LYM 155

Single Arm, Phase II Study of Acalabrutinib as Post-Autologous Blood or Marrow Transplant (BMT) Maintenance Therapy in Subjects with Mantle Cell Lymphoma

SARAH CANNON DEVELOPMENT INNOVATIONS STUDY NUMBER:	LYM 155
STUDY DRUG:	Acalabrutinib
ACERTA PHARMA PROTOCOL NUMBER:	ESR-18-13673
SPONSOR:	Sarah Cannon Development Innovations, LLC 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203 844-710-6157 CANN.InnovationsMedical@sarahcannon.com
STUDY CHAIR:	Michael Tees, MD Sarah Cannon Research Institute at Colorado Blood Institute (CBCI) at HealthOne's Presbyterian/St. Luke Medical Center 1721 East 19th Ave, Suites 200 & 300 Denver, CO 80218 720-754-4800
DATE FINAL:	24 July 2019
AMENDMENT 1	30 March 2020
AMENDMENT 2	22 December 2020
AMENDMENT 3	29 September 2023

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Clinical Study Statement of Compliance

LYM 155

Single Arm, Phase II Study of Acalabrutinib as Post-Autologous Blood or Marrow Transplant (BMT) Maintenance Therapy in Subjects with Mantle Cell Lymphoma

This clinical study shall be conducted in compliance with the protocol, as referenced herein, and all applicable local, national, and international regulatory requirements to include, but not be limited to:

- **International Council for Harmonisation (ICH) Guidelines on Good Clinical Practice (GCP)**
- **Ethical principles that have their origins in the Declaration of Helsinki**
- **Food and Drug Administration (FDA) Code of Federal Regulation (CFR):**
  - **Title 21CFR Part 50 & 45 CFR Part 46, Protection of Human Subjects**
  - **Title 21CFR Part 54, Financial Disclosure by Clinical Investigators**
  - **Title 21CFR Part 56, Institutional Review Boards (IRBs)**
  - **Title 21CFR Part 312, Investigational New Drug Application**
  - **Title 45 CFR Parts 160, 162, and 164, Health Insurance Portability and Accountability Act (HIPAA)**

As the Study Chair and/or Principal Investigator, I understand that my signature on the protocol constitutes my agreement and understanding of my responsibilities to conduct the clinical study in accordance with the protocol and applicable regulations. Furthermore, it constitutes my understanding and agreement that any changes initiated by myself, without prior agreement in writing from the Sponsor, shall be defined as a deviation from the protocol, and shall be formally documented as such.

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Clinical Study Protocol Approval Page

Single Arm, Phase II Study of Acalabrutinib as Post-Autologous Blood or Marrow Transplant (BMT) Maintenance Therapy in Subjects with Mantle Cell Lymphoma

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Study Chair	**Study Chair Signature**	**Date**
Michael Tees, MD Sarah Cannon Research Institute at Colorado Blood Institute (CBCI) at HealthOne's Presbyterian/St. Luke Medical Center 1721 East 19th Ave, Suites 200 & 300 Denver, CO 80218 720-754-4800		

Sarah Cannon Development Innovations, LLC	**Sarah Cannon Development Innovations, LLC Representative Signature**	**Date**
Vice President, Development Innovations Sarah Cannon Development Innovations 1100 Dr. Martin L. King Jr. Blvd. Suite 800 Nashville, TN 37203		

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Clinical Study Principal Investigator Signature Form

Single Arm, Phase II Study of Acalabrutinib as Post-Autologous Blood or Marrow Transplant (BMT) Maintenance Therapy in Subjects with Mantle Cell Lymphoma

INNOVATIONS STUDY NUMBER:	LYM 155
DATE FINAL:	24 July 2019
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By signing this protocol acceptance page, I confirm I have read, understand, and agree to conduct the study in accordance with the current protocol.

_____	_____	_____
Principal Investigator Name (Please Print)	**Principal Investigator Signature**	**Date**

Please retain a copy of this page for your study files and return the original signed and dated form to:

Sarah Cannon Development Innovations, LLC
1100 Dr. Martin L. King Jr. Blvd., Suite 800
Attention: LYM 155 Study Team
Nashville, TN 37203

LYM 155 Summary of Changes

AMENDMENT NUMBER: 3.0 **AMENDMENT DATE:** 29 September 2023

Additions are noted by **bolding**. Deletions are noted by ~~cross outs~~.

Title Page, Clinical Study Protocol Approval Page, and Contact Information

Study Chair transitioned from Ian Flinn, MD, PhD, to Michael Tees, MD.

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Contact Information

Regulatory email updated.

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Synopsis

Define the conversion rate from minimal residual disease positive (MRD+) to MRD negative (MRD-) during therapy **for up to 2 years post-BMT**

Beginning at Day +100 (±7 days) post-BMT, subjects will receive **129**~~100~~ mg acalabrutinib twice daily (BID) until they reach 2 years post-BMT.

Acalabrutinib **129**~~100~~ mg will be self-administered orally BID for up to 2 years **(approximately 22 cycles)** on a 28-day cycle ~~(approximately 22 cycles).~~

Synopsis and Section 3.2

5. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing **tablets**~~capsules~~ without difficulty.

Synopsis and Section 3.3

~~14. Requires treatment with proton-pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton-pump inhibitors who switch to histamine 2-receptor antagonists or antacids are eligible for enrollment to this study.~~

20. The inability to swallow **tablets**~~capsules~~.

Section 1.4.2

~~Acalabrutinib absorption may be lower in individuals being treated with proton-pump inhibitors, histamine 2 (H2) receptor antagonists, or antacids.~~

Section 1.6

In this study, we propose the use of acalabrutinib **129**~~100~~ mg PO BID as maintenance therapy post-BMT to prolong PFS.

Section 5

Subjects will self-administer **129**~~100~~ mg acalabrutinib BID until they reach 2 years post-BMT (approximately 22 cycles).

Figure 1
Subjects will self-administer acalabrutinib **129**~~100~~ mg BID on a 28-day cycle.

Section 5.1

Acalabrutinib **129**~~100~~ mg will be self-administered orally BID on a 28-day schedule, with or without food, until the patient has reached approximately 2 years post-BMT.

Section 5.3

~~The effect of agents that reduce gastric acidity (i.e., proton-pump inhibitors, or antacids) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this study indicate that subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and after taking acalabrutinib. Use of omeprazole, esomeprazole, lansoprazole or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the Investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib.~~

~~Although the effect of H2-receptor antagonists (e.g. famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.~~

Section 6.3

- Complete blood count (CBC)**,** ~~and~~ clinical chemistry panel**, and coagulation testing**

Section 6.4.1, Section 6.4.2, Section 6.4.3, and Section 6.4.4

- Treatment with acalabrutinib **129**~~100~~ mg PO BID

Section 6.5.5

Coagulation testing will include PT/INR or aPTT.

Section 7

7.1 Acalabrutinib

Investigational Product	Dosage Form and Strength	Manufacturer
Acalabrutinib	**129**~~100~~ mg **tablets**~~capsules~~	Acerta Pharma

7.2 Acalabrutinib Treatment Duration

Acalabrutinib **tablets**~~capsules~~ will be self-administered BID approximately every 12 hours. The **tablets**~~capsules~~ should be swallowed intact with approximately 1 cup of water. **Patients should not chew the tablets and should try to swallow tablets whole.** ~~Patients should not attempt to open capsules or dissolve them in water.~~

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been >3 hours, the dose should not be taken and the patient should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

~~Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 5.3.~~

7.2.1 Labeling, Packaging, and Supply of Acalabrutinib

The investigational product, acalabrutinib maleate tablet, is supplied as an orange film-coated tablet containing 129 mg of acalabrutinib maleate (equivalent to 100 mg of acalabrutinib) drug substance.

Each tablet also contains the following compendial inactive ingredients: mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and sodium stearyl fumarate. The tablet coating contains hypromellose, copovidone, titanium dioxide, polyethylene glycol, caprylic/capric triglyceride, yellow iron oxide, and red iron oxide.~~Acalabrutinib is supplied as yellow and blue, opaque hard gelatin capsules filled with 100 mg of active ingredient. Each capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose (which is composed of microcrystalline cellulose and colloidal silicon dioxide), partially pregelatinized starch, sodium starch glycolate, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide and indigotine (FD&C Blue 2).~~

~~Acalabrutinib will be provided in white, high-density polyethylene bottles. The recommended storage condition for acalabrutinib capsules is below 30°C (86°F).~~**Acalabrutinib maleate tablets are packed in white, high-density polyethylene (HDPE) bottles containing a silica gel desiccant and should be stored according to the storage conditions as indicated on the label. The recommended storage condition for acalabrutinib maleate tablets is below 30°C (86°F).**

Section 7.4

The subject will be instructed to bring the diary and any remaining **tablets**~~capsules~~ to the clinic at his/her next visit. The study staff will review the diary and ask the subject if all the **tablets**~~capsules~~ were administered. Any remaining or returned **tablets**~~capsules~~ will be counted and documented. Returned **tablets**~~capsules~~ must not be redispensed to another subject.

Table 1 Acalabrutinib Dose Reduction Options

Starting Dose	1st Dose Reduction	2nd Dose Reduction
129~~100~~ mg BID	**129~~100~~** mg QD	discontinue

Section 8.1

The maximum dose of acalabrutinib is **129~~100~~** mg BID.

Section 8.2

If the acalabrutinib dose should be reduced and the subject is receiving acalabrutinib **129~~100~~** mg QD, acalabrutinib should be discontinued.

Appendix D: Schedule of Assessments

Coagulation testing[u]

129~~100~~ mg twice daily continuously for 2 years post-BMT (~22 cycles).

Appendix D: Schedule of Assessments footnote u

u Coagulation testing will include PT/INR or aPTT.

LYM 155 PROTOCOL SYNOPSIS

Title of Study:	Single Arm, Phase II Study of Acalabrutinib as Post-Autologous Blood or Marrow Transplant (BMT) Maintenance Therapy in Subjects with Mantle Cell Lymphoma	
Innovations Study Number:	LYM 155	
Sponsor:	Sarah Cannon Development Innovations, LLC	
Study Duration:	The total duration of the study is planned to be approximately 7 years (2 years for recruitment).	**Phase of Study:** II
Number of Study Centers:	This study will be conducted at approximately 10 sites in the United States.	
Number of Patients:	Approximately 50 patients are planned to be enrolled in this study.	
Objectives:	**Primary Objective** The primary objective of this study is to: • Determine the progression-free survival (PFS) rate of subjects who received at least one dose of acalabrutinib and are alive and free of disease progression or relapse at 2 years post-blood or marrow transplant (BMT). **Secondary Objectives** The secondary objectives of this study are to: • Define the conversion rate from minimal residual disease positive (MRD^+) to MRD negative (MRD^-) during therapy for up to 2 years post-BMT • Assess how MRD correlates with PFS • Assess the incidence of adverse events (AEs) **Exploratory Objectives** The exploratory objectives of this study are to: • Determine how mutations correlate with disease relapse using next-generation sequencing • Determine the MRD correlation of bone marrow compared to blood	
Study Design:	This is a single arm, multi-center, Phase II study of subjects with mantle cell lymphoma (MCL) who will receive acalabrutinib as maintenance therapy post-BMT. The BMT is not considered part of this study. Beginning at Day +100 (±7 days) post-BMT, subjects will receive 129 mg acalabrutinib twice daily (BID) until they reach 2 years post-BMT. All subjects will be followed for up to 5 years post-BMT for progression-free survival.	
Study Drug, Dose, and Mode of Administration:	Acalabrutinib 129 mg will be self-administered orally BID for up to 2 years (approximately 22 cycles) on a 28-day cycle. Acalabrutinib will be self-administered until disease progression, unacceptable toxicity, or the subject discontinues treatment for any other reason.	
Inclusion Criteria for Initial Enrollment (Screening #1) :	1. Written informed consent according to local guidelines, signed by the subject or by a legal guardian prior to the performance of any study-related procedures. 2. Men and women ≥18 years-of-age. 3. A diagnosis of MCL confirmed by one of the following: – t(11;14) detected by fluorescence in situ hybridization (FISH), conventional cytogenetics, or other molecular evaluation – expression of cyclin D1 confirmed by immunohistochemistry 4. Subject must have completed induction chemotherapy and plan to and be eligible to receive their first BMT per standard of care 5. Availability of an archival paraffin-embedded tumor block for MRD testing	

	6. The Investigator anticipates that the subject will meet the appropriate lab requirements listed in Screening #2 by Day 100 7. Patients who received prior therapy with a Bruton's tyrosine kinase (BTK) inhibitor are eligible to enroll.
Inclusion Criteria after BMT, Prior to Day 100 (Screening #2)	1. Adequate organ system functions defined as: – Absolute neutrophil count ≥1,000/mm^3. – Platelet count ≥75,000/mm^3. Platelet infusions to meet eligibility criteria are not allowed within 3 days of study enrollment. – Calculated creatinine clearance (CrCl) ≥30 mL/min as calculated by the Cockcroft-Gault method. $\frac{\text{Estimated CrCl (glomerular filtration rate)} = (140\text{-age [years]}) \times (\text{weight [kg]}) \times F^a}{(72 \times \text{serum creatinine [mg/dL]})}$ [a] where F = 0.85 for females and F = 1 for males – Total bilirubin ≤1.5 x the upper limit of normal (ULN) (except for previously documented Gilbert's syndrome) – Alanine aminotransferase/aspartate aminotransferase ≤2.5 x ULN 2. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 3. Subjects who did not receive an anti-cancer therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) during the time between their transplant and the start of study therapy. Subjects must have recovered (e.g. Grade ≤1 or baseline) from AEs associated with prior cancer therapy. Note: Subjects with Grade ≤2 neuropathy or Grade ≤2 alopecia are an exception to the latter criterion and may qualify for the study. 4. Women of childbearing potential (WoCBP) who are sexually active with male partners must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib. For male subjects with a pregnant or non-pregnant WoCBP partner, no contraception measures are required. A WoCBP must have a negative pregnancy test (urine or serum) at the time of screening and 72 hours before starting the study drug or have evidence of non-childbearing potential by fulfilling one of the following criteria: – Post-menopausal women, defined as either women aged >50 years and amenorrheic for ≥12 months following cessation of all exogenous hormonal treatments or women <50 years old who have been amenorrheic for ≥12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the post-menopausal range for the institution. – Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation. – Medically confirmed, irreversible premature ovarian failure. 5. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing tablets without difficulty. 6. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

