Acalabrutinib, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment or have not progressed clinically. The patients may continue treatment via drug supply (provided by AstraZeneca) until disease progression or withdraw of drug due to side effects or investigators decision whichever comes first.

These subjects shall receive the study drug free of cost in case if there is no coverage / reimbursement through a separate patient support program and will not receive the medication via the clinical trial supply for this study. These subjects shall not be actively monitored for AE's and it will be the responsibility of the treating physician to ensure reporting of all SAE's,

pregnancies, overdose and medication errors to the relevant authorities as per the standard spontaneous safety reporting practice in India.

Safety Evaluations

Safety evaluations will include adverse event monitoring, physical examinations, ECG monitoring, clinical laboratory investigations (haematology and biochemistry), vital sign measurements, ECOG performance status, and death as observed by the Investigator. Based on previous *in vitro* studies, animal toxicological findings, and human studies with Acalabrutinib, arrhythmias (which includes atrial fibrillation), anaemia, hypertension, bleeding, infections, and second primary malignancies will be closely monitored. Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the Investigator according to the standard practice if clinically indicated.

Efficacy Evaluations

All patients who receive Acalabrutinib capsule 100 mg BID will be evaluated for efficacy once every 03 months during the treatment phase. Efficacy will be assessed based on iwCLL 2018 criteria for CLL/SLL (Hallek et al., 2018) and for MCL (Cheson et al., 2014). Efficacy will be based on objective response [Complete Remission (CR) + Partial Remission (PR) and partial response with lymphocytosis (PRL)] via Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI).

Statistical methods:

Sample Size Justification

The primary endpoint of the trial is to demonstrate the safety profile of Acalabrutinib in routine clinical practice as assessed by the incidence of adverse events (AEs) (Serious and Non-serious AEs) observed during the trial. As per the Health Authority requirement, the total sample size of the study will be approximately 100.

Hypothesis

No formal hypothesis testing will be conducted.

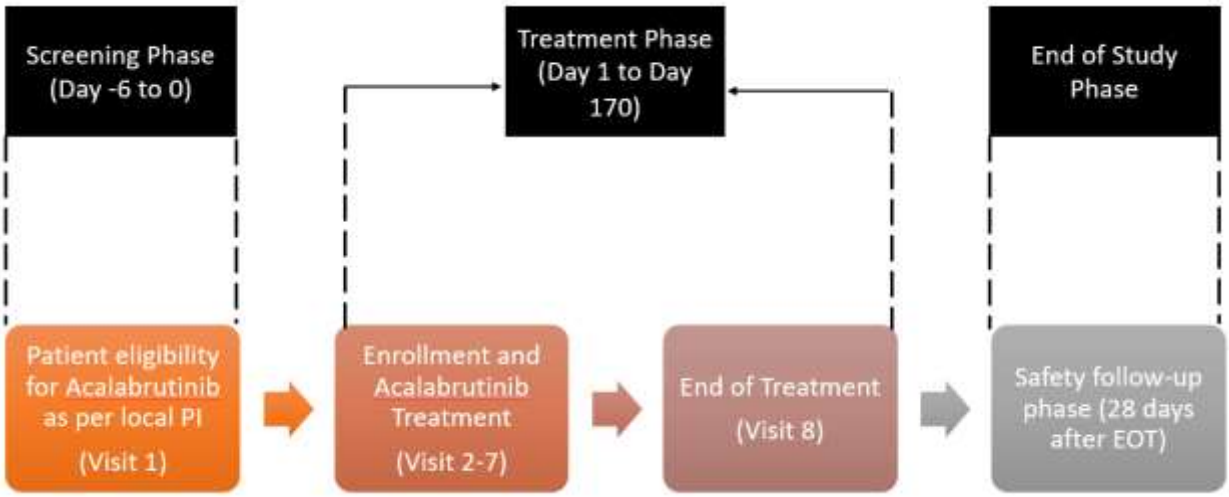
Statistical Analysis

Categorical data will be summarized using frequencies and percentages. Continuous data will be summarized with descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals will be supplied for key proportions (including objective response rate) using the Clopper-Pearson method.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1. Study design



2. INTRODUCTION

2.1 Study rationale

The Scientific Expert Committee (SEC) of Oncology and Haematology, nominated by Central Drugs Standard Control Organisation (CDSCO), met on 12-Feb-2020. The committee provided recommendations to obtain marketing authorization for Acalabrutinib in the treatment of patients with CLL/SLL, and patients with MCL who have received at least one prior therapy. The marketing authorization was provided with a condition to conduct a phase IV clinical trial as per the requirements in the latest New Drug and Clinical Trial Rules (2019) in India. The phase IV trial will be a part of the marketing authorization condition, which will be issued for the additional indication of CLL for Acalabrutinib in India.

In line with the SEC recommendation and to comply with the marketing authorization condition, the current phase IV study plans to assess the safety and efficacy of Acalabrutinib in Indian patients. The data obtained from the study will help to understand the safety and efficacy profile of Acalabrutinib in Indian patients with CLL/SLL, and patients with MCL who have received at least one prior therapy. The study will add information to currently available safety and efficacy data on Acalabrutinib.

2.2 Background

2.2.1 Acalabrutinib

B cell antigen receptor (BCR) expression is essential for B-cell function, and loss of expression leads to rapid cell death. (Buchner & Müschen, 2014) The BCR over-expression contributes to the majority of B-cell malignancies. Several downstream protein kinases such as BTK (Bruton Tyrosine Kinase) are critical in the BCR signalling cascade. Due to the influence of BTK on cell proliferation and survival, it is an attractive target for inhibition to treat diseases such as CLL and other B-cell lymphomas. (Isaac & Mato, 2020)

Acalabrutinib is a selective small-molecule inhibitor of BTK. BTK is a signalling molecule of the BCR and cytokine receptor pathways. In B cells, BTK signalling results in B-cell survival and proliferation and is required for cellular adhesion, trafficking, and chemotaxis.

Acalabrutinib and its active metabolite, ACP-5862, form a covalent bond with a cysteine residue in the BTK active site, leading to irreversible inactivation of BTK ($IC_{50} \leq 5$ nM) with minimal off-target interactions. In a screen of 380 mammalian wild-type kinases, the only additional kinase interactions at clinically relevant concentrations of Acalabrutinib and ACP-5862 were with BMX and ERBB4, with 3- to 4-fold less potency than BTK. In non-clinical studies, Acalabrutinib inhibited BTK-mediated activation of downstream signalling proteins CD86 and CD69, inhibited malignant B-cell proliferation and survival, and had minimal activity on other immune cells (T cells and Natural Killer cells). (PI, 2020)

In patients with B-cell malignancies dosed with Acalabrutinib 100 mg twice daily, median steady-state BTK occupancy of ≥ 95% in peripheral blood was maintained over 12 hours, resulting in inactivation of BTK throughout the recommended dosing interval.

2.2.2 Chronic Lymphocytic Leukaemia and Small Lymphocytic Lymphoma

CLL and SLL are characterized by a progressive accumulation of leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. Morphologically, these leukemic cells appear as small, mature lymphocytes that may be found admixed with occasional larger or atypical cells, or pro-lymphocytes. CLL and SLL are different manifestations of the same disease and are managed in much the same way. The major difference is that in CLL, a significant number of the abnormal lymphocytes are found in the peripheral blood in addition to bone marrow and lymphoid tissue, and in SLL, the bulk of disease is in lymph nodes, bone marrow, and other lymphoid tissues, and there are few (if any) abnormal lymphocytes circulating in the peripheral blood. (Wierda et al., 2020)

Chronic lymphocytic leukaemia is a malignancy of B cells that predominantly affects an elderly population. It is the most prevalent form of adult leukaemia, with an age-adjusted incidence of 3.3–6.4 per 100,000 person-years and a median age at diagnosis of 70 years (Noone AM, April 2018). The diagnosis of CLL is established using peripheral blood and immune-phenotyping and requires a minimum of 5 x 10^9/L monoclonal B cells that co-express the surface antigens CD5, CD19, CD20, and CD23. In routine practice, patients with asymptomatic early-stage disease should be monitored without therapy unless they have evidence of disease progression or disease-related symptoms. Treatment of CLL is initiated once there is evidence of progressive or symptomatic/active disease as defined by iwCLL guidelines (Hallek et al., 2018; Hallek et al., 2008). Despite the relatively long life expectancy for early-stage disease, CLL remains an incurable disease.

