LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

25 November, 2024

# SUMMARY OF CHANGES

**Protocol Amendment #6**

**LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas**

**AMENDMENT INCORPORATES:**

_X_ Editorial, administrative changes
__ Scientific changes
__ Therapy changes
__ Eligibility Changes

**Rationale for amendment:** The purpose of this amendment is to clarify the status of Acalabrutinib. AstraZeneca is providing a commercial supply of this drug for this study and the study is IND exempt, and therefore the references in the protocol to investigational drug have been updated.

**Editorial, administrative changes:**

| | |
|---|---|
| Throughout | Removed language referring to an Investigator's Brochure |
| Sections | |
| Sections 1.4 | Removed language referring to Acalabrutinib as investigational |
| Section 4.1.10 | Removed language referring to Acalabrutinib as investigational |
| Section 5.2 | Removed language referring to a Medical Monitor |
| Section 6.1 | Removed language referring to Acalabrutinib as investigational |
| Section 9.1.3 | Removed language referring to Acalabrutinib as investigational |
| Section 13.1 | Updated the URL for prohibited medication list in Appendix A |

***THE ATTACHED VERSION DATED 25 NOVEMBER, 2024 INCORPORATES THE ABOVE REVISIONS***

25 November, 2024

# SUMMARY OF CHANGES

**Protocol Amendment #5**

**LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas**

**AMENDMENT INCORPORATES:**

__ Editorial, administrative changes
_X_ Scientific changes
__ Therapy changes
_X_ Eligibility Changes

**Rationale for amendment:** The purpose of this amendment is to clarify that MYD88 and CXCR4 testing of tumor samples is optional, dependent on availability of tissue. Furthermore, eligibility criteria has been updated so that subjects who are currently receiving investigational treatments or have received an investigational agent within 28 days prior to dosing are not eligible for this study.

**Scientific changes:**

| | |
|---|---|
| Section 7.4.3 | Testing of tumor sample clarified as optional if available. |
| Section 8.1 | Time and events table and footnote 17 updated to clarify that tumor sample testing is optional if available. |

**Eligibility changes:**

| | |
|---|---|
| Section 4.2.3 | Exclusion criteria updated to state that subjects should not currently be receiving investigational treatment or have received an investigational agent within 28 days of dosing. |

***THE ATTACHED VERSION DATED July 26, 2023 INCORPORATES THE ABOVE REVISIONS***

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

25 November, 2024

# SUMMARY OF CHANGES

**Protocol Amendment #4**

**LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas**

**AMENDMENT INCORPORATES:**
_X_ Editorial, administrative changes
_X_ Scientific changes
___ Therapy changes
_X_ Eligibility Changes

**Rationale for amendment:** The purpose of this amendment is to remove antifungal prophylaxis from the protocol. Isavuconazole is cost prohibitive to the subject and evidence does not support antifungal prophylaxis in this setting.

**Editorial, administrative changes:**
Mechanical edits made as needed.

**Scientific changes:**

| | |
|---|---|
| Section 1.5 | Removed rationale for isavuconazole |
| Section 1.5.1.1 | Removed reference to isavuconazole relative to dose justification. |
| Section 1.5.1.2 | Removed isavuconazole section |
| Objective 2.3.2 | Removed isavuconazole from the objective. |
| Section 5.1 | Removed isavuconazole reference in schema and from Table 1. |
| Sections 5.2, 5.3 | Removed isavuconazole |
| Section 6.2 | Removed isavuconazole drug section |
| Section 8.1 | Removed isavuconazole from the Time and Events Table and removed associated footnote 15. |
| Section 13.5 | Removed reference to isavuconazole in the patient handout. |
| Appendix E | |

**Eligibility changes:**

| | |
|---|---|
| Criterion 4.1.10 | Removed inclusion criterion. |
| Criteria 4.2.8 and 4.2.16 | Removed isavuconazole from the criteria |

***THE ATTACHED VERSION DATED March 20, 2023 INCORPORATES THE ABOVE REVISIONS***

25 November, 2024

# SUMMARY OF CHANGES

**Protocol Amendment #3**

**LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas**

**AMENDMENT INCORPORATES:**
_X_ Editorial, administrative changes
_X_ Scientific changes
__ Therapy changes
_X_ Eligibility Changes

**Rationale for amendment:** The purpose of this amendment is to include the tablet form of acalabrutinib to the treatment plan. Eligibility was also updated given that the capsule form of acalabrutinib prohibits the enrollment of subjects who are currently being treated with acid reducing agents. Now the eligibility also states that the tablet form of acalabrutinib can be co-administered with all acid reducing agents. Drug information was updated throughout the protocol to account for both capsule and tablet forms of acalabrutinib. Honest broker language was also added to the protocol.

**Editorial, administrative changes:**
Section 7.4 Honest broker language added
Mechanical edits made throughout.

**Scientific changes:**
Section 6.1 Acalabrutinib tablet details added
Section 6.1 Storage conditions for Acalabrutinib tablet and capsule updated to 20°C-25°C (68°F-77°F) with excursions permitted to 15°C-30°C (59°F-86°F)
Section 6.1 Language for identified and potentials risks associated with Acalabrutinib updated.