Exclusion Criteria :	1. Subjects who have relapsed or progressed at any time prior to BMT 2. Subjects with known mutations that confer resistance to a BTK inhibitor. 3. Confirmed clinical disease progression since the time of BMT 4. Prior malignancy (or any other malignancy requiring active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥2 years or that will not limit survival to <2 years. The exceptions are: – Subjects treated with curative intent <2 years prior to enrollment and have a low probability of recurrence. 5. Clinically 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 disease as defined by the New York Heart Association Functional Classification (Appendix B). 6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass. 7. Known history of infection with human immunodeficiency virus (HIV) or any uncontrolled active systemic bacterial, fungal, parasitic or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of infection progression are present. 8. Known history of drug-specific hypersensitivity or anaphylaxis to study drug (including active product or excipient components). 9. Active bleeding or history of bleeding diathesis (e.g., hemophilia or von Willebrand disease). 10. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. 11. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer (see Appendix G). 12. Requires or is receiving anticoagulation treatment with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug. 13. Prothrombin time (PT)/international normalized ratio (INR) or activated partial thromboplastin time (aPTT) >2 x ULN (in the absence of lupus anticoagulant). 14. History of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug. 15. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug. 16. Hepatitis B or C serologic status: subjects who are hepatitis B core antibody (anti-HBc) positive and who are hepatitis B surface antigen (HbsAg) negative will need to have a negative polymerase chain reaction (PCR) result. Those who are HbsAg positive or hepatitis B PCR positive will be excluded. Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.

	17. Breastfeeding or pregnant. 18. Concurrent participation in another therapeutic clinical trial. 19. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol. 20. The inability to swallow tablets.
Statistical Methodology:	The primary endpoint is the percentage of subjects who are alive and free of disease progression or relapse at 2-years post-BMT. A sample size of 45 subjects produces a two-sided 95% confidence interval of 65%-95% when the observed percentage is 80%. To account for a 10% non-evaluable rate, the total sample size will be 50 patients.

LYM 155 CONTACT INFORMATION

Sponsor **Contact Information:**	Sarah Cannon Development Innovations 1100 Dr. Martin Luther King Jr. Blvd. Suite 800 Nashville, TN 37203 844-710-6157 CANN.InnovationsMedical@sarahcannon.com
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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
autoSCT	Autologous stem cell transplant
BID	Twice per day (dosing)
BM	Bone marrow (or bortezomib maintenance, depending on context)
BMT	Blood or marrow transplant
BTK	Bruton's tyrosine kinase
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CR	Complete response
CT	Computed tomography
CYP	Cytochrome p450
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose positron emission tomography
GCP	Good Clinical Practice
H2	Histamine 2
HBc	Hepatitis B core antibody
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPPA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
Innovations	Sarah Cannon Development Innovations
IRB	Institutional Review Board
IVIG	Intravenous immunoglobulin
MCL	Mantle cell lymphoma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next-generation sequencing
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival

PHI	Protected health information
PI	Principal Investigator
PML	Progressive multifocal leukoencephalopahthy
PR	Partial response
QD	Once per day (dosing)
RECIL	Response Evaluation Criteria in Lymphoma
R/R	Relapsed/refractory
SAE	Serious adverse event
SAR	Suspected adverse reaction
SD	Stable disease
SUSAR	Suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
WoCBP	Women of child bearing potential

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1. INTRODUCTION

1.1 Background

Mantle cell lymphoma (MCL) is one of approximately 100 different types of non-Hodgkin's lymphoma (NHL) and represents about 6% of new cases of NHL in the United States. Mantle cell lymphoma results from a malignant transformation of B lymphocytes in the outer edge of a lymph node follicle (the mantle zone). A minority of subjects (10% to 15%) are diagnosed with indolent disease and may not need therapy for several years; however, due to the aggressive and heterogeneous nature of MCL, the majority of subjects with MCL are diagnosed with advanced stage disease that requires immediate, diverse and aggressive courses of therapy to improve the outcome of the disease.

Younger patients with MCL, those ≤65 years of age, are often treated with several rituximab plus chemotherapy combinations followed by a blood or bone marrow transplant (BMT). The addition of BMT to the treatment regimen is a critical factor to prolong the duration of first complete remission (CR1). There has been significant progress in the development of novel agents for MCL, including the recent approvals of acalabrutinib, bortezomib, lenalidomide, and ibrutinib. Unfortunately, MCL still remains an incurable disease and the benefit of combination chemotherapy followed by BMT, is often temporary as patients experience disease progression (PD) and mortality.

This underscores the need for novel chemotherapy combinations as well as additional maintenance therapy strategies to prevent relapse post-BMT in patients with MCL.

1.2 Relevance of Minimal Residual Disease

Traditionally, the most important predictor of long-term remission after treatment in patients has been the achievement of complete response (CR). However, with the use of more sensitive polymerase chain reaction (PCR)-based/analytical techniques such as flow cytometry and next generation sequencing (NGS), many patients who achieve CR are found to have low-level disease in the absence of clinical signs or symptoms. This is called minimal residual disease (MRD). Several studies have reported MRD as a stronger predictor of progression-free survival (PFS) and overall survival (OS) than conventional CR; therefore, new trial designs favor MRD negativity (MRD-) rate as the primary endpoint over conventional CR rates.

In three published studies, MRD^- rates post-transplant have been analyzed with significant results, ranging from 22% to 58% of MCL patients achieving MRD- status before transplant and improving to 53% to 93% MRD^- status post-transplant (Brugger et al 2004, Armand et al 2016, Kolstad et al 2016).

Given that several studies have now shown MRD status to be predictive of outcome across the board, MRD- is expected to become a key endpoint in future MCL trials (Eskelund et al 2016).

1.3 Maintenance Therapy for Mantle Cell Lymphoma

Disease relapse is the number one cause of post-BMT therapy failure and mortality in subjects with MCL. This presents the need for additional studies looking at the prevention of post-BMT therapy failure through novel maintenance strategies. Studies of rituximab maintenance have resulted in improved PFS and OS among subjects with MCL (Damon et al 2009, Dietrich et al

2014, Graf et al 2015, Kaplan et al 2015, Kaplan et al 2018, Le Gouill et al 2017). Dietrich et al report a median time from autologous stem cell transplant (autoSCT) to relapse of 20 months (range: 0.4 to 117 months) in patients who either underwent autoSCT as first-line therapy, received rituximab and high-dose ARA-C, or had refractory disease prior to autoSCT. In the relapse group, 33% experienced PD within the first year post-autoSCT, whereas only 6% of patients relapsed >5 years post-autoSCT. Le Gouill et al. found that patients who received rituximab maintenance post-autologous transplant had a 4-year PFS rate of 83% (95% confidence interval [CI], 73 to 88) compared to 64% (95% CI, 55 to 73) in those who did not receive treatment post-transplant. In a study by Damon et al 2009 analysing the Cancer and Leukemia Group B (CALGB) 59909 regimen of high-dose chemotherapy and autoSCT with rituximab maintenance for newly diagnosed MCL, the authors reported a 2-year PFS rate of 76% (95% CI, 64%-85%) and a 5-year PFS rate of 56% (95% CI, 43%-68%). Utilizing the same CALGB 59909 treatment regimen of Damon et al, Kaplan et al randomized patients to receive either bortezomib maintenance (BM) or consolidation (BC) post-rituximab. Median PFS was significantly greater than the null hypothesis (4 years) for both arms, with 5-year PFS rates of 70% (55-81%) for BM and 69% (54-80%) for BC and 8-year PFS estimates of 77% (95% CI 66-90%) for BM and 58% (95% CI 44-75%) for BC. However, due to adverse events (AEs), BM is almost never used.

Acalabrutinib is a novel Bruton's tyrosine kinase (BTK) inhibitor that has shown positive results in lymphoma and may have fewer off-target effects compared to ibrutinib. Furthermore, acalabrutinib monotherapy increased PFS and OS in relapsed or refractory (R/R) MCL while maintaining a favorable safety profile (Wang et al 2018). Therefore, given acalabrutinib's increased efficacy compared to rituximab, acalabrutinib may prove to be a better maintenance therapy.

1.4 Acalabrutinib

Acalabrutinib, a selective, irreversible small molecule inhibitor of BTK, is approved for the treatment of adult patients with MCL who have received at least 1 prior therapy.

1.4.1 Mechanism of Action

Acalabrutinib inactivates BTK by forming a covalent bond with a cysteine residue in the kinase active site in vitro and in vivo. This leads to inhibition of signaling through the B-cell receptor (BCR) in sensitive cells. In nonclinical and clinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

Acalabrutinib shows encouraging activity, including improved selectivity for BTK compared to ibrutinib (Barf et al 2017, Byrd et al 2016) and an acceptable safety profile in nonclinical and clinical studies. In addition, laboratory studies have shown that acalabrutinib and ACP-5862 (an acalabrutinib metabolite) have limited off-target kinase activity, with specific inhibition of only 2 kinases (erb-b2 receptor tyrosine kinase 4 [ErbB4] and bone marrow tyrosine kinase gene in chromosome X [BMX]) at clinically relevant concentrations (Byrd et al 2016, Acalabrutinib IB, Armand et al 2016, Barf et al 2017). The lack of activity against other Tec- and Src-family kinases may contribute to the safety and efficacy profile of acalabrutinib.

1.4.2 Pharmacokinetics and Pharmacodynamics of Acalabrutinib

Acalabrutinib has a short pharmacokinetic (PK) half-life with a long-lasting pharmacodynamic (PDc) effect due to covalent binding to BTK. In a first-in-human (FIH) study in healthy subjects, acalabrutinib plasma time to maximum concentration (Tmax) values were between 0.5 and 1.0 hour for all dose cohorts (2.5 mg twice daily [BID] to 100 mg once daily [QD]), and mean half-life ranged from 0.97 hours to 2.1 hours. Acalabrutinib has an absolute oral bioavailability of 25%, is best taken with water, can be taken with or without food, and does not accumulate in plasma upon repeat-dose administration. Based on population PK analysis, acalabrutinib PK was linear over the 75 to 250 mg dose range. Variability in exposure to acalabrutinib is mainly due to a combination of gastric pH-dependent absorption and predominantly cytochrome P450 (CYP)3A mediated metabolism.

Acalabrutinib is extensively and almost completely metabolized. The most abundant circulating metabolite in humans was ACP-5862, which was formed by CYP3A-mediated oxidation and accounted for more than 10% of total acalabrutinib-related material. Within the Tec family of kinases, activities of acalabrutinib and ACP-5862 were quite similar.

ACP-5862 plasma area under the plasma-concentration time curve (AUC) was approximately 2- to 3-fold the AUC of acalabrutinib in healthy subjects, with a median half-life of 6.9 hours. Based on plasma profiling of radioactive metabolites, ACP-5862 exposure was higher in rats at a no observable adverse effect level (NOAEL) dose than in human subjects at a 100 mg dose. Excretion of [14C] acalabrutinib-related radioactivity was essentially complete by 48 to 96 hours post-dose, with predominantly biliary-fecal excretion in rats, dogs, and humans.

Co-administration of acalabrutinib with strong inhibitors and strong inducers of CYP3A should be avoided; however, coadministration with grapefruit juice did not increase acalabrutinib exposure in healthy subjects. Therapeutic and supratherapeutic plasma acalabrutinib concentrations did not prolong the corrected QT (QTc) interval in a thorough QT study.

1.4.3 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile. For detailed information on the safety pharmacology of acalabrutinib, refer to the acalabrutinib Investigator's Brochure (IB) (Acalabrutinib IB).

1.5 Acalabrutinib Monotherapy in Mantle Cell Lymphoma

As of 03 September 2017, acalabrutinib has been administered to over 2,000 subjects in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and subjects who were healthy or had mild to moderate hepatic impairment.

In a single-arm, Phase II study of 124 subjects with MCL who had relapsed after ≥1 (but not >5) prior treatment regimens, acalabrutinib (100 mg PO BID) demonstrated durable responses and an encouraging safety profile (Wang et al 2018). At a median follow-up of 15.2 months, 81% of subjects achieved an overall response: 40% achieved CR, and 41% achieved partial response (PR). The 12-month rates for duration of response, PFS, and OS were 72%, 67% and 87%, respectively. The estimated medians were not reached (Wang et al 2018).

Nearly all subjects (98%) experienced AEs, the most frequently reported being: headache (37.9%), diarrhea (30.6%), fatigue (28.2%), cough (21.0%), and myalgia (21.0%). Sixty-four

(51.6%) subjects had at least 1 Grade ≥3 AE. The most frequently reported Grade ≥3 AEs were neutropenia (10.5%), anemia (8.9%), pneumonia (4.8%), thrombocytopenia (4.0%), and diarrhea (3.2%). Three (2.4%) subjects had one Grade 5 (fatal) AE each that included non-small cell lung cancer, pulmonary embolism and aortic stenosis. All three Grade 5 events were considered not related to acalabrutinib.