The incidence of CLL in India is 0.41 per 100,000 person-years not; as common as in the western countries. However, estimates of the incidental cases are 5000 per year with a prevalence of 25000 patients (one-third that of the estimate for the United States). (Lad et al., 2018) In India, CLL accounts for 3-5% of all leukaemia types. CLL is a disease of the elderly and the median age of CLL presentation is >60yrs in India. The high-risk CLL is defined, at least in part, by a genetic aberration of the TP53 gene [i.e., del(17p) or TP53 mutation]. The incidence of high-risk characteristics (del 17p) increase up to 50% in patients with relapsed and refractory CLL (Gogia et al., 2019). An Indian study showed that high-risk cytogenetic abnormalities like del(17p) and

del(11q) were seen in 13.3% patients, which are more common in India than that reported in the West. (Saxena et al., 2016)

The safety and efficacy of Acalabrutinib in previously untreated CLL were evaluated in a randomised, multi-centre, open-label Phase 3 study (ELEVATE-TN) of 535 patients. Patients received Acalabrutinib plus Obinutuzumab, Acalabrutinib monotherapy, or Obinutuzumab plus Chlorambucil. Patients 65 years of age or older or between 18 and 65 years of age with coexisting medical conditions were included in ELEVATE-TN. The trial also allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists. (PI, 2020)

Patients were randomised in a 1:1:1 ratio into 03 arms to receive

- Acalabrutinib plus Obinutuzumab (Acalabrutinib+G): Acalabrutinib 100 mg was administered twice daily, starting on Cycle 1 Day 1 until disease progression or unacceptable toxicity. Obinutuzumab was administered starting on Cycle 2 Day 1 for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 2 followed by 1000 mg on Day 1 of Cycles 3 up to 7. Each cycle was of 28 days.
- Acalabrutinib monotherapy: Acalabrutinib 100 mg was administered twice daily until disease progression or unacceptable toxicity.
- Obinutuzumab plus Chlorambucil (GClb): Obinutuzumab and Chlorambucil were administered for a maximum of 6 treatment cycles. Obinutuzumab 1000 mg was administered on Days 1 and 2 (100 mg on Day 1 and 900 mg on Day 2), 8 and 15 of Cycle 1 followed by 1000 mg on Day 1 of Cycles 2 up to 6. Chlorambucil 0.5 mg/kg was administered on Days 1 and 15 of Cycles 1 up to 6. Each cycle was of 28 days.

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2), and geographic region (North America and Western Europe versus other). After confirmed disease progression, 45 patients randomised on the GClb arm crossed over to Acalabrutinib monotherapy.

The primary endpoint was progression-free survival (PFS) as assessed by an Independent Review Committee (IRC) per iwCLL 2008 criteria with the incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 28.3 months, PFS by IRC indicated a 90% statistically significant reduction in the risk of disease progression or death for previously untreated CLL patients in the Acalabrutinib + G arm compared to the GClb arm. At the time of analysis, median overall survival had not been reached in any arm with a total of 37 deaths: 9 (5%) in the Acalabrutinib +G arm, 11 (6.1%) in the Acalabrutinib monotherapy arm, and 17 (9.6%) in the GClb arm.

PFS results for Acalabrutinib with or without Obinutuzumab were consistent across subgroups, including high-risk features in the high-risk CLL population (17p deletion, 11q deletion, TP53 mutation, and un-mutated IGHV), the PFS hazard ratios of Acalabrutinib with or without Obinutuzumab versus Obinutuzumab plus Chlorambucil were 0.08 [95% CI (0.04, 0.15)] and 0.13 [95% CI (0.08, 0.21)], respectively.

Patients with CLL who received at least one prior therapy (PI, 2020)

The safety and efficacy of Acalabrutinib in relapsed or refractory CLL were evaluated in a randomised, multi-centre, open-label phase 3 study (ASCEND) of 310 patients who received at

least one prior therapy. Patients received Acalabrutinib monotherapy or Investigator's choice of either Idelalisib plus Rituximab or Bendamustine plus Rituximab. The trial allowed patients to receive antithrombotic agents other than warfarin or equivalent vitamin K antagonists.

Patients were randomised 1:1 to receive either: Acalabrutinib 100 mg twice daily until disease progression or unacceptable toxicity, or Investigator's choice:

- Idelalisib 150 mg twice daily until disease progression or unacceptable toxicity in combination with ≤8 infusions of rituximab (375 mg/m^2/500 mg/m^2) on Day 1 of each 28-day cycle for up to 6 cycles

- Bendamustine 70 mg/m^2 (Day 1 and 2 of each 28-day cycle) in combination with rituximab (375 mg/m^2/500 mg/m^2) on Day 1 of each 28-day cycle for up to 6 cycles

Patients were stratified by 17p deletion mutation status (presence versus absence), ECOG performance status (0 or 1 versus 2), and a number of prior therapies (1 to 3 versus ≥ 4). After confirmed disease progression, 35 patients randomised on the Investigator's choice of either Idelalisib plus Rituximab or Bendamustine plus Rituximab crossed over to Acalabrutinib.

The primary endpoint was PFS as assessed by IRC iwCLL 2008 criteria with the incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). With a median follow-up of 16.1 months, PFS indicated a 69% statistically significant reduction in the risk of death or progression for patients in the Acalabrutinib arm. At the time of analysis, median overall survival had not been reached in any arm with a total of 33 deaths: 15 (9.7%) in the Acalabrutinib monotherapy arm and 18 (11.6%) in the Investigator's choice of either Idelalisib plus rituximab or Bendamustine plus rituximab arm.

PFS results for Acalabrutinib were consistent across subgroups, including high-risk features. In the high risk CLL population (17p deletion, 11q deletion, TP53 mutation, and un-mutated IGHV), the PFS HR was 0.27 [95% CI (0.17, 0.44)].

2.2.3 Mantle Cell Lymphoma

MCL is a distinct sub-type of non-Hodgkin's lymphoma (NHL) comprising approximately 7% of all adult NHL, with a moderately aggressive clinical course and poor outcome. The primary cell of origin of MCL is thought to be a naive B cell of pre-germinal centre origin within the mantle zone of the lymph node. The incidence of MCL increases with age and an increase in incidence has been observed over time. (Zhou et al., 2008) The disease is characterized by the chromosomal translocation t(11;14)(q13·3; q32·33), resulting in over-expression of the cell cycle protein cyclin D1. (McKay, Leach, Jackson, Robinson, & Rule, 2018) the role of BTK inhibitors was demonstrated to manage relapse and refractory cases of MCL. (Schieber, Gordon, & Karmali, 2018)

The safety and efficacy of Acalabrutinib in MCL were evaluated in an open-label, multi-centre, single-arm Phase 2 study (ACE-LY-004) of 124 previously treated patients. All patients received Acalabrutinib 100 mg orally twice daily until disease progression or unacceptable toxicity. The trial did not include patients who received prior treatment with BTK inhibitors. The primary endpoint was Investigator-assessed overall response rate (ORR) per the Lugano classification for non-Hodgkin's lymphoma (NHL). Duration of Response (DoR) was an additional outcome measure. (PI, 2020)

The median age was 68 (range 42 to 90) years, 79.8% were male, and 74.2% were Caucasian. At baseline, 92.8% of patients had an ECOG performance status of 0 or 1. The median time since diagnosis was 46.3 months, and the median number of prior treatments was 02 (range 1 to 5), including 17.7% with prior stem cell transplant. The most common prior regimens were CHOP-based (51.6%) and ARA-C (33.9%). At baseline, 37.1% of patients had at least one tumour with the longest diameter ≥5 cm, 72.6% had extra-nodal involvement, including 50.8% with bone marrow involvement. The simplified Mantle Cell Lymphoma International Prognostic Index (MIPI) score, (which includes age, ECOG score, and baseline lactate dehydrogenase and white cell count) was intermediate in 43.5% and high in 16.9% of patients. (PI, 2020)

As per recommendation by the Regulatory Authority, the current phase-IV study is planned with the aim to assess the safety and efficacy of Acalabrutinib in Indian patients as a post-marketing requirement. The data obtained from the present study will help to understand the safety and efficacy profile of Acalabrutinib in Indian patients with CLL and MCL.