**Eligibility changes:**
Section 4.2.10 Exclusion criteria updated to allow for enrollment of subjects on acalabrutinib tablets and the co-administration of acid reducing agents.

***THE ATTACHED VERSION DATED October 19, 2022 INCORPORATES THE ABOVE REVISIONS***

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

25 November, 2024

# PROTOCOL AMENDMENT #2

## LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas

**AMENDMENT INCORPORATES (check all that apply):**

X Editorial, administrative changes
Scientific changes (IRB approval)
X Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

The primary purpose of this protocol amendment is to update the eligibility criteria as it pertains to subjects with prior or current malignancies. A clarification regarding Hy's law was also added within the adverse events section.

**Editorial/Administrative**

1. Minor edits made where appropriate.

**Therapy**

1. A section about Hy's law was added to Section 9.2.

**Eligibility**

2. Criterion 4.1.11 was added to clarify eligibility for subjects with prior or current malignancies and in turn, the previous exclusion criterion 4.2.5 was removed.

***THE ATTACHED VERSION January 27, 2022 INCORPORATES THE ABOVE REVISIONS***

**ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL**

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

25 November, 2024

# PROTOCOL AMENDMENT #1

## LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas

**AMENDMENT INCORPORATES (check all that apply):**

X Editorial, administrative changes
X Scientific changes (IRB approval)
Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

The primary purpose of this protocol amendment is to change the study design from a Phase 2 Simon Two-stage study to a pilot study. Given the rarity of the disease and the accrual goal of 28 patients, the study is not feasible to complete the study in a timely fashion. The definition for the evaluability for toxicity was edited to indicate that toxicity evaluation begins with the first dose of acalabrutinib as it is the first drug administered. Additional administrative changes were made to clarify the dosing of isavuconazole, to change the funding source from Acerta Pharma to AstraZeneca, and to update language related to acalabrutinib relative to the package insert and investigator's brochure.

**Editorial/Administrative**

2. Mechanical edits made where appropriate.
3. Title changed to "Pilot Study."
4. Section 1,4 was updated to provide updated study and risk information for acalabrutinib.
5. A typo in the dosing for isavuconazole was corrected in section 1.5.1.2
6. The funding source on the protocol title page is changed to AstraZeneca from Acerta Pharma B.V.
7. Section 5.2: Table 2. Acalabrutinib Dose Modifications. Updated with current package insert information.
8. Section 5.3: Added vaccine guidance for the study.
9. Section 6.1: Updated acalabrutinib drug information and risks
10. Section 9.3.3: Language added to align with section 9.1.2.
11. Section 9.4.2 updated with new funding source name and information.
12. Appendix I: Added to include highly effective contraceptive methods

**Scientific**

1. Section 1.1: The change from a Phase 2, Simon Two-stage study was described.
2. Sections 1.1, 8.4, 10.3: Updated to clarify the number of evaluable subjects to be recruited.
3. Section 5.0:

a. Schema was modified to include the number of evaluable subjects to be recruited.
b. The description of the study was modified to tailor it to the new pilot design.
c. Figure 2 is deleted as it is no longer relevant.

4. Sections 8.3 and 5.2 were edited for consistency to indicate that evaluability for toxicity will begin with the first dose of acalabrutinib since it is the first study drug given.
5. Section 10 is updated to provide details of the new study design.
    a. Section 10.1: Study design is updated.
    b. Section 10.2: Sample size, accrual time, and statistical power is updated.
    c. Section 10.3 Addition of sample size.

**Eligibility**

3. Criterion 4.1.1 was added to eligibility and in turn, the previous exclusion criterion 4.2.24 was removed.
4. Criterion 4.1.2: Criterion was updated.
5. Criterion 4.1.11 was updated.
6. Criterion 4.2.5: Updated to add carcinoma in situ of the prostate
7. Criterion 4.2.22: Updated criterion
8. Criterion 4.2.24: Added criterion to allow the investigator to exclude a subject with a disease that may make it undesirable for a subject to participate in the study.
9. Criterion 4.2.25: Added to exclude subjects with progressive PML
10. Criterion 4.2.26: Added to exclude subjects receiving live vaccine within 28 days of the first dose of study drug
11. Criterion 4.2.27: Added to exclude subjects with significant infection
12. Criterion 4.2.28: Added to exclude subjects in a concurrent clinical trial
13. Criterion 4.2.29: Added to exclude subjects with life-threatening illness or conditions or other conditions that may increase the risk to the subject or study.