Serious AEs (SAEs) occurred in 52 (41.9%) subjects. The most frequently reported SAEs were pneumonia (4.0%) and anemia (3.2%). SAEs reported as related to acalabrutinib occurred in a total of 15 (12.1%) subjects, and included colitis and vomiting (2 subjects each). Additional SAEs included headache, tumor lysis syndrome, interstitial lung disease, sepsis, anemia, leukostasis syndrome, respiratory syncytial virus infection, bacterial arthritis, abdominal pain, nausea, hematuria, acute coronary syndrome, B-cell lymphoma (verbatim term second malignancy of large B cell lymphoma), arthralgia, and pulmonary fibrosis (1 subject each).

For more detailed information on the clinical experience with acalabrutinib, please refer to the acalabrutinib IB.

1.6 Rationale for the Study

Minimal residual disease is the main cause of disease relapse and death post-BMT in subjects with MCL. Rituximab maintenance in subjects with MCL has demonstrated improved PFS and OS (Dietrich et al 2014, Graf et al 2015, Le Gouill et al 2017). However, acalabrutinib has demonstrated increased efficacy while maintaining a favorable safety profile in patients with R/R MCL. Therefore, we hypothesize that acalabrutinib will prove to be a more efficacious single agent for maintenance therapy.

In this study, we propose the use of acalabrutinib 129 mg PO BID as maintenance therapy post-BMT to prolong PFS. Moreover, built-in assessments of MRD will determine its impact on achieving an MRD- status post-BMT and after maintenance therapy with acalabrutinib.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to:

- Determine the PFS rate of subjects who received at least one dose of acalabrutinib and are alive and free of PD or relapse 2 years post-BMT.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Define the conversion rate from minimal residual disease positive (MRD^+) to MRD^- during therapy for up to 2 years post-BMT.
- Assess how MRD correlates with PFS
- Assess the incidence of AEs

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Determine how mutations correlate with disease relapse using NGS.
- Determine the MRD correlation of bone marrow compared to blood

3. STUDY PATIENT POPULATION AND DISCONTINUATION

3.1 Inclusion Criteria for Initial Enrollment (Screening #1)

Patients must meet all of the following criteria in order to be included in this research study:

1. Written informed consent, according to local guidelines, signed by the subject or by a legal guardian prior to the performance of any study-related screening procedures.
2. Men and women ≥18 years-of-age at the time of signature of the informed consent form (ICF).
3. A diagnosis of MCL confirmed by one of the following:
   - t(11;14) detected by fluorescence in situ hybridization (FISH), conventional cytogenetics, or other molecular evaluation
   - expression of cyclin D1 confirmed by immunohistochemistry
4. Subject must have completed induction chemotherapy and plan to and be eligible to receive their first BMT per standard of care.
5. Availability of an archival paraffin-embedded tumor block for MRD testing.
6. The Investigator anticipates that the subject will meet the appropriate lab requirements listed in Screening #2 by Day 100
7. Patients who received prior therapy with a BTK inhibitor are eligible to enroll.

3.2 Inclusion Criteria Post-BMT, Prior to Day 100 (Screening #2)

1. Adequate organ system function defined as:
   - Absolute neutrophil count (ANC) ≥1,000/mm^3.
   - Platelet count ≥75,000/mm^3. Platelet infusions to meet eligibility criteria are not allowed within 3 days of study enrollment.
   - Calculated creatinine clearance (CrCl) ≥30 mL/min as calculated by the Cockcroft-Gault method.

$$\text{Estimated CrCl (glomerular filtration rate [GFR])} = \frac{(140 - \text{age [years]}) \times (\text{weight [kg]}) \times F^{a}}{(72 \times \text{serum creatinine [mg/dL]})}$$

[a] where F = 0.85 for females and F = 1 for males

   - Total bilirubin ≤1.5 x the upper limit of normal (ULN) (except for previously documented Gilbert's syndrome)
   - Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤2.5 x ULN

2. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (Appendix A).
3. Subjects who did not receive an anti-cancer therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) during the time between their transplant and the start of study therapy. Subjects must have recovered (e.g., Grade ≤1 or baseline) from AEs associated with prior cancer therapy. Note: Subjects with Grade ≤2 neuropathy or Grade ≤2 alopecia are an exception to the latter criterion and may qualify for the study.
4. Woman of childbearing potential (WoCBP) who are sexually active with male partners must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib. For male subjects with a pregnant or non-pregnant WoCBP partner, no contraception measures are required. A WoCBP must have a negative pregnancy test (urine or serum) at the time of screening and 72 hours before starting the study drug or have evidence of non-childbearing potential by fulfilling one of the following criteria:
   - Post-menopausal women, defined as either women aged >50 years and amenorrheic for ≥12 months following cessation of all exogenous hormonal treatments or women <50 years old who have been amenorrheic for ≥12 months following the cessation of exogenous hormonal treatments, and have serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in the post-menopausal range for the institution.
   - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation.
   - Medically confirmed, irreversible premature ovarian failure.
5. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing tablets without difficulty.
6. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI).

3.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

1. Subjects who have relapsed or progressed at any time prior to BMT
2. Subjects with known mutations that confer resistance to a BTK inhibitor.
3. Confirmed clinical PD since the time of BMT
4. Prior malignancy (or any other malignancy requiring active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥2 years or that will not limit survival to <2 years. The exceptions are:
   - Subjects treated with curative intent >2 years prior to enrollment and have a low probability of recurrence.

5. Clinically 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 disease as defined by the New York Heart Association Functional Classification (Appendix B).
6. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
7. Known history of infection with human immunodeficiency virus (HIV) or any uncontrolled active systemic bacterial, fungal, parasitic or viral infection. Infections are considered controlled if appropriate therapy has been instituted and, at the time of screening, no signs of infection progression are present.
8. Known history of drug-specific hypersensitivity or anaphylaxis to study drug (including active product or excipient components).
9. Active bleeding or history of bleeding diathesis (e.g., hemophilia or von Willebrand disease).
10. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura.
11. Requires treatment with a strong CYP3A4 inhibitor/inducer (Appendix G).
12. Requires or is receiving anticoagulation treatment with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
13. Prothrombin time (PT)/international normalized ratio (INR) or activated partial thromboplastin time (aPTT) >2 x ULN (in the absence of lupus anticoagulant).
14. History of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.
15. Major surgical procedure within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
16. Hepatitis B or C serologic status: subjects who are hepatitis B core antibody (anti-HBc) positive and who are hepatitis B surface antigen (HbsAg) negative will need to have a negative PCR result. Those who are HbsAg positive or hepatitis B PCR positive will be excluded. Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.
17. Breastfeeding or pregnant.
18. Concurrent participation in another therapeutic clinical trial.
19. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol and/or follow-up procedures outlined in the protocol.
20. The inability to swallow tablets.

3.4 Discontinuation from Study Drug

Patients will be discontinued from the study drug for any of the following reasons:

- PD
- Completed treatment
- Start of alternative anticancer therapy
- Irreversible or intolerable toxicity or abnormal laboratory values thought to be related to drug toxicity
- Conditions requiring therapeutic intervention not permitted by the protocol
- Intercurrent illness (this will be at the Investigator's discretion)
- Inability of the patient to comply with study requirements
- Patient requests to discontinue treatment
- Patient withdraws consent from the study or study participation altogether
- Patient lost to follow-up
- Pregnancy
- Study termination

After discontinuation from protocol treatment, patients must be followed for AEs for 30 days after their last dose of study drug. All new AEs occurring during this period must be reported and followed until resolution, unless, in the opinion of the Investigator, these values are not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical records.

All patients who have Grade 3 or 4 laboratory abnormalities (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 5.0) at the time of discontinuation must be followed until the laboratory values have returned to Grade 1 or 2, unless it is, in the opinion of the Investigator, not likely that these values are to improve. In this case, the Investigator must record his or her reasoning for making this decision in the patient's medical records.

3.5 Study-wide Stopping Rules

If after 20 patients have been accrued to the study, 30% or more are unable to stay on acalabrutinib due to AEs, enrollment will be stopped, and a comprehensive review of safety will be performed by the study chair, primary investigators, and representatives of Acerta Pharma/AstraZeneca.

4. STUDY REGISTRATION

The patient must willingly consent to participate after being informed of the procedures to be followed, the experimental nature of the treatment, potential benefits, treatment alternatives, side-effects, risks, and discomforts. Institutional Review Board (IRB) approval of this protocol

and any associated ICFs are required. Eligible patients who wish to participate in the study will be enrolled into the study.

Registration must occur prior to the initiation of protocol therapy. Patients eligible to participate in the study may be enrolled by each site following the patient registration instructions provided by the Sarah Cannon Development Innovations (Innovations) study contact. Patient registration follow-up and/or confirmation will be provided via email within approximately 24 hours or by the next business day.

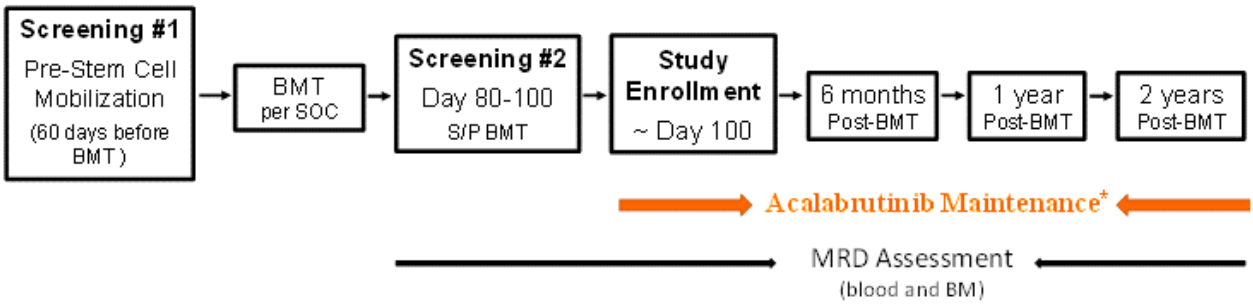
5. STUDY DESIGN

This is a single arm, multi-center, Phase II study of subjects with MCL who will receive acalabrutinib as maintenance therapy post-BMT. In general, subjects will provide informed consent prior to BMT to collect the required central labs. However, a limited number of subjects may be allowed to provide informed consent following BMT, determined on a case-by-case basis by the Principal Investigator (PI). In this event, any of the study assessments required prior to BMT not performed for standard of care will not be required.

Subjects will undergo a standard of care BMT with conditioning regimen determined by the treating physician per institutional guidelines. The BMT is not considered part of this study. Following completion of the BMT, a second screening will begin between Day 80 and Day 100. Maintenance therapy with acalabrutinib will begin on Day 100 in 28-day cycles. Subjects will self-administer 129 mg acalabrutinib BID until they reach 2 years post-BMT (approximately 22 cycles). Subjects who experience PD while on study will be encouraged to provide a fresh biopsy to assess lymphoma genome alterations. All subjects will be followed for up to 5 years post-BMT for PFS.

Approximately 50 subjects are planned to be enrolled after receiving BMT.

Figure 1 Study Schema



Subjects will self-administer acalabrutinib 129 mg BID on a 28-day cycle.
Abbreviations: BM, bone marrow; BMT, blood or marrow transplant; MRD, minimal residual disease; SOC, standard-of-care.

5.1 Treatment Plan

In this clinical trial, the study drug only refers to acalabrutinib. The BMT is a non-investigational medicinal product and is not the study drug.

Acalabrutinib 129 mg will be self-administered orally BID on a 28-day schedule, with or without food, until the patient has reached approximately 2 years post-BMT.

Acalabrutinib will be administered until PD, unacceptable toxicity, or the subject discontinues treatment for any other reason.

5.2 Concomitant Medications

Patients will be instructed not to take any additional medications during the course of the study without prior consultation with the research team. At each visit, the patient will be asked about any new medications he/she is taking or has taken after the start of the study drug.

5.2.1 Permitted Concomitant Medications

Standard post-BMT therapy is permitted and encouraged. Prophylaxes for *pneumocystis jirovecii* pneumonia (PJP) and herpes simplex/varicella zoster viruses (HSV/VZV) are recommended for 6 months and 1 year, respectively. Antiemetics are permitted if clinically indicated. Supportive medications in accordance with standard practice are permitted (such as for emesis, diarrhea, and nausea [Appendix H]).

Use of granulocyte growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) are permitted per institutional policy and in accordance with the American Society of Clinical Oncology (ASCO) guidelines (Smith et al 2006, Smith et al 2015). Blood and platelet transfusions may be given in accordance with institutional policy.

For subjects at risk for infectious pneumonitis based on prior history or comorbid conditions:

Infection control should be considered for select subjects (e.g., those with a history of recurrent pneumonias). Initiation of antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning before study drug administration may be warranted. Such support may also offer the benefit of

reducing the risk for other bacterial infections (Stern et al 2014). Prophylaxis with intravenous immunoglobulins (IVIG) may be appropriate in subjects with low immunoglobulin levels (Raanani et al 2009). Local practices or guidelines regarding infection prophylaxis may be followed.

For infections:

Bacterial/viral/fungal prophylaxis is allowed per institutional standards (see Appendix H).

5.2.2 Prohibited or Restricted Concomitant Medications

The following treatments are prohibited during the treatment period of the study:

- Any chemotherapy, anticancer immunotherapy, experimental therapy, radiotherapy, warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon), or corticosteroids (at dosages equivalent to prednisone >20 mg/day for longer than 2 weeks) are prohibited.
- The concomitant use of strong inhibitors/inducers of CYP3A4 (Appendix G) should be avoided when possible (Section 5.3). If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities. For additional information on drugs with potential drug-drug interactions, refer to Section 5.3.
- At study entry, subjects may be using topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions, but use of corticosteroids as therapy for the lymphoid cancer, other than palliative, is not permitted. During study participation, subjects may also receive corticosteroids at any required dosage as needed for treatment-emergent adverse events (TEAEs).