2.3 Benefit/risk assessment

Patients with CLL/SLL and patients with MCL who have received at least one prior therapy will be treated with Acalabrutinib 100 mg BID from Day1 Cycle 1 for 06 cycles (each treatment cycle is 28 days). During this time, the patient will be monitored for safety and efficacy according to the assessment frequency presented in Table 1. The efficacy and safety of Acalabrutinib is established in various studies in CLL/SLL and MCL patients (refer Section 2).

Overall, Acalabrutinib monotherapy demonstrated satisfactory safety profile in various studies conducted in patients of CLL/SLL, and MCL (Table 3). Most AEs are low-grade (Grade 1 to 2) with relatively few related high-grade (Grade 3 to 4) AEs.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of Acalabrutinib may be found in the Acalabrutinib India PI.

3. OBJECTIVES AND ENDPOINTS

Table 2: Study objectives

Primary objective	**Outcome measures**
To investigate the safety of Acalabrutinib among patients with CLL/ SLL, and relapsed & refractory MCL in Indian patients	Adverse Events (AEs), Serious Adverse Events (SAEs), and AEs of Special Interest (AESI) including Arrhythmias (Atrial Fibrillation), Anaemia, Hypertension, Bleeding, Infections, Reasons for discontinuation and second primary malignancies
Secondary objectives	**Secondary Outcome measures**

To assess the efficacy of Acalabrutinib in patients of CLL/SLL and relapsed & refractory MCL in Indian patients	Objective response to treatment.
Patient-reported outcome (PRO)	Health related quality of life (EORTC QLQ-C30 Questionnaire)

4. STUDY DESIGN

4.1 Overall design

The study is a phase IV, open-label, single-arm, multi-centre, prospective study to be conducted in India. The study will evaluate the safety and efficacy of Acalabrutinib in Indian adult patients with CLL/SLL, and patients with MCL who have received at least one prior therapy. The Investigator will be trained on the locally approved Prescribing Information before the enrolment of the first patient at their site to ensure compliance and proper dosing of the study drug. Patients will be monitored throughout the study period for AEs /SAEs/AESI of Acalabrutinib.

Patients with CLL/SLL and MCL who are eligible to receive Acalabrutinib treatment as per locally approved prescribing information and ratified by an independent clinical judgment of treating physician, will be evaluated for inclusion into the current phase IV trial. To enrol approximately 100 patients into the study, it is expected that approximately 150 patients will need to be screened.

The study will be initiated after approval by the Ethics Committee. Patients will undergo the following phases: Screening/Enrolment Phase, Treatment Phase, and Follow-up Phase.

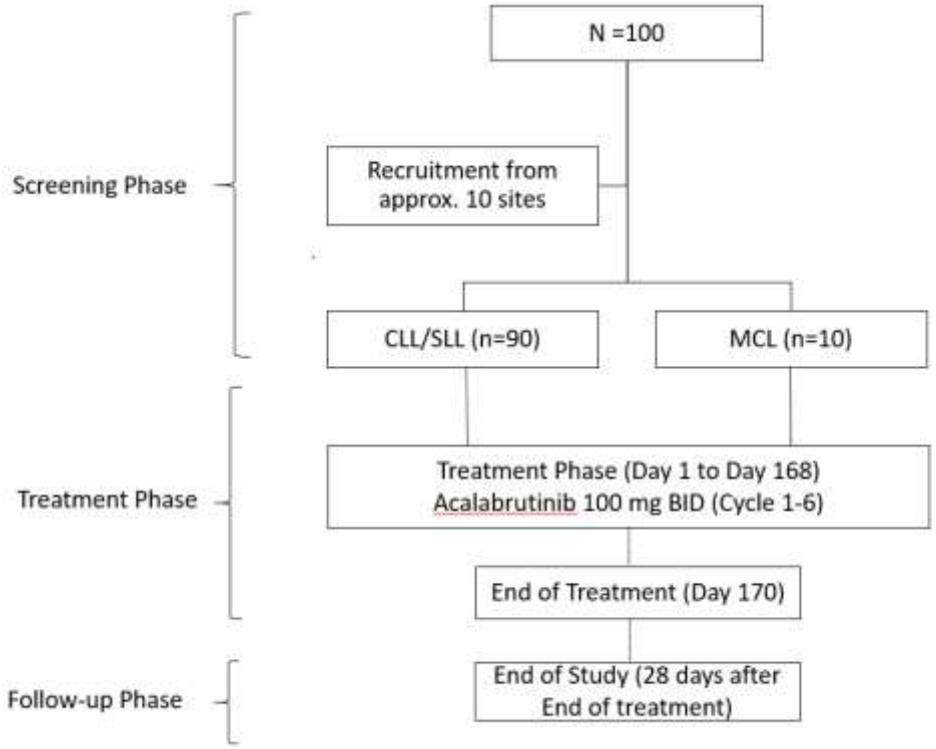
The decision of patients to participate in this study must not, in any way, impact the standard of care they are receiving or any benefits to which they are otherwise entitled. Prior to data collection, all patients must sign an ICF, allowing for data collection and source data verification to be performed in accordance with local requirements and Sponsor policy.

Two cohorts of patients will be included in the current study (a) patients with CLL/SLL who are treatment naïve or have received at least one prior therapy (N= 90) and (b) patients with MCL who have received at least one prior therapy (N= 10). Potential patients will undergo screening phase within 07 days prior to the first Acalabrutinib dose. Patients who meet the protocol-defined inclusion/exclusion criteria will be prospectively enrolled into the study.

Acalabrutinib capsules 100 mg administered orally twice daily (BID) for 06 cycles, starting from Cycle 1, Day 1, and continuing up to Cycle 6, Day 28; or until study drug discontinuation due to either disease progression or, unacceptable toxicity, or other reasons, whichever occurs earlier.

Acalabrutinib will be provided by the Sponsor to patients in the Treatment Phase. The Sponsor shall also conduct laboratory investigations for safety and efficacy evaluation, including haematology, biochemistry, radiology, and electrocardiography (ECG), as mentioned in the SoA table.

Figure 2: Study Flow



4.1.1 Screening Phase (Visit 1)

Patients, or their Legally Acceptable Representative (LAR), will provide written informed consent before any trial-specific procedures are performed. If the patient and/or LAR are unable to read, an impartial witness should be present during the entire informed consent discussion. During the Screening Phase, eligibility criteria will be reviewed, and a complete clinical evaluation will be performed as specified in the SoA (Table 1). Screening procedures will be performed up to 07 days prior to Cycle 1, Day 1. All baseline disease characteristics will be captured based on the evaluation performed as a part of routine clinical practice. The investigations that are required before the consideration of the patient for Acalabrutinib treatment must have been performed before the first dose (Cycle 1, Day 1). The NGS tests should be performed before the start of the treatment as per SoA (Table 1). Next-generation sequencing will be conducted to understand the genetic profile in Indian settings. Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), trisomy 12 in peripheral blood lymphocytes; TP53 mutation; immunoglobulin variable heavy chain (IGHV) mutational status will be assessed before the start of treatment in CLL/SLL-naïve patients, or CLL/SLL patients who did not have their report. However, MCL patients are Relapsed/Refractory and their previous report data will be used. A six months old report can be considered for both the conditions.