***THE ATTACHED VERSION November 15, 2021 INCORPORATES THE ABOVE REVISIONS***

**ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL**

25 November, 2024

# LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas

**Short Title**: Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas

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**Sponsor**: Lineberger Comprehensive Cancer Center

**Funding Source**: AstraZeneca
**Version:** Amendment 6
**Version date**: 25 November 2024

25 November, 2024

**LCCC1841: A Pilot Study of Acalabrutinib in Relapsed/Refractory Primary and Secondary CNS Lymphomas**

**Principal Investigator**
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**Signature Page**

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

**Principal Investigator (PI) Name**:_____

**PI Signature: _____**

**Date:_____**

**Version:** Amendment 6
**Version date**: November 25, 2024

# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AESI | Adverse event of special interest |
| AIHA | Autoimmune hemolytic anemia |
| ALP | Alkaline phosphatase |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| AUC | Area under the curve |
| BCR | B-cell receptor |
| BCRP | Breast cancer resistance protein |
| BID | *Bis in die* (twice daily) |
| BTK | Bruton's tyrosine kinase |
| CAP | College of American Pathologists |
| CBCD | Complete blood count with differential |
| CL/F | Oral clearance |
| CLIA | Clinical Laboratory Improvement Amendments |
| CLL | Chronic lymphocytic leukemia |
| Cmax | The maximum concentration of a drug in the body after dosing |
| CMP | Comprehensive metabolic panel |
| CNS | Central nervous system |
| CPO | Clinical Protocol Office |
| CR | Complete response |
| CRF | Case report form |
| Cru | Complete response/unconfirmed |
| CSF | Cerebrospinal fluid |
| CV | Curriculum vitae |
| CXCR | C-X-C chemokine receptor |
| CYP3A | Cytochrome P450 Family 3 Subfamily A |
| DLBCL | Diffuse large B-cell lymphoma |
| DoR | Duration of response |
| DSMB | Data and Safety Monitoring Board |
| DSMC | Data and Safety Monitoring Committee |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic case report form |
| FDA | Food and Drug Administration |
| FDG | Fludeoxyglucose |
| GCP | Good Clinical Practice |
| HBs-Ag | Hepatitis B surface antigen |
| HBc | Hepatitis B core |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| IDS | Investigational Drug Service |
| IEC | Institutional Ethics Committee |
| IL | interleukin |
| IRB | Institutional Review Board |
| ITP | Immune thrombocytopenic purpura |
| K | potassium |
| LCCC | Lineberger Comprehensive Cancer Center |
| LDH | Lactate dehydrogenase |
| MCL | Mantle cell lymphoma |
| Mg | Milligram |

| | |
|---|---|
| MMSE | Mini-Mental Status Examination |
| MRI | Magnetic resonance imaging |
| Na | Sodium |
| NC TraCS | North Carolina Translational and Clinical Sciences Institute |
| NCI | National Cancer Institute |
| NCI-CTCAE | National Cancer Institute – Common Terminology Criteria for Adverse Events |
| NFκB | Nuclear Factor kappa-light-chain enhancer of activated B cells |
| NK | Natural killer |
| NYHA | New York Heart Association |
| OHRE | Office of Human Research Ethics |
| ORR | Overall response rate |
| OS | Overall survival |
| PCNSL | Primary central nervous system lymphoma |
| PD | Progressive disease |
| PET | Positron emission tomography |
| PFS | Progression free survival |
| PI | Principal investigator |
| PCNSL | Primary CNS lymphoma |
| PCR | Polymerase chain reaction |
| PR | Partial response |
| PRC | Protocol review committee |
| Rb | Rubidium |
| RSNA | Radiological Society of North America |
| SAE | Serious adverse event |
| SAR | Suspected adverse reaction |
| SCNSL | Secondary central nervous system lymphoma |
| SD | Stable disease |
| SRS | Stereotactic radiosurgery |
| SUV | Standardized uptake value |
| TLR | Toll-like receptor |
| Tmax | The time after administration of a drug when the maximum plasma concentration is reached |
| TPF | Tissue Procurement Facility |
| ULN | Upper limit of normal |
| UNC | University of North Carolina |
| UNC-CH | University of North Carolina- Chapel Hill |
| UP | Unanticipated problem |
| USP | United States Pharmacopeia |
| Vss | Mean steady-state volume of distribution |
| WBRT | Whole-brain radiotherapy |

**TABLE OF CONTENTS**

# 1.0 BACKGROUND AND RATIONALE

## 1.1 Study Synopsis

LCCC 1841 is a multicenter open-label, single-arm, pilot study designed to investigate the antitumor effects of acalabrutinib in subjects with relapsed primary central nervous system lymphoma (PCNSL), and relapsed secondary CNS lymphoma (SCNSL) with no evidence of current systemic disease. Subjects with the following histological subtypes of lymphoma will be included in the study: diffuse large B-cell lymphoma (DLBCL, all subtypes); mantle cell lymphoma (MCL, all subtypes); plasmablastic lymphoma, and lymphoplasmacytic lymphoma. Up to 16 subjects will receive acalabrutinib at the dose of 100 mg approximately every 12 hours (See Study Schema) to attain a total of 15 evaluable subjects as defined in Section 8.4. If the study shows a positive effect of acalabrutinib in treating CNS lymphomas, acalabrutinib could become the standard relapsed CNS lymphoma regimen, not only for PCNSL, but also in certain subtypes of SCNSL. Any complete responses to acalabrutinib treatment will be clinically notable as spontaneous remissions do not occur.