5.3 Drug-Drug Interactions

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated.

However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increases exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin, decreases acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (Appendix G) should be avoided when possible.

If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A4 inhibitor or inducer while on study, monitor the subject closely for potential drug-related toxicities.

5.4 Exploratory Correlatives

Testing for circulating tumor DNA (ctDNA), lymphoma biopsies, and exploratory blood samples may be performed to evaluate MRD and lymphoma genome alterations.

Adaptive Biotechnologies will perform the MRD analysis to investigate potential changes in MRD status (MRD^+ to MRD^-) in response to acalabrutinib therapy as well as MRD correlations to bone marrow (BM) compared to whole blood as outlined in Section 6.5.12.

6. STUDY ASSESSMENTS AND EVALUATIONS

6.1 Overview

All patients should visit the study center on the days specified within this protocol. The complete Schedule of Assessments for this study is presented in Appendix D.

6.2 Baseline Study Assessments, Screening #1 Prior to BMT

The following information will be collected and procedures will be performed for each patient at a baseline study assessment. This screening assessment will take place following written informed consent (see Section 13.3) and within 3 days prior to taking the study drug.

- Medical history and demographics
- Physical examination (including height [screening only] and weight)
- Serum or urine pregnancy test for women of child-bearing potential (WoCBP)
- Archival lymphoma sample collection

6.3 Baseline Study Assessments, Screening #2 Post-BMT – Day 80 to Day 100

- Physical examination (including weight)
- ECOG performance status
- Vital signs (pulse, blood pressure, oxygen saturation, and body temperature)
- 12-lead electrocardiogram (ECG)
- Complete blood count (CBC), clinical chemistry panel, and coagulation testing
- Urinalysis
- Serum or urine pregnancy test for WoCBP
- Screening for HIV, Hepatitis B (HBV) and Hepatitis C (HCV) viruses (see Section 3.3 [exclusion criteria #7 and #17)
- Archival lymphoma biopsy collection, if not collected during Screening #1
- Blood sample collection and bone marrow aspirate for MRD analysis
- Computed tomography (CT)/ magnetic resonance imaging (MRI)/ positron emission tomography (PET) scans
- Concomitant medication review and AE evaluation

6.4 Study Assessment Timing

The maintenance treatment period begins on the day the patient receives the first administration of acalabrutinib (Day 100). Dates for study visits and assessments will be determined based upon the first day after the BMT and should occur based on the timing parameters outlined in this protocol.

6.4.1 Cycle 1, Days 1 and 15 (~ 4 months post-BMT)

- Physical examination and vital signs (including weight)
- ECOG performance status
- CBC and clinical chemistry panel
- Concomitant medication review and AE monitoring
- Treatment with acalabrutinib 129 mg PO BID

6.4.2 Cycles 2-6, Day 1 (~ 5-9 months post-BMT)

- Physical examination and vital signs (including weight)
- ECOG performance status
- CBC and clinical chemistry panel
- Screening for viruses (see Section 6.5.6)
- Blood sample collection for MRD analysis
- CT/MRI/PET scans (6 months post-BMT)
- Treatment with acalabrutinib 129 mg PO BID
- Concomitant medication review and AE monitoring

6.4.3 Cycles 7-12, Day 1 (~ 10-15 months post-BMT)

- Physical examination and vital signs (including weight)
- ECOG performance status
- CBC and clinical chemistry panel
- Screening for viruses (see Section 6.5.6)
- Blood sample collection and bone marrow aspirate for MRD analysis
- CT/MRI/PET scans (12 months post-BMT)
- Treatment with acalabrutinib 129 mg PO BID
- Concomitant medication review and AE monitoring

6.4.4 Cycle 13 and Beyond, Day 1 (≥16 months post-BMT)

- Physical examination and vital signs (including weight)
- ECOG performance status
- CBC and clinical chemistry panel
- Screening for viruses (see Section 6.5.6)
- Blood sample collection for MRD analysis

- CT/MRI/PET scans (18 and 24 months post-BMT)
- Treatment with acalabrutinib 129 mg PO BID
- Concomitant medication review and AE monitoring

6.4.5 End of Treatment/Early Termination Visit

Please refer to Section 3.4 for the reasons for study drug discontinuation/early termination. If either the study drug or observations are discontinued, the reason will be recorded in the electronic case report form (eCRF) and source document. Patients who complete or discontinue the study drug should have the following evaluations performed as soon as possible.

- Screening for viruses (see Section 6.5.6)
- Fresh lymphoma biopsy (at PD)
- Concomitant medication review and AE monitoring

Patients prematurely discontinuing from the study drug must be followed for AEs and concomitant medication use for 30 days following the last administration of study drug or until resolution/stabilization of any ongoing AEs attributed to the medication.

Patients who discontinue from the study drug may be treated with other therapies at the discretion of the Investigator.

6.4.6 Long-Term Follow-up/End of study

At 2 years post-BMT, a follow-up visit will be performed for all MRD^- and MRD^+ subjects every 3 months until the time of PD, death, withdrawal of consent, start of another anticancer therapy, the study is terminated, or the 5-year post-BMT time point is reached. The following procedures and tests will be done at each follow-up visit:

- Fresh lymphoma biopsy (at PD)
- PFS status

6.5 Study Assessments

6.5.1 Medical History and Demographics

A complete medical history will be taken. Information to be documented includes demographics, prior medical illnesses and conditions, prior surgical procedures, date and stage of original diagnosis and details of prior chemotherapy/radiotherapy administered and other treatments for cancer (including type of drugs, dosages, schedule or administration, response and response duration) and Mantle Cell Lymphoma International Prognostic Index (MIPI). Concurrent medical signs and symptoms must be documented to establish baseline severities.

6.5.2 Physical Examinations (Including Performance Scale and Vital Signs)

A complete physical examination will be done at baseline, at each visit, at the end-of-treatment visit, and long-term follow-up visit as well as at the discretion of the Investigator. Examinations will include documentation of height (at screening only), weight, vital signs, and ECOG

performance status (Appendix A). Any abnormal or clinically significant findings from the physical examination must be recorded on the appropriate eCRF page.

6.5.3 12-Lead Electrocardiogram

ECGs will be done according to Appendix D and at the discretion of the Investigator. Each will be performed with the patient in a supine position having rested in this position for at least 10 minutes before the reading.

6.5.4 Pregnancy Testing

In WoCBP, a serum beta human chorionic gonadotropin or urine pregnancy test must be performed at the time of screening and 72 hours prior to the start of treatment.

6.5.5 Laboratory Assessments

Laboratory samples (CBC, clinical chemistry, urinalysis, and virology) are to be collected as outlined in Appendix D. Laboratory results will be graded using NCI CTCAE Version 5.0.

Hematology studies must include CBC with differential including, but not limited to, white blood cell count, hemoglobin, hematocrit, platelet count, ANC, and absolute lymphocyte count.

Coagulation testing will include PT/INR or aPTT.

Serum chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid.

If an unscheduled ECG is done at any time, then an electrolyte panel (e.g., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

A urinalysis will include pH, ketones, specific gravity, bilirubin, protein, blood and glucose.

6.5.6 HIV and Hepatitis B and C Testing

Patients with a known history of HIV or who are HIV antibody positive should be tested for HIV ribonucleic acid (RNA) during screening. No further testing beyond screening is necessary if PCR results are negative, except if clinically indicated.

Patients who are anti-HBc positive, or have a known history of HBV, should have quantitative PCR testing for HBV DNA performed during screening and every 3 months thereafter. Monitoring (every 3 months) should continue until 12 months after last dose of acalabrutinib. Any patient with a rising viral load (above lower limit of detection) should discontinue acalabrutinib and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in patients who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

Patients with a known history of HCV or who are hepatitis C antibody positive should be tested for HCV RNA during screening. No further testing beyond screening is necessary if PCR results are negative, except if clinically indicated.

6.5.7 Clonality (ID) Sample

The clonoSEQ Clonality (ID) Test determines the clonal diversity of a sample and can also be used to identify the trackable immune receptor sequence(s) of a lymphoid clone. Please ensure slide box and individual slides are each labeled with **Subject ID and Collection Date**.

Details of sample collection, processing, shipping, and storage will be described in the laboratory manual.

6.5.8 Tracking (MRD) Sample

The clonoSEQ Tracking (MRD) Test uses follow-up samples for the purposes of following the immune receptor sequence(s) identified by the clonoSEQ Clonality (ID) Test. Please ensure individual samples are labeled with **Subject ID and Collection Date**.

Details of sample collection, processing, shipping, and storage will be described in the laboratory manual.

6.5.9 Fresh Lymphoma Biopsy Sample

When feasible, collection of a lymphoma biopsy at relapse is encouraged, but will not be considered a protocol deviation if the patient withdraws consent. This sample will be used to investigate changes in pathway signaling and potential mechanisms of resistance (i.e., genetic alterations or evidence of alternative pathway activation). For this reason, a relapse lymphoma biopsy is encouraged in patients who achieve an objective response to the study drug, but later relapse.

All fresh lymphoma biopsies will be formalin-fixed and paraffin-embedded slides. Failure to obtain a sufficient lymphoma sample after making best efforts to biopsy the lymphoma will not be considered a protocol deviation.

If additional lymphoma molecular profiling is required to further understand any response to the study drug, the Sponsor may request a sample of the most recent lymphoma biopsy for additional research.

The results of this exploratory research will be reported separately and will not form part of the clinical study report (CSR).

Details of sample collection, processing, shipping, and storage will be described in the laboratory manual.

6.5.10 Response and Activity Assessments

See Section 6.5.12, Section 6.5.13 and Section 9.

6.5.11 Adverse Event Assessments

Information regarding the occurrence of AEs, including infections, will be collected from the time the patient signs the ICF throughout their participation in the study, including a period of 30 days after the last dose of study drug. Adverse event severity will be determined using the CTCAE Version 5.0 grading scale. See Section 11 for more details.

6.5.12 Prior and Concomitant Medications

All concomitant medications are to be collected and recorded from the time the patient signs the ICF throughout the patient's participation in the study.

6.5.13 Minimal Residual Disease Assessment

Adaptive Biotechnologies will use the clonoSEQ® assay to investigate potential changes in MRD status (MRD^+ to MRD^-) in response to acalabrutinib therapy. Bone marrow aspirate will be collected at Day +100 (Screening #2) and 1 year post-BMT (~Cycle 10 Day 1). Blood samples will be collected at Day +100 (Screening #2), 6 months (~Cycle 4 Day 1), 1 year (~Cycle 10 Day 1) and 2 years post-BMT (~Cycle 22 Day 1). For time points where both blood and BM are tested, if a patient has an MRD^+ result from either sample source (blood or BM), then the patient is considered MRD^+. If the limit of detection and the limit of quantitation are not met and the MRD results are indeterminate, indicating an inadequate sample was used, then the patient will have a follow-up test performed at the discretion of the Investigator (see Section 9.3).

Next-generation sequencing (NGS) will be conducted on all bone marrow and blood samples.

6.5.14 Radiologic Assessments

Response assessments will be evaluated based on recent International Working Group consensus criteria Response Evaluation Criteria in Lymphoma (RECIL 2017) (Younes et al 2017), outlined in Appendix E and Appendix F.

Tumor assessments will be performed using radiologic imaging by CT scan with contrast covering neck, chest, abdomen, and pelvis and [^{18}F]2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) scan covering from base of skull to mid-thigh within 28 days before the first dose of study drug and as outlined in Appendix D. In certain cases, measurements may be performed on the CT component of a combined PET-CT image, provided that is of adequate resolution. In the latter instance, approval by the sponsor is required.

Magnetic resonance imaging (MRI) may be used for imaging assessments if a contrast CT scan is contraindicated or undesirable. In cases where MRI is desirable, the MRI must be obtained at baseline and at all subsequent response evaluations.

CT/MRI measurements

Assessment of tumor burden will use the sum of the longest diameters. In subjects with disseminated disease, a maximum of 3 target lesions should be selected to estimate tumor response.

Target lesions should be selected per the following:

- They should be selected from those of the largest size that can be measured reproducibly and preferably representing multiple sites and organs.
- Lymph nodes:
  - Lymph nodes can be considered target lesions if the lymph node longest diameter measures ≥15 mm.

- A lymph node measuring between 10 and 14 mm is considered abnormal but should not be selected as a target lesion.
- Lymph nodes measuring <10 mm in diameter are considered normal and cannot be used as target lesions.
- In certain anatomical sites (inguinal, axillary, and portacaval), normal lymph nodes may exist in a narrow, elongated form, and such nodes should not be selected as target lesions if alternatives are available.

- Extranodal lesions can be selected as target lesions if they have a soft tissue component, based on their size and the ease of reproducibility of repeated measurements, with a minimum measurement of the longest diameter of ≥15 mm.
- Nontarget lesions:
  - All other lesions should be identified as nontarget lesions and should be recorded at baseline, without the need to measure them.
  - Nontarget lesions should be followed and reported as present, absent, or clear progression.

FDG-PET measurements

Scoring is semi-quantitative using the Deauville 5-point scale (Deauville 5PS). It is a simple tool based on visual interpretation of [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) uptake. It takes advantage of two reference points on the individual subject which have demonstrated relatively constant uptake on serial imaging. The two reference organs are the mediastinum and the liver. The scale ranges from 1 to 5, where 1 is "no FDG uptake" and 5 is "markedly increased FDG uptake". Each FDG-avid (or previously FDG-avid) lesion is rated independently.