4.1.2 Treatment Phase (Visit 2 To 7)

The Treatment Phase will start from Cycle 1, Day 1 to Cycle 6, Day 28, or until study drug discontinuation due to either disease progression, unacceptable toxicity; or other reasons, whichever occurs earlier. Each cycle of treatment is defined as 28 days of twice-daily Acalabrutinib treatment.

Details of the procedures performed during the Treatment Phase are outlined in the Schedule of Activity table. Patients will be closely monitored for adverse events and other safety evaluations, including laboratory investigations, concomitant medications etc. as provided in SoA table. If disease progression is diagnosed before Day 168, then the patient will discontinue the study drug. The End-of-Treatment Visit evaluations will be completed on the day of progression and patient will enter the safety Follow-up Phase.

4.1.3 End–of–Treatment Visit (EOT)

An End-of-Treatment Visit will be scheduled on Day 170 (Visit 8) of the study. All patients who will complete the Treatment phase will be assessed for EOT. In the event where a patient discontinues the study treatment for any reason listed in Section 7.1 before Day 168, the last visit of the patient will be considered as the End-of-Treatment Visit and the patient will be assessed as per EOT visit.

4.1.4 Follow-Up Phase (End-Of-Study)

The Follow-up Phase will begin once a patient discontinues study drug or completes the Treatment Phase. The follow-up phase will continue until 28 days after last dose, loss to follow up, withdrawal of consent for study participation, or end of the study, whichever occurs earlier. A follow-up will be conducted 28 days after the EOT visit via a phone call. This will be considered as End-of-Study Visit. Every effort should be made to conduct the End-of-Study Visit.

Patients who are observed to receive clinical benefit from Acalabrutinib after completion of treatment phase, may continue to receive Acalabrutinib, if in the opinion of their treating physician they are continuing to derive clinical benefit from continued treatment or have not progressed clinically. The details on “Post-Trial Access” are provided in section 1.2.

For details on treatments given during the study, refer Section 6.1 Treatments Administered.

For details on what is included in the efficacy and safety endpoints, refer Section 3 and 8.

4.2 Scientific rationale for study design

The present study will be conducted to assess the safety and efficacy of Acalabrutinib in the Indian population of CLL/SLL and MCL. The efficacy and safety of Acalabrutinib 100 mg BID dose is established in CLL/SLL and refractory & relapsed MCL patients for 6 cycles (refer Section 2). Hence the present phase IV trial is planned to assess the safety and efficacy of Acalabrutinib 100 mg BID monotherapy for a treatment period of 168 days in Indian patients.

In the combined safety database with Acalabrutinib monotherapy, the commonest adverse events in patients receiving Acalabrutinib monotherapy as a treatment for haematological malignancies are related to blood and lymphatic system disorders, cardiac disorders, nervous system disorders, and gastrointestinal disorders. The current phase IV trial includes a treatment phase of 168 days, which would enable us to detect the incidence of adverse events and the objective response to treatment in an eligible Indian patient population. As the primary objective of the study will be an assessment of safety, the study design is a single arm, prospective open-label one.

The safety analysis (N = 1040) showed that the most common treatment-emergent AEs were anaemia, neutropenia, thrombocytopenia, headache, diarrhoea, bruising, rash, infections, and musculoskeletal pain.

4.3 Justification for dose

The dose used in the current study is based on the locally approved Prescribing Information.

4.4 End of study definition

The end of the study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit or last scheduled procedure shown in the SoA

Refer Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomised to study intervention. Under no circumstances can there be exceptions to this rule.

5.1 Inclusion criteria

Patients are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

1. Men and Women aged 18 yrs or more.

2. Eastern Cooperative Oncology Group (ECOG) performance status of 0,1, or 2

3. Able to receive all outpatient treatments, all laboratory monitoring, and all radiologic evaluations.

4. The following laboratory parameters:

    a. Absolute neutrophil count (ANC) ≥750 cells/µL or ≥500 cells/µL in patients with documented bone marrow involvement, and independent of growth factor support 07 days before the assessment

    b. Platelet count ≥50,000 cells/µL or ≥30,000 cells/µL in patients with documented bone marrow involvement, and without transfusion support 07 days before the assessment

    c. Aspartate transaminase (AST) and Alanine transaminase (ALT) ≤2.0 x ULN

d. Total bilirubin ≤1.5 x ULN

e. Estimated creatinine clearance of ≥30 mL/min

5. Refractory disease defined as achieving less than partial response with the most recent treatment before study entry

6. Provision of signed, written and dated informed consent prior to any study-specific procedures

7. The patients of either CLL or MCL:

a. **CLL patients:**

i. Treatment naïve or ≥1 prior systemic therapy for CLL

ii. Diagnosis of CD20+ CLL that meets published diagnostic criteria (Hallek et al. 2018)

iii. An active disease that meets≥1 of the following iwCLL 2018 criteria for requiring treatment

1) 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 an 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.

2) Massive (i.e., ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.

3) Massive nodes (i.e., ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.

4) Progressive lymphocytosis with an increase of ≥50% over a 2-months period or lymphocyte doubling time (LDT) in <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.

5) Autoimmune complications, including anaemia or thrombocytopenia poorly responsive to corticosteroids.

6) Symptomatic or functional extra-nodal involvement (e.g., skin, kidney, lung, spine).

7) Disease-related symptoms as defined by any of the following:

a) Unintentional weight loss of ≥10% within the previous 06 months.

b) Significant fatigue (i.e., ECOG performance scale 02 or worse; cannot work or unable to perform usual activities).

c) Fever ≥100.5°F or 38.0°C for 02 or more weeks without evidence of infection.

d) Night sweats for ≥1 month without evidence of infection.

b. MCL Patients:

i. Confirmed MCL with translocation t(11;14) (q13;q32) and/or overexpressed cyclin D1

ii. Measurable nodal disease (one or more lesions measuring ≥2 cm in the longest diameter)

iii. Relapsed after, or were refractory to, 1-5 previous treatments

5.2 Exclusion criteria

1. Known prolymphocytic leukaemia, Central Nervous System (CNS) lymphoma or leukaemia; or known history of (or currently suspected) Richter's syndrome

2. Treatment with chemotherapy, external beam radiation therapy, anticancer antibodies, or investigational drug within 30 days of the first dose of study drug

3. Prior radio-conjugated or toxin-conjugated antibody therapy

4. Anticoagulation therapy (e.g., warfarin or equivalent vitamin K antagonists) within 07 days of the first dose of study drug.

5. Major surgery ≤30 days before the first dose of study drug

6. History of stroke or intracranial haemorrhage ≤6 months before the first dose of study drug

7. History of bleeding diathesis

8. Prior exposure to a B-cell lymphoma-2 (Bcl-2) inhibitor or B-cell receptor inhibitor like BTKIs

9. Active Cytomegalovirus (CMV) infection or serologic status reflecting active Hepatitis B or C infection, known history of infection with Human immunodeficiency virus (HIV), or any uncontrolled active systemic infection.

10. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, Congestive Heart Failure, or Myocardial Infarction within 6 months of screening, or

any Class 3 or 4 cardiac diseases as defined by the New York Heart Association Functional Classification, or QTcB >480 msec at screening.

11. Requiring treatment with proton-pump inhibitors (e.g., Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Rabeprazole, or Pantoprazole).