In a previous study, ibrutinib showed a CR rate of 45% and an ORR of 68% [1]; in another study [2], ibrutinib showed a CR rate of 17% and an ORR of 55%. Thus, in order to recommend further investigation of acalabrutinib as a regimen for primary CNS lymphoma, acalabrutinib treatment must show an overall response rate (ORR) of at least 70%, which would demonstrate that it is not inferior to previously approved regimens.

## 1.2 Disease Background

PCNSL is an uncommon variant of extranodal non-Hodgkin lymphoma (NHL) that involves the brain, leptomeninges, eyes, or spinal cord without evidence of systemic disease. PCNSL represents approximately 4% of newly diagnosed primary CNS tumors [3, 4]. Secondary involvement of the CNS from systemic NHL may affect the nervous system at every level, including peripheral nerve, spinal nerve root, spinal cord, meninges, and brain. Such involvement may include direct invasion or compression of these structures, as well as non-invasive paraneoplastic effects of NHL. Both relapsed primary (PCNSL) and secondary CNS lymphomas (SCNSL) have a dismal prognosis, with untreated patients living for only several months [5]. Most data evaluating relapsed PCNSL are retrospective in nature, but traditional options are limited in this situation and include radiation, temozolomide, etoposide and cytarabine, all with modest response rates and poor long-term survival [5]. Furthermore, many of these patients are heavily pretreated and may have difficulty tolerating very aggressive cytotoxic chemotherapy regimens. In a study of aggressive chemotherapy in patients with SCNSL, the CR rate was only 22% with a one-year overall survival (OS) of 25% demonstrating the need for novel approaches other than traditional cytotoxic agents [6]. Therefore, more effective and well tolerated regimens are desperately needed.

## 1.3 Current Standard of Care

Initial frontline therapy in both primary and secondary CNS lymphomas includes high-dose methotrexate-based regimens. There is no standard of care for relapsed disease although patients who had a good initial response may be re-challenged with high-dose methotrexate. Unfortunately, this approach is often not possible due to poor performance status. Additionally, the majority of patients will relapse after second administration of methotrexate and will have few other available options.

Recent small studies evaluating novel agents have shown promise. These agents include ibrutinib, lenalidomide, and nivolumab.

### 1.3.1 Bruton Tyrosine Kinase Pathway and Ibrutinib

Bruton tyrosine kinase (BTK), a member of the Tec family of kinases, is a key enzyme in the B-cell receptor (BCR) signaling pathway and is essential for normal B-cell development [7, 8]. BTK functions as a bridge between the BCR and the activation of key downstream survival signals, including NF-κB. BTK integrates BCR and Toll-like receptor (TLR) signaling. Genes encoding members of these pathways frequently harbor mutations in DLBCL. These include the BCR-associated protein CD79B [9] and myeloid differentiation primary response 88 (MYD88), a cytosolic adapter protein that links IL1 and TLRs with NF-κB [10]. Activating mutations in MYD88 and CD79B have also been reported in PCNSL [11-14]. In a subset of B-cell malignancies, BTK is essential for proliferation and survival [15, 16]. In particular, knockdown of BTK induces tumor cell death in lymphoma cell lines that are dependent on BCR signaling[9, 17].

The first-in-class oral BTK inhibitor ibrutinib induced death of diffuse large B-cell lymphoma cells with deregulated BCR signaling [9] and showed promising results for the treatment of both primary and secondary CNS lymphomas with response rates of 68% (CR=45%) and 56% (CR=17%), respectively [18, 19]. Based on these data, further study into BTK inhibitors for use in the treatment of CNS lymphomas is warranted.

## 1.4 Acalabrutinib

Acalabrutinib is a potent inhibitor of BTK *in vitro* and *in vivo*. Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. Functional inhibition of non-target cells (e.g., T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations.

Acalabrutinib (also known as ACP-196 and/or Calquence®) is a selective, irreversible small molecule inhibitor of BTK. Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL).

### 1.4.1 Clinical Experience

As of 30 October 2020, more than 5000 subjects have participated in acalabrutinib clinical studies, with approximately 4600 subjects receiving acalabrutinib as monotherapy or in combination with other agents.

Evidence for the efficacy of acalabrutinib in subjects with CLL/SLL is based on 2 pivotal clinical studies (ACE-CL-007 and ACE-CL-309) and 3 supportive clinical studies (ACE-CL-001, ACE-CL-003, and 15-H-0016). The pivotal studies are described below.