1. No uptake or no residual uptake (when used interim)
2. Slight uptake, but below blood pool (mediastinum)
3. Uptake above mediastinal, but below or equal to uptake in the liver
4. Uptake slightly to moderately higher than liver
5. Markedly increased uptake or any new lesion (on response evaluation)

7. DRUG FORMULATION, AVAILABILITY, ADMINISTRATION, AND TOXICITY INFORMATION

7.1 Acalabrutinib

Investigational Product	Dosage Form and Strength	Manufacturer
Acalabrutinib	129 mg tablets	Acerta Pharma

7.2 Acalabrutinib Treatment Duration

Acalabrutinib tablets will be self-administered BID approximately every 12 hours. The tablets should be swallowed intact with approximately 1 cup of water. Patients should not chew the tablets and should try to swallow tablets whole.

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been >3 hours, the dose should not be taken and the patient should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

7.2.1 Labeling, Packaging, and Supply of Acalabrutinib

The investigational product, acalabrutinib maleate tablet, is supplied as an orange film-coated tablet containing 129 mg of acalabrutinib maleate (equivalent to 100 mg of acalabrutinib) drug substance.

Each tablet also contains the following compendial inactive ingredients: mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, and sodium stearyl fumarate. The tablet coating contains hypromellose, copovidone, titanium dioxide, polyethylene glycol, caprylic/capric triglyceride, yellow iron oxide, and red iron oxide.

Acalabrutinib maleate tablets are packed in white, high-density polyethylene (HDPE) bottles containing a silica gel desiccant and should be stored according to the storage conditions as indicated on the label. The recommended storage condition for acalabrutinib maleate tablets is below 30°C (86°F).

Study drug will arrive commercially labeled as CALQUENCE®. Innovations will affix labels reading “LYM 155 – For Investigational Use Only” before distribution.

7.3 Accountability for the Study Drug

The PI (or designee) is responsible for accountability of all used and unused study drug supplies at the site. Innovations representatives must be granted access on reasonable request to check drug storage, dispensing procedures, and accountability records.

All study drug inventories must be made available for inspection by Innovations or its representatives and regulatory agency inspectors upon request.

Throughout the study and at its completion, Innovations Drug Accountability Record Form(s) will be completed by the site and sent to the Innovations Regulatory Department. Study drug supplies must not be destroyed unless prior approval has been granted by Innovations. Please contact Innovations regarding disposal of any study drug.

7.4 Assuring Subject Compliance

Most acalabrutinib doses will be taken by the subjects at home. Therefore, subjects will receive an acalabrutinib drug diary to record the specific time each dose was taken and to record reasons for any missed doses. Subject compliance with acalabrutinib dosing will be assessed at every visit and recorded in the eCRF. The subject will be instructed to bring the diary and any remaining tablets to the clinic at his/her next visit. The study staff will review the diary and ask the subject if all the tablets were administered. Any remaining or returned tablets will be counted and documented. Returned tablets must not be redispensed to another subject. The investigational products should only be used as directed in this protocol and as detailed in the pharmacy manual and handling instructions.

The study personnel at the investigational site will account for all drugs dispensed and for appropriate destruction or return of unused drugs to the sponsor or designee. All study supplies and associated documentation will be regularly reviewed and verified by the Site Monitor before destruction or return to the sponsor or designee. Certificates of delivery and destruction/return should be signed and copies must be retained by the sponsor.

7.5 Toxicity of Study Drug and Study Regimen

7.5.1 Precautions and Risks Associated with Acalabrutinib

7.5.1.1 Hemorrhage

Hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhages, have been reported in clinical trials with acalabrutinib. Some of these bleeding events resulted in fatal outcomes.

The mechanism for hemorrhage is not well understood. Subjects receiving antiplatelet or anticoagulant therapies may be at increased risk of hemorrhage and should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery. Subjects with haemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

7.5.1.2 Infection

Serious infections, including fatal events, have been reported in clinical studies with acalabrutinib. The most frequently reported Grade 3 or 4 infection was pneumonia. Across the acalabrutinib clinical development program (including subjects treated with acalabrutinib in combination with other drugs), cases of HBV reactivation (resulting in liver failure and death in 1 case) and cases of progressive multifocal leukoencephalopathy (PML) have occurred in subjects with hematologic malignancies.

Subjects should be monitored for signs and symptoms of infections and treated as medically appropriate. Subjects with infection events should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

7.5.1.3 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as medically appropriate.

7.5.1.4 Second Primary Malignancies

Events of second primary malignancies, including non-skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer.

Subjects with a second primary malignancy should be managed according to institutional guidelines with maximal supportive and therapeutic care and diagnostic evaluations as clinically indicated.

7.5.1.5 Atrial Fibrillation

Events of atrial fibrillation/flutter have been reported in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation. The mechanism for atrial fibrillation is not well understood.

Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

7.5.1.6 Overdose

Clinical information relevant to overdose is not available. For results from nonclinical overdose studies in rats and dogs, please refer to the IB.

In the event of subject ingestion of more than the recommended acalabrutinib dosage, the subject should be observed for any symptomatic side effects, and vital signs and biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion of acalabrutinib is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

7.5.1.7 Pregnancy, Breastfeeding, and Contraception

In acalabrutinib nonclinical reproductive toxicity studies, including definitive embryo-fetal development studies, oral acalabrutinib at ≥100 mg/kg/day produced maternal toxicity, and at 100 mg/kg/day resulted in decreased fetal body weights and delayed skeletal ossification in rabbits. Please refer to the current acalabrutinib IB for further details.

There has been one reported pregnancy in a subject exposed to acalabrutinib, in which the subject was exposed during the first trimester. Acalabrutinib was discontinued, and the subject gave birth to a live, full term male infant by Caesarean section.

The potential for acalabrutinib to be excreted in breast milk of nursing mothers is unknown. In studies of lactating rats, acalabrutinib and its metabolite ACP-5862 were measured in milk and in the plasma of nursing pups on postnatal Day 12.

There have been no positive genotoxicity findings during development of acalabrutinib. Additionally, based on modeled estimates of fetal exposures to active product ingredient levels in ejaculated material using assumptions for small molecules, direct embryofetal exposure (i.e., female partner exposure following a vaginal dose of estimated seminal concentration) and male-mediated developmental risk with acalabrutinib treatment is considered to be very low, and risk

mitigation measures for male-mediated developmental risk are therefore not required for acalabrutinib.

For further guidance and definitions, see Appendix C.

8. DOSE MODIFICATIONS

If toxicity occurs, the toxicity will be graded using the NCI CTCAE Version 5, and appropriate supportive care treatment will be administered to decrease the signs and symptoms thereof. Dose adjustments will be based on the organ system exhibiting the greatest degree of toxicity.

8.1 Criteria and Procedures for Dose Interruptions and Adjustments of Acalabrutinib

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib-related toxicity. If a subject experiences a treatment-related toxicity or other intolerable AE during the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE resolves or stabilizes to an acceptable degree.

Dose modifications for the following TEAEs are provided in Table 1.

- Grade 4 neutropenia (<500/μL) for >7 days (neutrophil growth factors are permitted per ASCO guidelines [Smith et al 2006, Smith et al 2015] and use must be recorded on the eCRF)
- Grade 3 thrombocytopenia (<50,000/μL) in the presence of significant bleeding.
- Grade 4 thrombocytopenia (<25,000/μL)
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 AE or unmanageable Grade 3 AE

Table 1 Acalabrutinib Dose Reduction Options

Starting Dose	1st Dose Reduction	2nd Dose Reduction
129 mg BID	129 mg QD	discontinue

Temporarily withholding acalabrutinib for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Transient worsening of disease during temporary interruption of study therapy (e.g. for drug-related toxicity, surgery, or intercurrent illness) may not indicate PD. In such circumstances, and if medically appropriate, following discussion with the Medical Monitor, subjects may resume therapy and relevant clinical, laboratory, and/or radiologic assessments should be done to document whether lymphoma control can be maintained or whether actual PD has occurred.

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (i.e., once per week) until abnormalities have recovered to Grade ≤1. If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or

no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥4 weeks then the dose may be increased to the next higher dose level, at the discretion of the PI. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. The maximum dose of acalabrutinib is 129 mg BID.

Treatment with acalabrutinib should be withheld for any unmanageable, potentially study drug-related toxicity that is Grade ≥3 in severity. Any other clinically important events where dose delays may be considered appropriate must be discussed with the PI.

8.2 Dose Modifications for Hematologic Toxicities

If the acalabrutinib dose should be reduced and the subject is receiving acalabrutinib 129 mg QD, acalabrutinib should be discontinued. Refer to Table 2 for dose modifications due to hematologic toxicities.

Table 2 Dose Modifications for Hematologic Toxicities

NCI CTCAE Grade	Acalabrutinib Action
Febrile neutropenia Grade 3 or 4	Withhold acalabrutinib until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline. Then, restart acalabrutinib at the same dose.
2nd episode: **febrile neutropenia** Grade 3 or 4	Withhold acalabrutinib until infection is resolved, antibiotics no longer required and ANC Grade ≤2 or baseline. Then, restart acalabrutinib with 1 level dose reduction or discontinue (Table 1).
3rd episode: **febrile neutropenia** Grade 3 or 4	Discontinue acalabrutinib
Neutrophil count decrease Grade 4 lasting >7 days despite growth factor support	Withhold acalabrutinib until Grade ≤2 or baseline. Then, restart acalabrutinib at the same dose.
2nd episode: **neutrophil count decrease** Grade 4 lasting >7 days despite growth factor support	Withhold acalabrutinib until Grade ≤2 or baseline. Then, restart acalabrutinib with 1 level dose reduction or discontinue (Table 1).
3rd episode: **neutrophil count decrease** Grade 4 lasting >7 days despite growth factor support	Discontinue acalabrutinib
Platelet count decrease Grade 4 without bleeding requiring blood or platelet transfusion	Withhold acalabrutinib until Grade ≤2 or baseline. Then, restart acalabrutinib at the same dose (Table 1).
2nd episode: **platelet count decrease** Grade 4 without bleeding requiring blood or platelet transfusion	Withhold acalabrutinib until Grade ≤2 or baseline. Then, restart acalabrutinib with 1 level dose reduction or discontinue (Table 1).
3rd episode: **platelet count decrease** Grade 4 without bleeding requiring blood or platelet transfusion	Discontinue acalabrutinib
Platelet count decrease Grade 3 or 4 **with bleeding** requiring blood or platelet transfusion	Withhold acalabrutinib until Grade ≤2 or baseline. Then, restart acalabrutinib with 1 level dose reduction or discontinue (Table 1).
2nd episode: p**latelet count decrease** Grade 3 or 4 **with bleeding** requiring blood or platelet transfusion	Discontinue acalabrutinib

8.3 Dose Modifications for Non-hematologic Toxicities

In case of Grade 4 treatment-related non-hematologic toxicity, discontinue acalabrutinib.

Grade 3 toxicities require dose modifications, temporary treatment interruptions or discontinuation of acalabrutinib (Table 3).

Table 3 Dose Modification Guidance for Grade 3 Non-hematologic Toxicities, Except Liver Dysfunction

Occurrence	Acalabrutinib Action
First	Withhold acalabrutinib until recovery to Grade ≤2 or baseline. Then, restart acalabrutinib at the same dose (Table 1).
Second	Withhold acalabrutinib until recovery to Grade ≤2 or baseline. Then, restart acalabrutinib with 1 level dose reduction or discontinue (Table 1).
Third	Withhold acalabrutinib until recovery to Grade ≤2 or baseline. Then, restart acalabrutinib with 1 level dose reduction or discontinue (Table 1).

8.4 Management of Acalabrutinib-Related Adverse Events

Management for acalabrutinib-related AEs are located in Appendix H.

9. RESPONSE EVALUATIONS AND MEASUREMENTS

9.1 Progression-free Survival

Progression-free survival is defined as the time from Day 0 of BMT until the date of objective radiological PD according to RECIL or death (by any cause in the absence of PD). Patients who are alive and free from PD will be censored at the date of last tumor assessment. Patients who begin subsequent therapy prior to PD or death will be censored at the date of last tumor assessment prior to the start of subsequent therapy.

9.2 Complete Response

Any RECIL assessments determined to be a CR will be confirmed by no morphologic, immunohistochemical, or flow cytometric evidence of disease by BM biopsy or aspirate (Brugger et al 2004).

9.3 Minimal Residual Disease

Minimal residual disease (MRD) is defined as the minimal traceable persistence of lymphoma after treatment with acalabrutinib. The clonoSEQ® assay, developed by Adaptive Biotechnologies, is an NGS-based immunosequencing platform that will be used for the detection, quantification and analysis of MRD. The assay uses multiplex PCR, high throughput sequencing and a proprietary algorithm for evaluating lymphoid clonal distribution and expansions in genomic DNA. MRD positive or negative results will be determined by detection

of residual clonal cells (with assay sensitivity of 10^{-6}) per Adaptive Technologies' reporting methods.

An MRD^- status will be defined as all results from whole blood and BM that meet the assay testing requirements and are negative for the presence of residual clonal cells. An MRD^+ status will be defined as all results from whole blood or BM that are positive for residual clonal cells per Adaptive Biotechnologies' reporting methods. In addition to MRD positivity or negativity, MRD level will be captured by recording the number of residual clonal cells detected.

10. STATISTICAL CONSIDERATIONS

10.1 Statistical Design

This is a Phase II, single arm, multi-center trial designed to assess the safety and efficacy of acalabrutinib as maintenance therapy post-BMT in subjects with MCL. The primary objective of this trial is to determine the percentage of subjects who receive at least one dose of acalabrutinib and who are alive and free of PD or relapse at 2 years post-BMT.