12. Breastfeeding or pregnant.

13. Current life-threatening illness, medical condition, or organ system dysfunction which, in the Investigator's opinion, could have compromised the subject's safety or put the study at risk.

14. Concurrent participation in another therapeutic clinical trial.

5.3 Lifestyle restrictions

Not Applicable

5.4 Screen failures

Screen failures are defined as patients who sign the informed consent form to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and eligibility criteria. The reason/s for screen failure for these patients should be recorded in the electronic Case Report Form (eCRF).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product, comparator, and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to Acalabrutinib.

6.1 Treatments administered

Table 3: Study Treatments

	Treatment
Study treatment name:	Acalabrutinib
Dosage formulation:	Capsule
Route of administration	Per Oral (PO)

Dosing instructions:	The recommended dose is 100 mg (1 capsule) twice daily. Acalabrutinib should be swallowed whole with water at approximately the same time each day. Acalabrutinib can be taken with or without food. The capsule should not be chewed, dissolved or opened.
Packaging and labelling	Study treatment will be provided and labelled in accordance with Good Manufacturing Practice (GMP) Annex 13 and per country regulatory requirement.
Provider	AstraZeneca/ delegate will be providing the Investigational Medicinal Product (IMP) to site.

The recommended dose of Acalabrutinib is 100 mg given PO twice daily for 06 cycles (each cycle is 28 days) until disease progression or unacceptable toxicity. Dose escalation or reduction is not recommended. Dose withholding or discontinuation may be required based on individual safety and tolerability.

6.1.1 Duration of treatment

The Treatment Phase will be from the start of Cycle 1, Day 1 to end of Cycle 6, Day 28, or until study drug discontinuation due to either disease progression or unacceptable toxicity, or other reasons whichever occurs earlier, as listed in Section 7.1. as continue

6.1.2 Administration

The recommended dose of Acalabrutinib is 100 mg (1 capsule) twice daily. Acalabrutinib should be swallowed whole with water at approximately the same time each day. Acalabrutinib can be taken with or without food. The capsule should not be chewed, dissolved, or opened.

6.2 Handling/storage/accountability

Acalabrutinib does not require any special storage conditions.

Only patients enrolled in the study may receive study treatment, and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the Investigator and authorised site staff.

The Investigator, Institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

6.3 Measures to minimise bias: randomisation and blinding

Since the present study is an open-label phase IV trial, blinding and randomisation are not applicable.

6.4 Treatment compliance

Any change from the dosing schedule: dose interruptions, dose reductions, dose discontinuations should be recorded in the eCRF. There should be 100% compliance with the study medication. No drug interruptions and missed doses will be permitted in the study.

The Investigational Product Storage Manager(Investigator/delegate) is responsible for managing the IMP from receipt by the study site until the destruction or return of all unused IMP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IMP.

6.5 Concomitant therapy

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the patient is receiving at the time of enrolment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed below:

- Any investigational anticancer therapy
- Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

  NOTE: Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (e.g., by local surgery or radiotherapy).
- Strong inducers of CYP3A activity (e.g., Phenytoin, Rifampin, Carbamazepine).
- Strong CYP3A inhibitors (e.g., Clarithromycin, Telithromycin, Nefazodone, Itraconazole, Ketoconazole, Atazanavir, Darunavir, Indinavir, Lopinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir).
- Proton pump inhibitors (e.g., Omeprazole, Esomeprazole, Lansoprazole, Dexlansoprazole, Rabeprazole, Or Pantoprazole).

  NOTE: If treatment with an acid-reducing agent is required, consider using an antacid (e.g., calcium carbonate), or an H2-receptor antagonist (e.g., Ranitidine).

6.5.1 Other concomitant treatment/s

Other medication/s other than that described above, which is/are considered necessary for the patient’s safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the electronic Case Report Form.

6.5.2 Rescue medication/s

Rescue medication/s, if required, will be provided by the Investigator as per the Standard of Care. The date and time of rescue medication administration, as well as the name and dosage regimen of the rescue medication, will be recorded

6.6 Dose modification

Dose escalation or reduction are recommended in the study. In addition, there are certain circumstances in which the study drug should be permanently discontinued (refer Appendix C and Section 7).

Acalabrutinib discontinuation will not be required for AEs that are clearly not attributed to study drug (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

7. DISCONTINUATION OF STUDY DRUG

7.1 Discontinuation of study treatment

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

- Patient decision. The patient is at any time free to discontinue treatment without prejudice to further treatment.
- Adverse Event that in the opinion of the Investigator or the Sponsor contraindicates further dosing
- Severe non-compliance to study protocol that, in the opinion of the Investigator or Sponsor, warrants withdrawal, e.g., refusal to adhere to scheduled visits etc.
- Any AE that meets criteria for discontinuation, as defined in Appendix D
- Initiation of alternative anticancer therapy including another investigational agent
- Disease progression as per the Investigator's clinical and imaging assessment.
- Pregnancy or intent to become pregnant.

If the patient is discontinued from the study, the patient will be followed up until the start of subsequent anti-cancer intervention or up to a duration of 28 days, whichever is earlier.

7.2 Withdrawal from the study

A patient may withdraw from the study (e.g., withdraw consent), at any time at his/her own request, without prejudice to further treatment.

A patient who considers withdrawing from the study must be informed by the Investigator that the day of withdrawal will be considered as the end of the study phase for the patient. However, the patient will still have the provision of spontaneous AE reporting.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he/she may request the destruction of any samples taken, and the Investigator must document this in the site study records.

A patient who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up with patients, as medically indicated.

AstraZeneca or its delegate will request Investigators to collect information on patients' vital status (dead or alive; date of death when applicable) at the end of the study from publicly available sources, in accordance with local regulations. Knowledge of the vital status of all patients at the end of the study is crucial for the integrity of the study.

Refer SoA, Table 1, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA, Table 1.

Written informed consent for participation in the study must be obtained before performing any study specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

Documented evidence of CLL/SLL and MCL positive status from previous testing is acceptable, otherwise it has to be assessed at a local laboratory that is experienced/certified in CLL/SLL and MCL testing using an accurate and validated assay.

Women with child bearing potential and male patients with partners of child bearing potential who are sexually active will have to agree to use a highly effective, non-hormonal form of contraception (such as surgical sterilization) or two effective forms of non-hormonal contraception (such as a barrier method of contraception in conjunction with spermicidal jelly) during and for at least 6-months post-study treatment.

Screening tests and evaluations will be performed within 7 days prior to the first study medication administration (dosing). CT or MRI scans will be performed prior to the first study medication administration (dosing). CT or MRI scans are applicable for the patients with lymphadenopathy or organomegaly. Patients with abnormalities of blood parameters without any lymphadenopathy or organomegaly will not undergo CT or MRI scans. Patients who will be undergoing CT, should have baseline and every 3-months reports.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrolment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

The safety assessments during the treatment visit will be performed at the start of each treatment cycle. However, efficacy assessments will be scheduled every three months during the study treatment period and EOT.

The Investigator will ensure that data are recorded in the eCRF.

The Investigator ensures the accuracy, completeness for eCRFs that includes: timeliness of the data recorded and query resolution according to the Clinical Study Agreement. The Investigator will sign the completed eCRFs.

Immediate safety concerns should be immediately discussed with the Sponsor upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened, confirm their eligibility for the trial, or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each patient will not exceed approximately 10 mL/visit. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples

8.1 Efficacy and Safety assessments

8.1.1 Efficacy Assessment

Objective Response

All patients who receive Acalabrutinib capsule 100 mg BID will be evaluated for efficacy once every 03 months during the treatment phase. The following assessments must be performed every three treatment cycles: tumour assessment, ECOG performance status, and partial remission (PR), partial response with lymphocytosis (PR-L) and complete remission (CR).