In subjects with R/R CLL (Study ACE-CL-309), with a median follow-up of 16.1 months in the acalabrutinib arm and 15.7 months in the IR/BR arm, acalabrutinib demonstrated a 69% reduction in risk of IRC-assessed disease progression or death compared with IR/BR (HR = 0.31 [95% CI: 0.20, 0.49], $p < 0.0001$). The median estimated PFS for acalabrutinib was not reached; the median estimated PFS for IR/BR was 16.5 months (95% CI: 14.0, 17.1). The Kaplan Meier estimated 18-month PFS rates for acalabrutinib and IR/BR were 79.0% (95% CI: 69.7, 85.8) and 38.6% (95% CI: 27.3, 49.8), respectively. The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib compared with IR/BR (HR = 0.33; $p < 0.0001$). All other sensitivity analyses were also consistent with the primary analysis, confirming the robustness of the primary analysis. Analysis on the secondary endpoint of investigator-assessed PFS was consistent with primary analysis (HR = 0.28 [95% CI: 0.18, 0.45]; $p < 0.0001$). The clinical benefit with acalabrutinib was further demonstrated by a clinically relevant improvement in DOR for acalabrutinib compared with IR/BR, both by IRC assessment (HR = 0.33) and investigator-assessment (HR = 0.20), and a significant prolongation of TTNT for acalabrutinib compared with IR/BR (HR = 0.35; $p < 0.0001$). ORR (CR + CRi + nPR + PR) for acalabrutinib and IR/BR was similar based on IRC assessment (81.3% and 75.5%, respectively) and investigator assessment (79.4% and 83.2%, respectively). The median OS was not reached in either treatment arm, with a HR of 0.84 (95% CI: 0.42, 1.66; $p = 0.6089$).

In subjects with previously untreated CLL (Study ACE-CL-007), with a median follow-up of 28.5 months, 28.4 months, and 28.0 months in the acalabrutinib + obinutuzumab, acalabrutinib monotherapy, and obinutuzumab + chlorambucil arms, respectively, acalabrutinib + obinutuzumab demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with a 90% reduction in risk of disease progression or death (HR = 0.10 [95% CI: 0.06, 0.17]; $p < 0.0001$). Acalabrutinib monotherapy also demonstrated a statistically significant improvement in IRC-assessed PFS compared with obinutuzumab + chlorambucil, with an 80% reduction in risk of disease progression or death (HR = 0.20 [95% CI: 0.13, 0.30]; $p < 0.0001$). The median estimated PFS was not reached for acalabrutinib + obinutuzumab or acalabrutinib monotherapy and was 22.6 months (95% CI: 20.2, 27.6) for obinutuzumab + chlorambucil. The KM estimated 24-month PFS rate for

acalabrutinib + obinutuzumab was 92.7% (CI 95%: 87.4, 95.8), acalabrutinib monotherapy was 87.3% (CI 95%: 80.9, 91.7), and obinutuzumab + chlorambucil was 46.7% (CI 95%: 38.5, 54.6).

The key sensitivity analysis of PFS without censoring for subsequent anticancer therapy was consistent with the primary analysis and showed similar improvement in PFS for acalabrutinib + obinutuzumab and acalabrutinib monotherapy compared with obinutuzumab + chlorambucil (HR = 0.11 [95% CI: 0.06, 0.18] and HR = 0.20 [95% CI: 0.13, 0.31], respectively). All other sensitivity analyses were also consistent with the primary analysis. The clinical benefit with acalabrutinib was further demonstrated by a significant prolongation of TTNT compared with obinutuzumab + chlorambucil for both acalabrutinib + obinutuzumab (HR = 0.14 [95% CI: 0.08, 0.26]; $p < 0.0001$) and acalabrutinib monotherapy (HR = 0.24 [95% CI: 0.15, 0.40]; $p < 0.0001$). IRC-assessed ORR for acalabrutinib + obinutuzumab and obinutuzumab + chlorambucil was 93.9% (95% CI: 89.3, 96.5) and 78.5% (95% CI: 71.9, 83.9), respectively, with a statistically significant difference between treatment arms of 15.3% ($p < 0.0001$). The IRC-assessed ORR in the acalabrutinib monotherapy arm was 85.5% (95% CI: 79.6, 89.9) ($p = 0.0763$ compared with the obinutuzumab + chlorambucil arm). The median OS was not reached in any treatment arm, with an HR of 0.47 (95% CI: 0.21, 1.06; $p = 0.0577$) for acalabrutinib + obinutuzumab compared with obinutuzumab + chlorambucil, and an HR of 0.60 (95% CI: 0.28, 1.27; $p = 0.1556$) for acalabrutinib monotherapy compared with obinutuzumab + chlorambucil.

### 1.4.2 Adverse Events

An aggregate safety analysis of acalabrutinib monotherapy was conducted in order to assess safety for acalabrutinib-exposed subjects with hematologic malignancies without confounding toxicity from combination therapy drugs. The analysis was performed on a 9-study integrated monotherapy population (hereafter called 'Mono HemMalig population'), which consisted of treated subjects in 6 acalabrutinib monotherapy studies (ACE-CL-309, 15-H-0016, ACE-CL- 001, ACE-LY-002, ACE-LY-004, and ACE-WM-001) and treated subjects in the acalabrutinib monotherapy treatment arms of 3 additional combination studies (ACE-CL-007, ACE-LY-003 and ACE-MY-001). As of the 30 October 2020 data extraction date, the pooled Mono HemMalig population represented 1079 acalabrutinib-exposed subjects with a median exposure of 28.5 months (range: 0.0 to 65.3 months). On the basis of the analysis of data from this pooled population, the overall safety of acalabrutinib monotherapy in subjects with hematologic malignancies is considered acceptable.