10.2 Sample Size Considerations

The primary endpoint is the percentage of patients who are alive and free of PD or relapse at 2 years post-BMT. A sample size of 45 patients produces a two-sided 95% CI of 65%-90% when the observed percentage is 80%. To account for a 10% non-evaluable rate, the total sample size will be 50 patients.

10.3 Analysis Population

The following analysis populations will be used:

- The Safety Analysis Set is defined as all patients who receive at least one dose of acalabrutinib.
- The Efficacy Analysis Set is defined as all patients who receive at least one dose of acalabrutinib, who have an adequate baseline disease assessment and an adequate post-baseline assessment, and those who discontinue due to death or PD prior to their first assessment.

10.4 Data Analysis

Descriptive statistics, including mean, median, standard deviation, and range for all continuous measures, will be tabulated and reported. Percentages and frequencies for all categorical measures will also be presented. Time-to-event endpoints will be reported using Kaplan-Meier estimates, with 95% CIs for median time to event. A full description of the analysis will be included in the Statistical Analysis Plan.

10.4.1 Demographics and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized using descriptive statistics. Data to be tabulated will include demographic features such as age, sex, and race, as well as disease-specific characteristics.

The number and percentages of patients enrolled, treated, completed the treatment/study and withdrawn from treatment/study for any reason will be presented.

10.4.2 Efficacy Analysis

All efficacy analyses will be performed using the Efficacy Analysis Set.

- PFS is defined as the time from Day 0 of BMT to objective radiological PD or death on study. PFS will be evaluated as Kaplan-Meier estimates of the percentage of subjects who receive at least one dose of study drug and who are alive and free of PD or relapse at 2 years post-BMT according to RECIL (Younes et al 2017). Data for subjects who are still alive and free from progression at the time of data cut-off date, are lost to follow-up, have discontinued the study, or have initiated a subsequent protocol therapy will be censored on last assessment (or, if no post-baseline tumor assessment, at the time of first dose plus 1 day). Approximate 95% CI for median duration of PFS will be computed using the formula proposed by Brookmeyer and Crowley.
- Minimal residual disease status will be examined by NGS on all bone marrow aspirate and blood samples collected up to 2 years post-BMT to determine the conversion rate from MRD^+ to MRD^- while taking acalabrutinib, correlate MRD status with PFS, and identify mutations that correlate with disease relapse. An MRD^- status will be defined as all results from whole blood and BM that are negative for the presence of residual clonal cells (with assay sensitivity of 10^{-6}). An MRD^+ status will be defined as all results from whole blood or BM that are positive for residual clonal cells per Adaptive Biotechnologies' reporting methods.

10.4.3 Safety Analysis

Safety will be assessed through the analysis of the reported incidence of treatment-emergent AEs. Treatment-emergent AEs are those with an onset on or after the initiation of therapy, and will be graded according to NCI CTCAE Version 5.0. A copy of the CTCAE scoring system may be downloaded from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf.

The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and summarized using system organ class and preferred term for all patients in the Safety Analysis Set. In addition, summaries of SAEs, AEs leading to treatment discontinuation, AEs by maximum NCI CTCAE grade, and AEs related to the study drug will also be presented.

Other safety endpoints including laboratory results, vital signs, ECG findings, and other protocol-specified tests will be listed and/or summarized for all patients in the Safety Analysis Set.

Concomitant medications will be coded using the WHO Drug Dictionary and they will be listed and summarized.

10.5 Analysis Time Points

10.5.1 Final Analysis

The final analysis of the study will occur following the last visit of the last patient.

11. SAFETY REPORTING AND ANALYSES

Safety assessments will consist of monitoring and recording protocol-defined AEs and SAEs, and measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables, and measurement of protocol-specified vital signs.

The PI is responsible for recognizing and reporting SAEs to the Innovations Safety Department (Section 11.1.5). It is Innovations' responsibility to report relevant SAEs to the applicable local, national, or international regulatory bodies. In addition, Investigators must report SAEs and follow-up information to their responsible IRBs according to the policies of each IRB.

The PI is also responsible for ensuring that every staff member involved in the study is familiar with the content of this section.

11.1 Definitions

11.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. An AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality. An AE can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including overdose.

11.1.2 Serious Adverse Events

An AE or a suspected adverse reaction (SAR) is considered "serious" if it results in any of the following outcomes:

- **Death**
- **A life-threatening AE**
- **Inpatient hospitalization of at least 24 hours or prolongation of existing hospitalization**
- **A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
- **A congenital anomaly/birth defect**
- **Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include:**
    - **allergic bronchospasm requiring intensive treatment in an emergency room or at home,**
    - **blood dyscrasias or convulsions that do not result in hospitalization, or**
    - **development of drug dependency or drug abuse.**

It is important to distinguish between "serious" and "severe" AEs, as the terms are not synonymous. Severity is a measure of intensity; however, an AE of severe intensity need not necessarily be considered "serious." Seriousness serves as the guide for defining regulatory reporting obligations and is based on patient/event outcome or action usually associated with events that pose a threat to a patient's life or vital functions. For example, nausea which persists for several hours may be considered "severe" nausea, but may not be considered an SAE. On the other hand, a stroke which results in only a limited degree of disability may be considered only a mild stroke, but would be considered an SAE. "Severity" and "seriousness" should be independently assessed when recording AEs on the eCRF and SAEs on the SAE Report Form.

11.1.3 Adverse Reaction

An adverse reaction (AR) means any AE caused by a drug. Adverse reactions are a subset of all SARs where there is a reason to conclude that the drug caused the event.

11.1.4 Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE. An SAR implies a lesser degree of certainty about causality than an AR, which means any AE caused by a drug.

11.1.5 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) for subjects exposed to acalabrutinib, and must be reported to the sponsors expeditiously (see Section 11.1.6.2 for reporting instructions), irrespective of regulatory seriousness criteria or causality.

- Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.).

11.1.6 Recording and Reporting of Adverse Events

11.1.6.1 Recording of Adverse Events

All AEs of any patient during the course of the research study will be recorded in the eCRF, and the Investigator will give his or her opinion as to the relationship of the AE to the study drug (e.g., whether the event is related or unrelated to study drug administration).

All AEs should be documented. A description of the event, including its date of onset and resolution, whether it constitutes an SAE or not, any action taken (e.g., changes to study drug), and outcome should be provided along with the Investigator's assessment of causality (e.g., the relationship to the study drug). For an AE to be a suspected TEAE there should be at least a reasonable possibility of a causal relationship between the protocol treatment and the AE. Adverse events will be graded according to the NCI CTCAE Version 5.0, and changes will be documented.

If the AE is serious, it should be reported immediately to the Innovations Safety Department. Other untoward events occurring in the framework of a clinical study are to be recorded as AEs (e.g., AEs that occur prior to assignment of the study drug that are related to a protocol-mandated intervention, including invasive procedures such as biopsies, medication washout, or no treatment run-in).

Any clinically significant signs and symptoms, abnormal test findings, changes in physical examination, hypersensitivity, and other measurements that occur will be reported as AEs and collected on the relevant eCRF screen.

Test findings will be reported as an AE if: the test result requires an adjustment in the study drug(s) or discontinuation of treatment; test findings require additional testing or surgical intervention; a test result or finding is associated with accompanying symptoms; and/or a test result is considered to be an AE by the Investigator.

11.1.6.2 Reporting Period for Adverse Events

All AEs regardless of seriousness or relationship to the study drug spanning from the first dose of acalabrutinib until 30 calendar days after discontinuation or completion of study drug, as defined by this clinical study protocol, are to be recorded on the corresponding screen(s) included in the eCRF.

All AEs resulting in discontinuation from the study should be followed until resolution or stabilization. All new AEs occurring during the AE reporting period must be reported and followed until resolution unless, in the opinion of the Investigator, the AE or laboratory abnormality is not likely to improve because of the underlying disease. In this case, the Investigator must record his or her reasoning for this decision in the patient's medical record.

Thirty days or more after completion of protocol-specific treatment or discontinuation, only AEs, SAEs, or deaths assessed by the Investigator as treatment-related are to be reported.

11.1.7 Assessment of Adverse Events

All AEs and SAEs whether volunteered by the patient, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (e.g., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to the study drug (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, Investigators should apply the following general guideline:

> **YES:** There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies, and/or the AE follows a known pattern of response to the study drug, and/or the AE abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re-challenge.
>
> **NO:** Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or the AE has no plausible temporal relationship to study drug administration (e.g., cancer diagnosed 2 days after first dose of study drug).

11.2 Serious Adverse Event Reporting by Investigators

Adverse events classified by the treating Investigator as "serious" require expeditious handling and reporting to the Innovations Safety Department in order to comply with regulatory

requirements. Determination of "life-threatening" or "serious" is based on the opinion of either the Sponsor or the Investigator.

Serious AEs may occur at any time from the first dose of acalabrutinib through the 30-day follow-up period after the last dose of study drug. **The Innovations Safety Department must be notified of all SAEs, regardless of causality, within 24 hours of the first knowledge of the event by the treating physician or research personnel.**

To report an SAE, the SAE Report Form should be completed with the necessary information.

The SAE Report Form should be sent to the Innovations Safety Department via fax or e-mail using the following contact information (during both business and non-business hours):

Sarah Cannon Innovations Safety Department

Safety Dept. Fax #: 1-866-807-4325

Safety Dept. Email: CANN.SAE@SCRI-Innovations.com

Transmission of the SAE report should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to the Innovations Safety Department as soon as it is available; these reports should also be submitted using the Innovations SAE Report Form. The detailed SAE reporting process will be provided to the sites in the SAE reporting guidelines contained in the study reference manual.

11.3 Recording of Adverse Events and Serious Adverse Events

11.3.1 Diagnosis versus Signs and Symptoms

All AEs should be recorded individually in the patient's own words (verbatim) unless, in the opinion of the PI or designated physician, the AEs constitute components of a recognized condition, disease, or syndrome. In the latter case, the condition, disease, or syndrome should be named rather than each individual sign or symptom. If a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE as appropriate on the relevant form(s) (SAE Report Form and/or AE eCRF screen). If a diagnosis is subsequently established, it should be reported as follow-up information is available. If a diagnosis is determined subsequent to the reporting of the constellation of symptoms, the signs/symptoms should be updated to reflect the diagnosis.

Progression of malignancy (including fatal outcomes), if documented by use of an appropriate method (e.g., as per RECIL), should not be reported as an SAE.

11.3.2 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once on the SAE Report Form and/or the AE eCRF screen. If a persistent AE becomes more severe or lessens in severity, it should be recorded on a separate SAE Report Form and/or AE eCRF screen.

A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on an SAE Report Form and/or AE eCRF screen.

11.3.3 Abnormal Laboratory Values

If an abnormal laboratory value or vital sign is associated with clinical signs and/or symptoms, the sign or symptom should be reported as an AE or SAE, and the associated laboratory value or vital sign should be considered additional information that must be collected on the relevant eCRF screen. If the laboratory abnormality is a sign of a disease or syndrome, only the diagnosis needs to be recorded on the SAE Report Form and/or AE eCRF screen.

Abnormal laboratory values will be reported as an AE if: the laboratory result requires an adjustment in the study drug(s) or discontinuation of treatment, and/or laboratory findings require additional testing or surgical intervention, a laboratory result or finding is associated with accompanying symptoms, or a laboratory result is considered to be an AE by the Investigator.

11.3.4 Deaths

Deaths that occur during the protocol-specified AE reporting period that are attributed by the Investigator solely to PD will be recorded on the "End of Study" eCRF screen. All other on-study deaths, regardless of attribution, will be recorded on an SAE Report Form and expeditiously reported to the Innovations Safety Department.

When recording an SAE with an outcome of death, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the SAE Report Form and AE eCRF screen. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Death NOS" ("death cause unknown") on the AE eCRF screen. During post-study survival follow-up, deaths attributed to PD will be recorded on the "Follow-up Summary" and "Death Page" eCRF screens.

11.3.5 Hospitalization, Prolonged Hospitalization, or Surgery

Any AE that results in hospitalization of >24 hours or prolongation of pre-existing hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalizations that do not require reporting as an SAE.

Treatment within or admission to the following facilities is not considered to meet the criteria of "inpatient hospitalization" (although if any other SAE criteria are met, the event must still be treated as an SAE and immediately reported):

- Emergency department or emergency room
- Outpatient or same-day surgery units
- Observation or short-stay unit
- Rehabilitation facility
- Hospice or skilled nursing facility
- Nursing homes, custodial care, or respite care facility

Hospitalization during the study for a pre-planned surgical or medical procedure (one which was planned prior to entry in the study) does not require reporting as an SAE.

11.3.6 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the General Medical History eCRF screen. A pre-existing medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an SAE Report Form and/or AE eCRF screen, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors.

11.3.7 New Cancers

The development of a new primary cancer should be regarded as an AE, with the exception of early non-melanoma cancers, and will generally meet at least one of the seriousness criteria (see Section 11.1.2). New primary cancers are those that are not the primary reason for the administration of the study drug and have developed after the inclusion of the patient in the study. They do not include metastases of the original cancer. Symptoms of metastasis or the metastasis itself should not be reported as an AE/SAE, as they are considered to be PD.

11.3.8 Pregnancy, Abortion, Birth Defects/Congenital Anomalies

If a patient becomes pregnant while enrolled in the study, a Pregnancy Form (a paper report form, not available within the eCRF) should be completed and faxed to the Innovations Safety Department. The Innovations Safety Department should be notified expeditiously, irrespective of whether or not it meets the criteria for expedited reporting. Abortions (spontaneous, accidental, or therapeutic) must also be reported to the Innovations Safety Department.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, this must be reported to the Innovations Safety Department immediately. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Congenital anomalies/birth defects always meet SAE criteria, and should therefore be expeditiously reported as an SAE, using the previously described process for SAE reporting. A Pregnancy Form should also have been previously completed, and will need to be updated to reflect the outcome of the pregnancy.