A characteristic feature of BTK inhibitor is that it may transiently increase the peripheral lymphocyte count while the lymph nodes are shrinking and patients are improving. Some patients were taken off study very early in ibrutinib trials because their lymphocyte count began to go up and it was assumed that they were progressing. The transient lymphocytosis is now understood to be an effect of redistributing parts of the disease into the blood. It is not considered as a sign of disease progression. There is now a response criterion known as PRL, which refers to patients who have a greater than 50% shrinkage of nodal disease and who fulfil all criteria of partial response (PR) except for a persistent lymphocytosis. (Woyach et al., 2014) In the present study the objective response will evaluate PR, PR-L, and CR.

The efficacy endpoint will be objective response, defined as the proportion of patients achieving either a PR or CR per the iwCLL 2018 criteria for CLL/SLL (Hallek et al., 2018) and Lugano classification for NHL for MCL (Cheson et al., 2014) as presented in Table 4 and Table 5, respectively. Efficacy will be based on objective response [Complete Remission (CR) + Partial Remission (PR)] via Computed Tomography (CT) scans or Magnetic Resonance Imaging (MRI).

Table 4: Response (CR and PR) definition after treatment of CLL/SLL patients (Hallek et al., 2018)

Parameter	Complete Remission (CR)	Partial Remission (PR)
Lymph nodes	None ≥1.5 cm	Decrease ≥50% from baseline*
Liver and/or spleen size†	Spleen size <13 cm; liver size normal	Decrease ≥50% from baseline
Constitutional symptoms	None	any
Circulating lymphocyte count	Normal	Decrease ≥50% from baseline
Platelet count	≥100 x 10^9L	≥100 x 10^9/L or increase ≥50% over baseline
Haemoglobin	≥11.0 g/dL (untransfused and without erythropoietin)	≥11.0 g/dL or increase ≥50% over baseline

*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, it is <13 cm. There is no firmly established international consensus of the size of a normal liver; therefore, liver size should be evaluated by imaging and manual palpation

A CT-based Response Assessment Criteria for MCL will be assessed as per Table 5 (Cheson et al., 2014). Patients with abnormalities of blood parameters without any lymphadenopathy or organomegaly will not undergo CT or MRI scans. Patients who will be undergoing CT, should have baseline and every 3-months reports.

Table 5: Response Assessment Criteria for MCL patients

Response and Site	Complete Response	Partial Response
Lymph nodes and extra lymphatic sites	Target nodes/nodal masses must regress to ≤1.5 cm in LDi	≥ 50% decrease in SPD of up to 6 target measurable nodes and extra-nodal sites
	No extra lymphatic sites of disease	When a lesion is too small to measure on CT, assign 5 mm ×5 mm as the default value
		When no longer visible, 0 × 0mm
		For a node >5 mm × 5 mm, but smaller than the normal, use the actual measurement for calculation
Non-measured lesion	Absent	Absent/normal, regressed, but no increase

Response and Site	Complete Response	Partial Response
Organ enlargement	Regress to normal	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None

LDi: longest transverse diameter of a lesion; SPD: sum of the product of the greatest diameters

Patient-Reported Outcome

A health-related quality of life questionnaire i.e., QLQ-C30 Questionnaire will be administered to each subject at screening/visit 1 before the dosing, every three months during the treatment period and at the end of the study. Most of the items in the questionnaire use a "past week" recall period. The patients will be assessed on the functional, symptoms, and global quality of life scale.

8.1.2 Safety assessments

Safety evaluations will include clinical laboratory parameters (haematology and biochemistry), physical examinations, vital sign measurements, ECG monitoring, ECOG performance status, adverse event monitoring, and death, as observed by the Investigator. Based on the previous *in vitro* studies, animal toxicological findings, and human studies with Acalabrutinib, arrhythmias (which includes atrial fibrillation), anaemia, hypertension, bleeding, infections, and second primary malignancies will be closely monitored. Any of the safety monitoring assessments may be performed more frequently, and adverse events should be evaluated by the Investigator according to the standard practice if clinically indicated.

Clinical safety laboratory assessments

The list of clinical safety laboratory tests to be performed are provided in Table 6 and Table 7. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the timing and frequency outlined in the SoA.

The Investigator should assess the available results with regard to clinically relevant abnormalities. The laboratory results should be signed, dated, and retained at the site as source data for laboratory variables.

For information on how AEs based on laboratory tests should be recorded and reported, refer Section 8.2.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) should be appropriately recorded in the eCRF.

The haematology (Table 6), clinical chemistry (Table 7) and urinalysis (routine and microscopy) measurements will be performed at a local laboratory at or near the Investigator site.

A complete blood cell count will be conducted as per SoA (Table 1). It includes white blood cell count, haemoglobin, haematocrit, reticulocyte, platelet count and differential leukocyte count, including both percent and an absolute number of lymphocytes.

Table 6: Haematology

Haematocrit
Haemoglobin
Basophils
Eosinophils
Monocytes
Lymphocytes
Reticulocytes
Absolute Neutrophil Count
Platelet count
Total leucocyte count

Table 7: Clinical chemistry (serum or plasma)

Albumin
Glucose
Amylase
Lipase
Alkaline phosphatase
Lactate dehydrogenase
Alanine aminotransferase
Aspartate aminotransferase
Potassium
Bicarbonate
Sodium
Calcium
Total bilirubin
Chloride
Total protein
Creatinine (creatinine clearance)
Urea or Blood Urea Nitrogen, depending on local practice
Gamma-glutamyl transferase
Magnesium
Haptoglobin
b2-microglobulin

Note: CMV serology, HIV (anti-HIV1 Ab, anti-HIV2 Ab), Hepatitis serology testing will be conducted at the screening that includes hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and HCV antibody.

The local GLP certified laboratory will perform haematology and clinical chemistry tests. Additional analyses may be performed if clinically indicated.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded in the eCRF.

All patients who have any Common Toxicity Criteria (CTC) Grade 3 or 4 laboratory values at the time of completion or discontinuation from study must have further tests performed until the laboratory values have returned to CTC Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

Urine Pregnancy Test

Urine pregnancy tests will be required only for women of childbearing potential. Urine pregnancy tests will be performed at Screening; on Cycle 1 Day 1; on Day 28 of Cycles 1-6; and at the early termination or End of study visit.

Physical examinations

For timing of individual measurements refer to the schedule outlined in (Table 1).

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head, neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal (including spine and extremities), and genital/rectal and neurological systems.

Symptom-directed physical exams, including tumour assessments by palpation, will be done during the treatment period and at the EOT visit.

Lymph nodes: The bi-dimensional diameters of the largest palpable lymph node/s in each of the following sites should be recorded: cervical, axillary, and inguinal. The dimensions of the liver and spleen below their respective costal margins, as assessed by palpation, should also be recorded.

Performance status will be assessed using ECOG performance status.

Vital signs

The timings of assessments for vital signs are provided in Table 1 (SoA). Patients will be monitored with the assessment of vital signs (Blood Pressure, pulse, respiratory rate, and temperature) at screening and at each subsequent visit in the treatment phase. Additional monitoring with the assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated. The date and time of collection and measurement will be recorded in the eCRF.

Electrocardiograms (ECG)

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study. ECGs should be obtained after the patient has been rested in a supine position for at least 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTc value >480 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

All ECGs should be assessed by the Investigator for clinically significant abnormalities. If there is a clinically significant abnormal finding, the Investigator will record it as an AE on the eCRF.

At screening, the mean QTc with Bazett's correction (QTcB = QT/√R) must be <480 msec as per the eligibility criteria of the study.

Chest X-Ray

Patients with signs and symptoms of Pneumonia will be allowed to go for chest X-ray investigation. A symptom directed chest X-ray will be conducted at screening and all subsequent visits during the study duration.

8.2 Collection of adverse events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section. The definitions of an AE or SAE can be found in Appendix B.