A total of 1052 subjects (97.5%) had at least 1 AE, and over half (650 subjects [60.2%]) had at least one Grade ≥ 3 AE. The most commonly reported AEs (≥ 20%) of any grade were diarrhea (37.7%), headache (37.4%), upper respiratory tract infection (26.3%), cough (23.6%), fatigue (23.0%), contusion (22.5%), nausea (22.2%), and arthralgia (21.3%). The most frequently reported Grade ≥ 3 AEs (≥

2%) were neutropenia (12.0%), anemia (7.8%), pneumonia (6.3%), hypertension (3.8%), thrombocytopenia (3.5%), diarrhea (3.0%), syncope (2.4%), and dyspnea (2.0%).

Treatment-related AEs were reported for 792 subjects (73.4%), and 284 subjects (26.3%) had Grade ≥ 3 treatment-related AEs. The most frequently reported treatment-related AEs (≥ 5%) of any grade were headache (26.1%), diarrhea (17.9%), contusion (14.5%), neutropenia (9.5%), nausea (8.8%), fatigue (8.6%), arthralgia (6.9%), petechiae (6.0%), and upper respiratory tract infection (5.5%). The most frequently reported treatment-related Grade ≥ 3 AE (≥ 2%) was neutropenia (8.5%).

In the Mono HemMalig population, 5 subjects experienced fatal AEs that were considered by the investigator to be related to study treatment. These events included intracranial hematoma (Study ACE-WM-001), hepatic failure (Study 15-H-0016), febrile neutropenia (Study ACE-CL-007), malignant brain neoplasm (Study ACE-CL-309), and pneumonia (Study ACE-CL-309).

## 1.5 Rationale for Clinical Study

As mentioned above, BTK inhibitor, ibrutinib, has shown particular efficacy in PCNSL with response rates of 56-68% with reported complete response (CR) rates of 17-45% [18, 19]. Case reports of the treatment of systemic mantle cell lymphoma that has relapsed in the CNS, have also shown efficacy for ibrutinib in the setting of secondary CNS lymphoma [20, 21]. These are very encouraging results warranting further investigation of BTK inhibitors in this setting. Acalabrutinib is another BTK inhibitor which may be studied in the context of CNS lymphoma.

We hypothesize that acalabrutinib, a potent and selective BTK inhibitor, may be safe and effective for the treatment of relapsed CNS lymphomas. Published literature on acalabrutinib suggests good outcomes in the treatment of MCL [22, 23]. Phase 2 trials of acalabrutinib in relapsed/refractory MCL reported an ORR of 80.6% with a CR rate of 39.5%. Importantly, there were no cases of atrial fibrillation in the acalabrutinib study, and only 1 case of grade 3 or higher gastrointestinal hemorrhage. The safety profile is particularly relevant to CNS lymphomas, as many patients with this disease are older and may have comorbidities. These factors can increase their chance of having adverse events. With good response rates and tolerability profile, acalabrutinib is an attractive agent to study in CNS lymphomas. As a result, acalabrutinib is an exciting candidate for further study in relapsed/refractory primary and secondary CNS lymphomas.

### 1.5.1 Dose Rationale

#### 1.5.1.1 Acalabrutinib

The pharmacokinetics (PK) of acalabrutinib has been studied in healthy subjects and patients with B-cell malignancies. Acalabrutinib exhibits linear PK across a

dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dose of 100 mg) and exhibits dose-proportionality. Acalabrutinib is highly permeable and is rapidly absorbed after oral administration (median Tmax 0.75 hours in plasma). In healthy subjects receiving a single dose of acalabrutinib (100 mg), an absolute oral bioavailability was 25% (range 20% to 30%). Acalabrutinib solubility is pH-dependent across the physiologic pH range and concurrent use of proton pump inhibitors on this protocol is prohibited. Acalabrutinib may be taken without regard to meals. Acalabrutinib is known to be reversibly bound (97.5%) to human plasma protein. The *in vitro* mean blood-to plasma ratio was 0.7. The mean steady-state volume of distribution (Vss) in healthy subjects following an intravenous administration (100 mg, single dose) was approximately 34 L. *In vitro* assays suggest that acalabrutinib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP); however, the extent that acalabrutinib or its active metabolite, ACP-5862 penetrate the blood-brain barrier is unknown.

Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{1/2}$) of acalabrutinib was 0.9 (range: 0.6 to 2.8) hours. The $t_{1/2}$ of the active metabolite, ACP-5862, was 6.9 hours. Acalabrutinib does not accumulate in plasma upon repeat-dose administration. Acalabrutinib mean apparent oral clearance (CL/F) was 159 L/hr with similar PK between patients and healthy subjects, based on population PK analysis. Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis. The most abundant circulating metabolite in human was ACP-5862, which was formed by CYP3A-mediated oxidation. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean exposure (AUC) that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition. Please refer to Appendix A for a list of medications that are either prohibited or should be used with caution when used with drugs such as acalabrutinib that are metabolized by the CYP3A family of enzymes.

Acalabrutinib will be administered in this study at 100 mg once every 12 hours.