11.3.9 Overdose

Symptomatic and non-symptomatic overdose must be reported in the eCRF. Any accidental or intentional overdose with the study drug that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to the Innovations Safety Department no greater than 24 hours from first knowledge of the event using the corresponding screens in the eCRF and following the same process described for SAE reporting (Section 11.2) if the overdose is symptomatic.

For information on how to manage an overdose of acalabrutinib, see Section 7.5.1.6 and the IB.

11.4 Funding Partner Serious Adverse Event Reporting Requirements

The Innovations Safety Department will forward SAE information regarding acalabrutinib to Acerta Pharma/AstraZeneca at AEMailboxClinicalTrialTCS@astrazeneca.com within 7 calendar days (for life-threatening/fatal SAEs) of the Innovations Safety Department personnel becoming

aware of the SAE or 15 calendar days for other SAEs, Suspected Unexpected Serious Adverse Reactions (SUSARs), pregnancy (unless fatal/life-threatening) and special situations.

Innovations is responsible for reporting relevant SAEs to the competent authority, other applicable regulatory authorities, and participating Investigators, in accordance with International Council for Harmonisation (ICH) guidelines and US Food and Drug Administration (FDA) regulations in parallel with Acerta Pharma/AstraZeneca.

New information will be submitted to Acerta Pharma within the same time frame as initial reports. Whenever possible, SAEs should be reported by diagnosis term not as a constellation of symptoms. Death due to PD should be recorded on the appropriate form in the electronic data capture (EDC) system. If the primary cause of death is PD, the death due to PD should not be reported as an SAE. If the primary cause of death is something other than PD, then the death should be reported as an SAE with the primary cause of death as the event AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and post-mortem reports must be forwarded to AEMailboxClinicalTrialTCS@astrazeneca.com. If study drug is discontinued because of an SAE, this information must be included in the SAE report.

11.4.1 Sponsor Assessment of Unexpected Events

The Sponsor is responsible for assessing an AE or SAR as "unexpected."

An AE or SAR is considered "unexpected" when the following conditions occur:

- Event(s) is not mentioned in the IB
- Event(s) is not listed at the specificity or severity that has been observed
- An event(s) is not consistent with the General Investigative Plan or in the current application
- Includes AEs or SARs that may be anticipated from the pharmacological properties of the study drug, or that occur with members of the drug class, but that have not previously been observed under investigation

When applicable, an unexpected AE may also apply to an event that is not listed in the current IB or an event that may be mentioned in the IB, but differs from the event because of greater severity or specificity.

Known as SUSARs, these events suspected (by the Investigator or Sponsor) to be related to the study drug, are unexpected (not listed in the IB), and are serious (as defined by the protocol) and require expedient submission to relevant health authorities within 7 days (for fatal or life-threatening event) or 15 days (for all serious events), or as defined by law. The term SUSAR is used primarily in the reporting of events to regulatory authorities.

Expected AEs are those events that are listed or characterized in the current IB.

11.4.2 Funding Partner Reporting for Clinical Studies Under an Investigational New Drug Application

All written investigational new drug (IND) Safety Reports submitted to the FDA by the Innovations Safety Department are not required to be distributed to pharmaceutical company(ies) that are supporting the study with either funding or drug supply.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1 Study Monitoring, Auditing, and Inspecting

The Investigator will permit study-related monitoring, quality audits, and inspections by Innovations, or its representative(s), government regulatory authorities, and the IRB(s) of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, CRFs). The Investigator will ensure the capability for inspections of applicable study-related facilities. The Investigator will ensure that the study monitor or any other compliance or Quality Assurance reviewer is given access to all study-related documents and study-related facilities.

At the discretion of Innovations, Source Document Verification (SDV) may be performed on partial or all data items as defined in study documents and/or plans.

Participation as an Investigator in this study implies the acceptance of potential inspection by government regulatory authorities, the IRB(s), and/or Innovations or its representative(s).

13. ETHICAL, FINANCIAL, AND REGULATORY CONSIDERATIONS

This research study will be conducted according to the standards of Good Clinical Practice (GCP) outlined in the ICH E6 Tripartite Guideline and the Code of Federal Regulations (CFR) Title 21 part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s).

13.1 Institutional Review Board Approval

The clinical study protocol, ICF, IB, available safety information, patient documents (e.g., study diary), patient recruitment procedures (e.g., advertisements), information about payments (e.g., PI payments) and compensation available to the patients, and documentation evidencing the PI's qualifications should be submitted to the IRB for ethical review and approval if required by local regulations, prior to the study start.

The PI/Sponsor and/or designee will follow all necessary regulations to ensure appropriate, initial, and on-going IRB study review. The PI/Sponsor (as appropriate) must submit to and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the ICF. Investigators will be advised by the Sponsor or designee whether an amendment is considered substantial or non-substantial and whether it requires submission for approval or notification only to an IRB.

Safety updates will be prepared by the Sponsor or its representative as required, for distribution to the Investigator(s) and submission to the relevant IRB.

13.2 Regulatory Approval

As required by local regulations, the Sponsor will ensure all legal aspects are covered and approval of the appropriate regulatory bodies obtained prior to study initiation. If required, the Sponsor will also ensure that the implementation of substantial amendments to the protocol and other relevant study documents happen only after approval by the relevant regulatory authorities.

13.3 Informed Consent

Informed consent is a process by which a patient voluntarily confirms his or her willingness to participate in a particular study after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated ICF.

The ICF will be submitted for approval to the IRB that is responsible for review and approval of the study. Each ICF must include all of the relevant elements currently required by the FDA, as well as local country authority or state regulations and national requirements.

Before recruitment and enrollment into the study, each prospective candidate will be given a full explanation of the research study. Once the essential information has been provided to the prospective candidate, and the Investigator is sure that the individual candidate understands the implications of participating in this research study, the candidate will be asked to give consent to participate in the study by signing an ICF. A notation that written informed consent has been obtained will be made in the patient's medical record. A copy of the ICF, to include the patient's signature, will be provided by the Investigator to the patient.

If an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

13.3.1 Confidentiality

13.3.1.1 Patient Confidentiality

Confidentiality of patients' personal data will be protected in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require that, in order to participate in the study, a patient must sign an authorization form for the study that he or she has been informed of the following:

- What PHI will be collected from patients in this study
- Who will have access to that information and why
- Who will use or disclose that information
- That health information may be further disclosed by the recipients of the information, and that if the information is disclosed the information may no longer be protected by federal or state privacy laws
- That the information collected about the research study will be kept separate from the patient's medical records, but the patient will be able to obtain the research records after the conclusion of the study
- Whether the authorization contains an expiration date

- The rights of a research patient to revoke his or her authorization.

In the event that a patient revokes authorization to collect or use his or her PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (e.g., that the patient is alive) at the end of their scheduled study period.

In compliance with ICH GCP guidelines and applicable parts of 21 CFR it is a requirement that the Investigator and institution permit authorized representatives of Innovations, the regulatory authorities, and the IRB direct access to review the patient's original medical records at the site for verification of study-related procedures and data.

One measure to protect confidentiality is that only a unique study number will identify patients in the eCRF or other documents submitted to Innovations. This information, together with the patient's year of birth, will be used in the database for patient identification. Patient names or addresses will not be entered in the eCRF. No material bearing a patient's name will be kept on file by Innovations. Patients will be informed of their rights within the ICF.

13.3.1.2 Investigator and Staff Information

Personal data of the Investigators and sub-Investigators may be included in the Innovations database, and shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator or sub-Investigator, Innovations shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized party.

13.4 Financial Information

The finances for this clinical study will be subject to a separate written agreement between Sarah Cannon Development Innovations, LLC and applicable parties. Any Investigator financial disclosures as applicable to 21 CFR Part 54 shall be appropriately provided.

14. RESEARCH RETENTION AND DOCUMENTATION OF THE STUDY

14.1 Amendments to the Protocol

Amendments to the protocol shall be planned, documented, and signature authorized prior to implementation.

If an amendment to the protocol is required, the amendment will be originated and documented by Innovations. All amendments require review and approval of all pharmaceutical companies providing funding for the study and of the PI supporting the study. The written amendment must be reviewed and approved by Innovations, and submitted to the IRB at the Investigator's facility for the board's approval.

Items requiring a protocol amendment approved by the IRB of record for the Investigator's facility and the FDA or other regulatory authorities include, but are not limited to, the following:

- Change to study design
- Risk to patients

- Increase to dose or patient exposure to drug
- Patient number increase
- Addition or removal of tests and/or procedures
- Addition/removal of an Investigator

The amendment will be submitted formally to the IRB and the FDA or other regulatory authorities by Innovations.

It should be further noted that, if an amendment to the protocol substantially alters the study design or the potential risks to the patients, the patient's consent to continue participation in the study should be obtained.

14.2 Documentation Required to Initiate the Study

Before the study may begin, certain documentation required by FDA regulations and ICH GCP must be provided by the Investigator. The required documentation should be submitted to:

Sarah Cannon Development Innovations
Regulatory Department
1100 Dr. Martin L. King Jr. Blvd.,
Suite 800
Nashville, TN 37203

Documents at a minimum required to begin a study in the US include, but are not limited to, the following:

- A signature-authorized protocol and contract
- A copy of the official IRB approval of the study and the IRB members list
- Current curricula vitae for the PI and any associate Investigator(s) who will be involved in the study
- Indication of appropriate accreditation for laboratories (as required) to be used in the study and the normal ranges for tests to be performed by those laboratories
- Original Form FDA 1572 (Statement of Investigator), appropriately completed and signed
- A copy of the IRB-approved ICF containing permission for audit by representatives of Innovations, the IRB, and the FDA and other regulatory agencies (as applicable)
- Financial disclosure forms for all Investigators listed on Form FDA 1572 (if applicable)
- Verification of PI acceptability from local and/or national debarment list(s).

14.3 Study Documentation and Storage

The PI must maintain a list of appropriately qualified persons to whom he/she has delegated study duties and should ensure that all persons assisting in the conduct of the study are informed of their obligations. All persons authorized to make entries and/or corrections on the eCRFs are to be included on this document. All entries in the patients' eCRFs are to be supported by source documentation where appropriate.

Source documents are the original documents, data, records, and certified copies of original records of clinical findings, observations, and activities from which the patient's eCRF data are obtained. These can include, but are not limited to, hospital records, clinical and office charts, laboratory, medico-technical department and pharmacy records, diaries, microfiches, ECG traces, copies or transcriptions certified after verification as being accurate and complete, photographic negatives, microfilm or magnetic media, x-rays, and correspondence.

The PI and study staff members are responsible for maintaining a comprehensive and centralized filing system (e.g., regulatory binder or Investigator study file [ISF]) of all essential study-related documentation, suitable for inspection at any time by representatives from the Sponsor and/or applicable regulatory authorities. The ISF must consist of those documents that individually or collectively permit evaluation of the conduct of the study and the quality of the data produced. The ISF should contain at a minimum all relevant documents and correspondence as outlined in ICH GCP Section 8 and 21 CFR Part 312.57, including key documents such as the IB and any amendments, the protocol and any amendments, signed ICFs, copies of completed eCRFs, IRB approval documents, Financial Disclosure forms, patient identification lists, enrollment logs, delegation of authority log, staff qualification documents, laboratory normal ranges, and records relating to the study drug including accountability records. Drug accountability records should, at a minimum, contain information regarding receipt, shipment, and disposition. Each form of drug accountability record, at a minimum, should contain PI name, date the drug shipped/received, and the date, quantity, and batch/code or lot number for the identity of each shipment. In addition, all original source documents supporting entries in the eCRF must be maintained and readily available.

Innovations shall maintain adequate investigational product and financial interest records as per 21 CFR Part 54.6 and Part 312.57 for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, for no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued and the FDA has been notified of the discontinuation.

The Investigator shall maintain adequate records of drug disposition, case histories, and any other study-related records as per 21 CFR Part 312.62, for no less than 2 years after the last marketing application has been approved by FDA; or, in the event that the marketing application has not been approved by FDA, no less than 2 years after the last shipment/delivery of the drug for investigational use or the drug is discontinued and FDA has been notified of the discontinuation.

To enable evaluations and/or audits from regulatory authorities or from the Sponsor or its representative, the Investigator additionally agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., eCRF records and medical records), all original signed ICFs, copies of all eCRF records, SAE Reporting forms, source documents, detailed records of treatment disposition, and related essential regulatory documents. The documents listed above must be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). Sponsor will notify the Investigator(s)/institutions(s) when the study-related records are no longer required.

If the Investigator relocates, retires, or for any reason withdraws from the study, Innovations must be prospectively notified. The study records must be transferred to an acceptable designee,

such as another Investigator, another institution, or to Innovations. The Investigator must obtain Innovations' written permission before disposing of any records, even if retention requirements have been met. All study files will be maintained by Innovations throughout the study, and will be held by Innovations at the conclusion of the study.

14.4 Data Collection

The study eCRF is the primary data collection instrument for the study. Case report forms will be completed using the English language and should be kept current to enable Innovations to review the patients' status throughout the course of the study.

In order to maintain confidentiality, only study number, patient number, and year of birth will identify the patient in the eCRF. If the patient's name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to Innovations and be replaced instead with the patient number and other identifier (e.g., patient initials) as allowed per institutional policy. The Investigator will maintain a personal patient identification list (patient numbers with corresponding patient identifiers) to enable records to be identified and verified as authentic. Patient data/information will be kept confidential, and will be managed according to applicable local, state, and federal regulations.