All adverse events occurring during the study will be recorded and reported. AEs observed/ elicited by the Physician/ Site Investigator during physical examination and vital signs recording or derived from safety assessments; reported by patients during site visits will be documented in the source notes and in the AE log of eCRF. AEs can be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow-up AEs, refer Section 8.2.3.

The nature of adverse events will be recorded in the eCRF. This will include reporting of duration, severity, seriousness, causality/ relationship with the study drug, action taken in terms of any medication or any other intervention and outcome of the event. These assessments will be performed by the Physician/Site Investigator. In the event an AE is being assessed in real time and a Co-Investigator (other than the Site Investigator) is evaluating the event, then the final conclusion on the nature of AE can be revised based on the judgement arrived at by the Site Investigator.

The events will be coded by the data management team using Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 or above.

8.2.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.2.2 Time period and frequency for collecting AE and SAE information

Adverse events and SAEs will be collected from the time of signature of informed consent, throughout the treatment period (168 days), End of study visit (Day 170) and including the follow-up period (28 days after the last dose of study drug) in patients who discontinue before 168 days.

If a patient discontinues from study drug for reasons other than disease progression, drug-related SAEs must be captured until the patient is initiated on an alternate intervention or up to 28 days, whichever is earlier.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify the Sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix B.

8.2.3 Follow-up of AEs and SAEs

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

AEs that are unresolved at the patient's last visit in the study must be followed up by the Investigator for as long as medically indicated.

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

8.2.4 Adverse event data collection

'The following variables will be collected for each AE;

- AE (verbatim).
- The date and time when the AE started and stopped.
- CTCAE grade 3 or more: whether the AE is serious or not
- Investigator's causality rating against the Investigational Product (yes or no).
- Action taken with regards to Investigational Product(s).
- Select the appropriate as required: AE caused patient's withdrawal from study (yes or no).
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Reason for AE becoming serious
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication/s

8.2.5 Causality collection

The Investigator will assess the causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, a causal relationship will also be assessed for other medication/s and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes.'

A guide to the interpretation of the causality questions is found in Appendix B to the Clinical Study Protocol.

8.2.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to open question/s from the study site staff: or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known, and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis, and each sign or symptom will be recorded separately.

8.2.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol-mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should, therefore, only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE, and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator will use the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new, or progression of existing metastasis to primary cancer under study should

be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

New cancers

The development of new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the study drug and have been identified after the patient's inclusion in this study.

Deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly the result of disease progression should be reported to the study monitor at the next monitoring visit and should be documented in the eCRF but should not be reported as an SAE.
- Where death is not due (or not clearly due) to Progressive Disease (PD) under study, the AE causing the death must be reported to the study monitor as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem maybe helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to AstraZeneca or its representative within the usual timeframes.

8.3 Safety reporting and medical management

8.3.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs during the study, the Investigator or other site personnel should inform the appropriate AstraZeneca representatives within one day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The Investigator will also inform the chairperson of Institutional Ethics Committee (IEC) and Licensing Authority (LA) i.e., Drugs Controller General (India), about the SAE within **24 hours**. In addition, the Investigator will provide a detailed report on the SAE after due analysis to the IEC chairperson, the Head of Institute and the LA within **14 calendar days** of its occurrence.

The IEC will forward its report on the SAE along with its opinion on the financial compensation, if any, (to be paid by Sponsor) within **30 calendar days** of occurrence of SAE to LA. The timeline for the order from Licensing Authority on the quantum of compensation to be paid will be within **150 calendar days** of occurrence of SAE or receiving report. Sponsor will pay the compensation to subject within **30 calendar days** of order from LA.

In case the Investigator fails to report any SAE within stipulated period, he shall furnish the reason for the delay to the satisfaction of the Licensing Authority along with the SAE report.

The designated AstraZeneca representative will co-ordinate with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 01 calendar day** of the initial receipt for fatal and life-threatening events **and within 05 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigator or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff on how to proceed.

Investigators or other site personnel will then send relevant eCRF modules by fax to the designated AstraZeneca representative. For further guidance on the definition of an SAE, please refer to Appendix B of the Clinical Study Protocol.

8.3.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the patient has received the study drug
- Pregnancies in the partner of male patients.

  If pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

  Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.2.1 Maternal exposure

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel will inform the appropriate AstraZeneca representatives within one day, i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will co-ordinate with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 01 or 05 calendar days for SAEs (refer Section 8.3.1) and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

8.3.3 Overdose

The use of Acalabrutinib in excess dose than specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of an overdose of Acalabrutinib, and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose Case Report Form module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel must inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with an SAE, the standard reporting timelines apply, refer Section 8.2.2. For other overdoses, reporting must occur within 30 days.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

No formal hypothesis testing will be conducted.

9.2 Sample size determination

The primary endpoint of the trial is to demonstrate the safety profile of Acalabrutinib in routine clinical practice as assessed by the incidence of adverse events (AEs) (Serious and Non-serious) observed during the trial. As per the Health Authority requirement, the total sample size of the study is approximately 100.

The table below illustrates the estimated incidence and the precision of the estimate that could be expected for a variety of sample sizes (indicative of possible subgroup and total sample) for an observed numbered of patients with a particular event.

Table 8: Estimated Incidence and Precision

	Estimated incidence/precision*				
Number of observed events	n=10	n=20	n=50	n=90	n=100
0	0.0% (0.00%, 30.85%)	0.0% (0.00%, 16.84%)	0.0% (0.00%, 7.11%)	0.0% (0.00%, 4.02%)	0.0% (0.00%, 3.62%)
1	10.0% (0.25%, 44.50%)	5.0% (0.13%, 24.87%)	2.0% (0.05%, 10.65%)	1.1% (0.03%, 6.04%)	1.0% (0.03%, 5.45%)
2	20.0% (2.52%, 55.61%)	10.0% (1.23%, 31.70%)	4.0% (0.49%, 13.71%)	2.2% (0.27%, 7.80%)	2.0% (0.24%, 7.04%)
3	30.0% (6.67%, 65.25%)	15.0% (3.21%, 37.89%)	6.0% (1.25%, 16.55%)	3.3% (0.69%, 9.43%)	3.0% (0.62%, 8.52%)
4	40.0% (12.16%, 73.76%)	20.0% (5.73%, 43.66%)	8.0% (2.22%, 19.23%)	4.4% (1.22%, 10.99%)	4.0% (1.10%, 9.93%)
10	100.0% (69.15%, 100%)	50.0% (27.20%, 72.80%)	20.0% (10.03%, 33.72%)	11.1% (5.46%, 19.49%)	10.0% (4.90%, 17.62%)
20		100.0% (83.16%, 100%)	40.0% (26.41%, 54.82%)	22.2% (14.13%, 32.21%)	20.0% (12.67%, 29.18%)
30			60.0% (45.18%, 73.59%)	33.3% (23.74%, 44.05%)	30.0% (21.24%, 39.98%)
40			80.0% (66.28%, 89.97%)	44.4% (33.96%, 55.30%)	40.0% (30.33%, 50.28%)
50			100.0% (92.89%, 100%)	55.6% (44.70%, 66.04%)	50.0% (39.83%, 60.17%)

* Clopper-Pearson exact 95% confidence interval

9.3 Populations for analyses

The Full Analysis Set (FAS) will consist of all enrolled patients who received at least one dose of Acalabrutinib. The FAS will be used for all analyses of safety and efficacy.

9.4 Statistical analysis

Categorical data will be summarized using frequencies and percentages. Continuous data will be summarized with descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals will be supplied for key proportions (including objective response rate) using the Clopper-Pearson method. The details will be provided into statistical analysis plan.

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11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, Informed Consent Document (ICD), Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

A 2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit a complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for a year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorised representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, ICH-GCP guidelines, and New Drugs & Clinical Trials Rules, 2019 (India)

where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study with a mention of the date and time of the same. The authorised person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study as applicable.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorised representative.