## 1.6 Correlative Studies

In addition to assessments driven by the study treatment, this study will evaluate blood and CSF pharmacokinetic parameters of acalabrutinib and its active metabolite, ACP-5862. Molecular testing will be performed on biopsy samples to evaluate the presence of mutations in the MYD88 and CXCR4 genes, if there is sufficient tissue from the original biopsy. Additionally, the utility of $^{82}$Rubidium as a positron emission tomography-radiotracer will be evaluated in the first five subjects at the University of North Carolina who consent to this scan.

### 1.6.1 Pharmacokinetic Profile of Acalabrutinib

Standard plasma pharmacokinetic parameters including area under the plasma concentration versus time curve for acalabrutinib and its active metabolite, ACP-5862 will be estimated using non-compartmental analysis.

Uptake of acalabrutinib and its active metabolite, ACP-5862 will also be characterized in cerebrospinal fluid at sparse time points.

### 1.6.2 Somatic Mutations in MYD88 and CXCR4

MYD88 and CXCR4 testing on specimens will be used to determine correlation of mutational status and response to treatment with acalabrutinib. Myeloid differentiation primary response 88 (MYD88) L265P mutation and wild-type C-X-C chemokine receptor type 4 (CXCR-4) have been previously shown to be predictors of good response to ibrutinib therapy, while wild-type MYD88 and wild-type CXCR-4 have been shown to be predictors of poor response. Note, testing will only be done if there is sufficient tissue available.

### 1.6.3 Rubidium-82 Positron-Emission Tomography

Magnetic resonance imaging (MRI) scans have traditionally been used to monitor for responses and relapses in patients with CNS lymphoma. However, early scanning using $^{18}$F-FDG PET scans may offer earlier and more reliable information about treatment responses [28]. Birsen *et al.* performed $^{18}$F-FDG PET of the brain pre-treatment and after 2 cycles in 25 patients treated with intensive chemotherapy for newly diagnosed PCNSL. The 2-year PFS was 72% for patients with a negative $^{18}$F-FDG PET scan after 2 cycles ($^{18}$F-FDG PET 2) versus only 33% in patients with residual disease on PET2. However, $^{18}$F-FDG PET scans can be difficult to interpret in the brain since there is intense FDG uptake in the normal brain tissue [28]. The PET radiotracer, $^{82}$Rubidium may have even better predictive power since Rb is taken up by tumor cells, but not normal brain.

Therefore, we will evaluate the utility of $^{82}$Rubidium as a PET-radiotracer in a small subset of subjects enrolled at the University of North Carolina for a radiographic correlative study. $^{82}$Rubidium is a potassium analog, which is taken up by tumor and myocardial cells actively through sodium-potassium (Na-K) ATPase. $^{82}$Rubudium chloride (RbCl) has been used as a PET radiotracer for more than four decades. Its high first-pass effect and extraction fraction make it particularly suitable for myocardial stress perfusion PET imaging for which it is approved by the FDA. UNC has operated a Rb cardiac PET program for more than a decade, performing about 1000 scans annually.

Rubidium has also been studied in cancer imaging [29-31]. Its success has been greatly limited by relatively high physiologic Rb uptake in normal organs and surrounding structures in the body, and success and availability of $^{18}$F-FDG PET. However, there is intense FDG uptake in normal brain, while rubidium uptake is indicative of loss of integrity of the blood brain barrier [32]. Therefore, Rb has the potential to be used for imaging and therapy monitoring in brain tumors, including

brain lymphomas. Of note, Thallium-201 chloride (Tl), another potassium analog, is avidly taken up by CNS lymphomas and has been used clinically to differentiate lymphoma from toxoplasmosis in HIV patients [33]. While biologic characteristics of Rb are very similar to those of Tl, Rb has much superior imaging characteristics as a PET radiotracer compared to Tl, which is a SPECT radiotracer. In short, Rb has a much higher resolution than Tl and is quantifiable using SUV.

The Division of Nuclear Medicine at UNC has been interested in Rb as a cancer imaging biomarker. We have published our incidental findings on Rb cardiac PET [34]. Recently, we have quantified Rb uptake in malignant tumors with SUV and presented our findings at 2017 RSNA [35]. Another abstract was presented at the 2018 Society of Nuclear Medicine and Molecular Imaging meeting [36].

# 2.0 STUDY OBJECTIVES

## 2.1 Primary Objectives

Determine overall response rate (ORR) in subjects with relapsed/refractory primary and secondary CNS lymphoma receiving acalabrutinib.

## 2.2 Secondary Objectives

**2.2.1** Assess toxicity of acalabrutinib in subjects with relapsed/refractory primary and secondary CNS lymphoma.

**2.2.2** Determine clinical activity of acalabrutinib in subjects with relapsed/refractory primary and secondary CNS lymphoma by assessment of the median progression free survival (PFS).

**2.2.3** Determine the complete response (CR) rate of acalabrutinib for the treatment of relapsed/refractory primary and secondary CNS lymphoma.

**2.2.4** Determine duration of response (DoR) in subjects with relapsed/refractory primary and secondary CNS lymphoma receiving acalabrutinib.

**2.2.5** Determine overall survival (OS) in subjects with relapsed/refractory primary and secondary CNS lymphoma receiving acalabrutinib.