All data requested in the eCRF system must be supported by and be consistent with the patient's source documentation. All missing data must be explained. When a required laboratory test, assessment, or evaluation has not been done or an "Unknown" box is not an option on the eCRF, a note should be created verifying that the test was "Not Done" or the result was "Unknown." For any entry errors made, the error(s) must be corrected, and a note explaining the reason for change should be provided. The Investigator will electronically sign and date the patient eCRF casebook indicating that the data in the eCRF has been assessed. Each completed eCRF will be signed and dated by the PI, once all data for that patient is final.

14.5 Disclosure and Publication Policy

All information provided regarding the study, as well as all information collected/documented during the course of the study, will be regarded as confidential. The Sponsor reserves the right to release literature publications based on the results of the study. Results from the study will be published/presented as per the Sponsor's publication process.

Inclusion of the Investigator in the authorship of any multi-center publication will be based upon substantial contribution to the study design, the analysis, or interpretation of data, or the drafting and/or critically revising of any manuscript(s) derived from the study. The Investigator acknowledges that the study is part of a multi-center study and agrees that any publication by the Investigator of the results of the study conducted at the research site shall not be made before the first multi-center publication.

In the event there is no multi-center publication within fifteen (15) months after the study has been completed or terminated at all study sites, and all data has been received, the Investigator shall have the right to publish his/her results from the study, subject to the notice requirements described herein and subject to acknowledgement of the Sponsor as appropriate. The Investigator shall provide the Sponsor thirty (30) days to review a manuscript or any poster presentation, abstract or other written or oral material which describes the results of the study for the purpose only of determining if any confidential or patentable information is disclosed

thereby. If the Sponsor requests in writing, the Investigator shall withhold any publication or presentation an additional sixty (60) days solely to permit the Sponsor to seek patent protection and to remove any Innovations confidential information from all publications.

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16. APPENDICES

Appendix A: ECOG Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	**Descriptions**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

Appendix B: New York Heart Association (NYHA) Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

Appendix C: Guidelines for Female Patients of Childbearing Potential and Fertile Male Patients

Acceptable Contraception Methods:

Women of childbearing potential (WoCBP), defined as all women physiologically capable of becoming pregnant, must use highly-effective contraception during the study and until 2 days following the last dose of acalabrutinib. For male subjects with a pregnant or non-pregnant WoCBP partner, no contraception measures are required.

Highly effective contraception is defined as either:

True Abstinence	When this is in line with the preferred and usual lifestyle of the patient during the entire period of risk associated with the study drug. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
Sterilization	When a WoCBP has had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks prior to study entry. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
Female condom	Barrier methods of contraception: condom or an occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository.
Male Partner Sterilization	With the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate.
Intrauterine device	Placement of an intrauterine device (IUD) or intrauterine system (IUS)
Hormonal contraception	Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal. Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable.

Hormonal contraception may be susceptible to interaction with the study drug or other drugs, which may reduce the efficacy of the contraception method.

If a contraceptive method is restricted by local regulations/guidelines, then it does not qualify as an acceptable highly effective method of contraception for subjects participating at sites in the relevant country/region.

Subjects should promptly notify the Investigator if they, or for male subjects their partner, become pregnant during this study, or within 2 days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 11.3.8.

Acceptable forms of barrier contraception include:

- Latex condom, diaphragm or cervical/vault cap when used with spermicidal foam/gel/film/cream/suppository

Unacceptable methods of contraception include:

- Periodic abstinence
- Natural family planning (rhythm method) or breastfeeding
- Fertility awareness
- Withdrawal
- Triphasic combined oral contraceptives
- All progesterone only pills, except Cerazette™
- All barrier methods, if intended to be used alone
- Non-copper containing intrauterine devices

Pregnancies

To ensure patient safety, each pregnancy in a patient on the study drug must be reported to the Innovations Safety Department within 24 hours of learning of its occurrence. The pregnancy should be followed up for 3 months after the termination of the pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Study Pregnancy Form and reported by the Investigator to the Innovations Safety Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took the study drug in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Women Not of Childbearing Potential are Defined as Follows:

- Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e., age appropriate, history of vasomotor symptoms).
- Women <45 years of age a high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

- Women who are permanently sterilized at least 6 weeks before screening (e.g., bilateral tubal ligation/occlusion, hysterectomy, bilateral salpingectomy, bilateral oophorectomy).
- Women who are >45 years-of-age, not using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have a FSH value >40 mIU/mL and an estradiol value <40 pg/mL (140 pmol/L).
- Women who are >45 years-of-age, using hormone-replacement therapy and who have experienced total cessation of menses for at least 1 year OR who have had documented evidence of menopause based on FSH >40 mIU/mL and estradiol <40 pg/mL prior to initiation of hormone-replacement therapy.
- Women who had have a congenital or acquired condition that prevents childbearing.

Appendix D: Schedule of Assessments

ASSESSMENTS	Screening		Acalabrutinib Maintenance post-BMT[a]						
	Pre-BMT	Post-BMT[b]	Cycle1[c] ~4 mos. Post-BMT		Cycles 2-6[d] ~5-9 mos. post-BMT	Cycles 7-12[e] ~10-15 mos. post-BMT	Cycles 13 & beyond[f] ≥16 mos. post-BMT	End of treatment visit[g]	Follow-Up[h]
			D1	D15	D1 (±7 days)	D1 (±7 days)	D1		
Medical history & demographics	X								
Physical examination & weight	X	X	X	X	X	X	X		
ECOG PS		X	X		X	X	X		
Vital signs[i]		X	X		X	X	X		
ECG[j]		X							
CBC & CMP		X	X	X	X	X	X		
Coagulation testing[u]		X							
Urinalysis		X							
Pregnancy test[k]	X	X							
HIV test[l]		X							
Hepatitis B virus PCR[m]		X			X[m]	X[m]	X[m]	X[m]	
Hepatitis C virus PCR[n]		X[n]							
Archival tumor sample[o]	X	X[o]							
Fresh tumor biopsies[p]								X[p]	X[p]
MRD analysis (blood)[q]		X[q]			X[q]	X[q]	X[q]		
MRD analysis (BM aspirate)[r]		X[r]				X[r]			
CT/MRI/PET[s]		X			X[s]	X[s]	X[s]		
Acalabrutinib (oral) & drug compliance			129 mg twice daily continuously for 2 years post-BMT (~22 cycles)						
Concomitant medications	X	X	X	X	X	X	X	X	
AE evaluations[t]			X	X	X	X	X	X	
PFS follow-up									X

a. Acalabrutinib maintenance therapy begins on Day 100 post-BMT

b. Post-BMT screening should occur between Day +80 and Day +100

c. Begin between Day +100 and Day +120

d. Clinic visits will be monthly on Day 1 for Cycles 2-6 only (See Planned Clinic Visits table below)

e. Cycles 7-12 only: clinic visits will **occur every 2 months for 6 months** (See Planned Clinic Visits table below)

f. Cycle 13 and beyond until 5 years post-BMT: **clinic visits will occur every 3 months** (See Planned Clinic Visits table below)

g. Within 30 days of last dose of acalabrutinib

h. A telephone call to assess PFS every 3 months can be made in lieu of an office visit

i. Blood pressure, pulse, oxygen saturation, and temperature

j. Subjects should be in supine position and resting for at least 10 minutes before any study-related ECGs are taken.

k. For women of childbearing potential only at the time of screening (post- and prior to BMT) and 72 hours before the start of treatment. Urine or serum pregnancy tests are acceptable.

l. Patients with a known history of human immunodeficiency virus (HIV) or who are HIV antibody positive should be tested for HIV RNA during screening. No further testing beyond screening is necessary if PCR results are negative, except if clinically indicated (see Section 6.5.6).

m. Only patients who are anti-HBc positive, or have a known history of HBV, should have quantitative PCR testing for HBV DNA performed during screening and every 3 months thereafter. Monitoring (every 3 months) should continue until 12 months after last dose of acalabrutinib. As IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in patients who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy (see Section 6.5.6).

n. Patients with a known history of hepatitis C virus (HCV) or who are hepatitis C antibody positive should be tested for HCV RNA during screening. No further testing beyond screening is necessary if PCR results are negative, except if clinically indicated (see Section 6.5.6).

o. If not obtained during Screening #1 (prior to BMT)

p. Collect a fresh lymphoma biopsy at disease progression

q. **MRD analysis with blood sample:** Collect a blood sample prior to beginning maintenance on Day +100 (Screening #2), 6 months (~Cycle 4 Day 1), 1 year (~Cycle 10 Day 1) and 2 years post-BMT (~Cycle 22 Day 1).

r. **MRD analysis with bone marrow biopsy and aspirate:** Collect a bone marrow biopsy and aspirate prior to beginning maintenance on Day +100 (Screening #2) and at 1 year post-BMT (~Cycle 10 Day 1).

s. CT/MRI/FDG-PET scans will be done post-BMT (Day 80-100), at 6 months, 12 months, 18 months and 24 months. Thereafter, scans will be done per institutional standard operating procedures.

t. Record all AEs regardless of seriousness or relationship spanning from the first dose of acalabrutinib until 30 calendar days after discontinuation or completion of study drug.

u. Coagulation testing will include PT/INR or aPTT.

Planned Clinic Visits

Cycle 1		d. Cycles 2-6 only: clinic visits will occur every month					e. Cycles 7-12 only: clinic visits will occur every 2 months						f. Cycle 13 and beyond until 5 years post-BMT: clinic visits will occur every 3 months									
C1 D1	**C1 D15**	**C2 D1**	**C3 D1**	**C4 D1**	**C5 D1**	**C6 D1**	**C7 D1**	**C8 D1**	**C9 D1**	**C10 D1**	**C11 D1**	**C12 D1**	**C13 D1**	**C14 D1**	**C15 D1**	**C16 D1**	**C17 D1**	**C18 D1**	**C19 D1**	**C20 D1**	**C21 D1**	**C22 D1**
Visit	Visit	Visit	Visit	Required for 6 mo imaging	Visit	Visit	No Visit	Begin every 2 mo visits	No Visit	Required for 12 mo imaging	No Visit	Visit	Begin every 3 mo visits	No Visit	No Visit	Required for 18 mo imaging	No Visit	No Visit	Visit	No Visit	No Visit	Required For 24 mo imaging

Appendix E RECIL 2017: Response Categories Based on Assessment of Target Lesions

	% Change in sum of diameters of target lesions from nadir				
	CR	**PR**	**MR[a]**	**SD**	**PD**
% change from baseline	Complete disappearance of all target lesions and all nodes with long axis <10mm. ≥30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤ 20% increase in the sum of longest diameters of target lesions	>20% increase in the sum of longest diameters of target lesions For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauville score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

[a] A provisional category

Abbreviations: CR, complete response; CT, compute tomography; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, disease progression; PR, partial response; SD, stable disease.

Source: Younes et al 2017

Appendix F Response Designation Incorporating Best Response of Target Lesions and Nontarget Lesions

Target lesion	Nontarget lesion	New lesion	Response designation
CR	CR	No	CR
CR	PR, MR, or SD	No	PR[a]
CR	UE	No	UE
PR	UE	No	UE
PR	CR	No	PR
PR	PR, MR, or SD	No	PR
MR	UE	No	UE
MR	CR	No	MR
MR	PR, MR, or SD	No	MR
SD	UE	No	UE
SD	CR, PR, or MR	No	SD
SD	SD	No	SD
PD	Any	Yes/No	PD
Any	PD	Yes/No	PD
Any	Any	Yes	PD
CR	No	No	CR
PR	No	No	PR
MR	No	No	MR
SD	No	No	SD

[a] Compute tomography scan-based PR with complete normalization of [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography activity is considered CR

Abbreviations: CR, complete response; MR, minor response; PD, disease progression; PR, partial response; SD, stable disease; UE, unevaluable

Source: Younes et al 2017

Appendix G Cytochrome P450 3A4 Inhibitors and Inducers

Source: http://www.mayomedicallaboratories.com/it-mmfiles/Cytochrome_P450_3A4_and_3A5_Known_Drug_Interaction_Chart.pdf

CYP3A4 Inhibitors

Strong Inhibitors

Clarithromycin
Indinavir
Itraconazole
Ketoconazole
Nefazodone
Posaconazole
Ritonavir
Saquinavir
Suboxone
Telithromycin
Voriconazole
Conivaptin
Lopinavir/ritonavir
Nefazodone
Nelfinavir

Intermediate Strength Inhibitors

Aprepitant
Erythromycin
Fluconazole
Isavuconazole
Verapamil
Diltiazem

Weak Inhibitors

Cimetidine

Other Possible Inhibitors

Amiodarone
Boceprevir
Chloramphenicol
Ciprofloxacin
Delaviridine
Diethyl-dithiocarbamate
Fluvoxamine
Gestodene
Imatinib
Mibefradil
Mifepristone
Norfloxacin
Norfluoxetine
Starfruit
Telaprevir

CYP3A4 Inducers

Barbiturates
Carbamazepine
Efavirenz
Glucocorticoids
Modafinil
Nevirapine
Oxcarbazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
St. John's Wort
Troglitazone

Appendix H Management of Acalabrutinib-Related Adverse Events

Progressive multifocal leukoencephalopathy (PML)

Cases of PML have been reported in subjects treated with acalabrutinib.

Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.

If PML is suspected, hold further treatment with acalabrutinib until PML is excluded. A diagnostic evaluation may include (but is not limited to):

- Neurologic consultation
- Brain MRI
- PCR analysis for John Cunningham (JC) virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

Infections

Subjects receiving treatment with acalabrutinib may be at an increased risk of infection. Subjects should be made aware of the risk of possible overlapping toxicities of infections while receiving the study drug. This should be managed as per clinical practice. In case of Grade 3 infections, the guidelines provided in Table 3 should be followed.