A 4 Data protection

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities, without his/her identity being revealed

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com, and CTRI (http://ctri.nic.in/Clinicaltrials), as will the summary of the study results when they are available. The clinical trial summary of study results may also be available on other websites according to the regulations of India in which the study is conducted.

A 7 Data quality assurance

All patient data pertaining to the study will be recorded in an eCRF and transferred to the Sponsor or designee electronically at the end of the study. The Investigator will be responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Clinical Research Organization (CRO) or designee is responsible for the data management of this study, including the quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the e-CRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 9 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support the publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors' authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse event

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (e.g., an abnormal laboratory finding), symptom (for example, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definition of serious adverse event

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

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused the death (e.g., hepatitis that resolved without hepatic failure).

B 4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

B 6 For oncology studies, the following may be used instead

The grading scales found in the revised National Cancer Institute CTCAE version 5.0 or above will be utilised for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When assessing causality, the following factors must be considered when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug:

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host, or environmental factors.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

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

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

The causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data, including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related.'

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study, a medication error is an unintended failure or mistake in the treatment process for the study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not a lack of efficacy of the drug, but rather a human or process-related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances that could have led to an error were recognized

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g., medication dispensed incorrectly
- Drug not administered as indicated, for example, wrong dose/frequency/duration
- Drug not stored as instructed

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Participant accidentally missed drug dose(s), e.g., forgot to take medication

- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication/s, or standard of care medication in open-label studies, even if an AZ product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Recommended Treatment Modifications for Acalabrutinib and Management Recommendations

Recommended dose modifications of Acalabrutinib for Grade ≥3 adverse reactions are provided in Table 9.

The administration of Acalabrutinib must be temporarily interrupted to manage a Grade ≥3 non-haematological treatment-related adverse reaction, Grade 3 thrombocytopenia with significant bleeding, Grade 4 thrombocytopenia, or Grade 4 neutropenia lasting longer than 07 days. Upon resolution of the adverse reaction to Grade 1 or baseline (recovery), administration of Acalabrutinib must be restarted as recommended in Table 9.

Table 9: Recommended Dose Adjustments for Adverse Reactions*

Adverse Reaction Occurrence	**Dose Modification** (Starting dose = 100 mg twice daily)
1st and 2nd	Restart at 100 mg twice daily
3rd	Restart at 100 mg daily
4th	Discontinue Acalabrutinib

*Adverse reactions graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.

Appendix D: EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): 31 _____

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix E: Abbreviations

Abbreviation or special term	Explanation
AE	Adverse Event
AESI	AEs of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ARA-C	Cytosine Arabinoside
BCR	B cell antigen receptor
BID	Twice daily
BP	Blood Pressure
BTK	Bruton Tyrosine Kinase
BUN	Blood Urea Nitrogen
CDSCO	Central Drugs Standard Control Organisation
CHOP	Cyclophosphamide, Hydroxy-daunorubicin, Oncovin, and Prednisone
CLL	Chronic Lymphocytic Leukaemia
CMV	Cytomegalovirus
CNS	Central Nervous System
CONSORT	Consolidated Standards of Reporting Trials
eCRF	electronic Case Report Form
CR	Complete Remission
CSA	Clinical Study Agreement
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	Discontinuation of investigational product due to Adverse Event
DNA	Deoxyribonucleic Acid
DoR	Duration of Response
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
EOS	End of Study
GGT	Gamma-glutamyl transferase
GMP	Good Manufacturing Practice
Hb	Haemoglobin

Abbreviation or special term	Explanation
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IEC	Institutional Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IGHV	Immunoglobulin Variable Heavy Chain
iwCLL	International Workshop on Chronic Lymphocytic Leukaemia
LAR	Legally Acceptable Representative
LDT	Lymphocyte Doubling Time
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NGS	Next-Generation Sequencing
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
PD	Progressive Disease
PFS	Progression-Free Survival
PO	Per Oral
PI	Principal Investigator
PR	Partial Remission
PRL	Partial Response with Treatment-Induced Lymphocytosis
PRO	Patient-reported outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SEC	Scientific Expert Committee
SLL	Small Lymphocytic Lymphoma
SoA	Schedule of Activities
SPD	Sum of The Product Of The Greatest Diameters

ASTRAZENECA SIGNATURE(S)

A prospective, multi-centre, Phase-IV clinical trial to assess the safety and efficacy of Acalabrutinib capsules in Indian adult patients with chronic lymphocytic leukaemia and relapsed and refractory mantle cell lymphoma

This Clinical Study Protocol has been subjected to an internal AstraZeneca review

I agree to the terms of this Study protocol.

AstraZeneca representative

PPD

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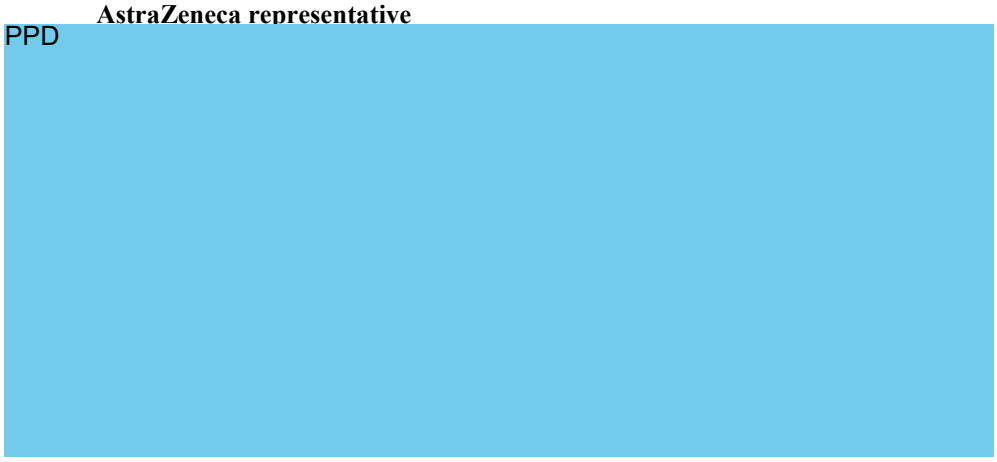

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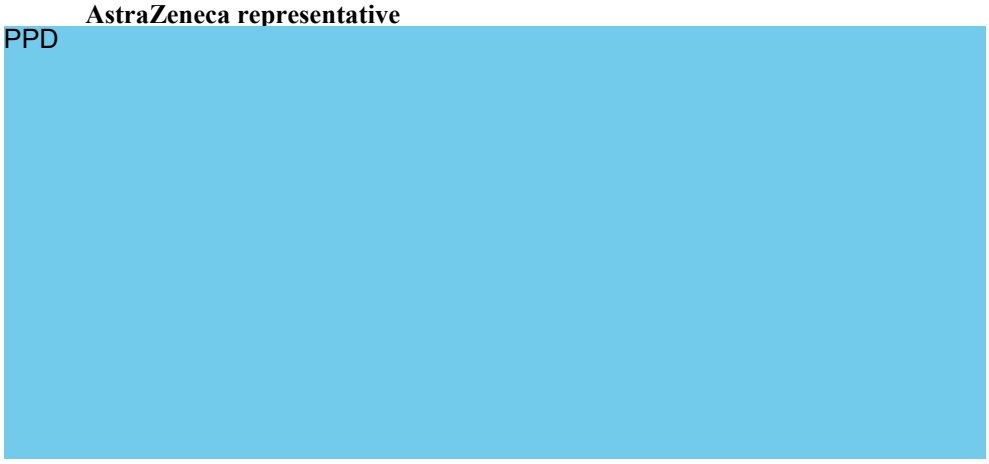

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