## 2.3 Exploratory Objectives

**2.3.1** [redacted].

**2.3.2** [redacted]

**2.3.3** [redacted].

**2.3.4** [redacted]

# 3.0 STUDY ENDPOINTS

## 3.1 Primary Endpoint

Determine overall response rate (ORR; ORR= Partial Response + Complete Response) at 2 months as measured by the International Primary CNS Lymphoma Collaborative Group Response assessment criteria [37] in subjects with relapsed/refractory primary and secondary CNS lymphoma receiving acalabrutinib.

## 3.2 Secondary Endpoints

**3.2.1** Toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 5.0).

**3.2.2** Progression-free survival (PFS) is defined from the date of initiating study treatment to the date of disease progression per the International Primary CNS Lymphoma Collaborative Group response assessment criteria [37] or death as a result of any cause.

**3.2.3** Complete Response (CR) is defined using the International Primary CNS Lymphoma Collaborative Group response assessment criteria for primary CNS lymphoma [37].

**3.2.4** Duration of response (DoR) is defined as time from documentation of tumor response to disease progression according to the International Primary CNS Lymphoma Collaborative Group response assessment criteria [37].

**3.2.5** OS will be measured from the date of initiating study treatment to the date of death or 5 years (whichever is first). Subjects who have not died by the analysis data cut-off date will be censored at their last date of contact.

## 3.3 Exploratory Endpoints

**3.3.1** [redacted]

[redacted]

**3.3.2** [redacted]

**3.3.3** [redacted].

**3.3.4** [redacted]

# 4.0 SUBJECT ELIGIBILITY

In order to participate in this study a subject must meet *all* of the eligibility criteria outlined below.

## 4.1 Inclusion Criteria

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

**4.1.2** Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations)..

**4.1.3** Age ≥18 years at the time of consent.

**4.1.4** Subject has adequate performance status as defined by ECOG of ≤ 2. (*Note*: Performance status can be assessed after administration of corticosteroids.)

**4.1.5** Subject has histological confirmation of biopsy-proven CNS lymphoma OR MRI findings consistent with CNS lymphoma if biopsy is not possible (due to inaccessible location). Subjects with intra-ocular lymphoma will not be excluded as long as there is also parenchymal disease.

**4.1.6** Subject has B-cell Non-Hodgkin Lymphoma.

**4.1.7** Subject has no evidence of systemic involvement of lymphoma confirmed by CT or PET-CT imaging within 28 days prior to first dosing in the study.

**4.1.8** Subject must have received at least one prior line of chemotherapy for primary or secondary CNS lymphoma. There is no limit on the number of prior treatment regimens.

**4.1.9** Subject has adequate organ function as demonstrated by:

| System | Laboratory Value |
|---|---|
| **Hematological*** | |
| Absolute Neutrophil Count (ANC) | ≥ 1 x $10^9$/L |
| Platelets | ≥ 75 x $10^9$/L |
| **Renal*** | |
| Calculated creatinine clearance | ≥ 30 mL/min using the Cockcroft-Gault formula (Appendix B) |

| | |
|---|---|
| **Hepatic*** | |
| Bilirubin | ≤ 1.5 × upper limit of normal (ULN). Subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level >1.5 mg/dL if their conjugated bilirubin is <1.5× ULN) |
| Aspartate aminotransferase (AST) | ≤ 2.5 × ULN |
| Alanine aminotransferase (ALT) | ≤ 2.5 × ULN |
| **Coagulation*** | |
| International Normalized Ratio (INR) or Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) | ≤ 2 × ULN (in the absence of lupus anticoagulant) |

**4.1.10** Subjects with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the treatment are eligible for this trial.

**4.1.11** Female subjects of childbearing potential must have a negative serum pregnancy test within three days (72 hours) prior to initiating study treatment.

**4.1.11.1** *Note*: Females subjects of childbearing potential are women who are fertile following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Women are considered to be of non-reproductive potential if they meet any of the following criteria:

- Postmenopausal, defined as at least 12 months with no menses without an alternative medical cause; in 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.
- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks before Screening
- Have a congenital or acquired condition that prevents childbearing.
- Females of childbearing potential must be willing to abstain from heterosexual activity or to use 2 forms of effective methods of contraception (as defined in Appendix I) from the time of informed consent until 2 days after the last dose of acalabrutinib. The two contraception methods can be comprised of two barrier methods, or a barrier method plus a hormonal method.

## 4.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria will *not* be able to participate in this study

**4.2.1** Prior cancer treatment that was completed less than 14 days prior to Day 1 of study dosing or if subject has not recovered from all reversible acute toxic effects of the regimen to grade ≤1 or baseline.

**4.2.2** Prior brain radiotherapy under the following conditions:

- Whole-brain radiotherapy (WBRT) that was completed less than 28 days prior to Day 1 of study dosing
- Stereotactic radiosurgery (SRS) that was competed less than 14 days prior to Day 1 of study dosing.

**4.2.3** Currently receiving or has received an investigational agent within 28 days of first dosing with study treatment. Subjects should not currently be receiving investigational treatment or have received an investigational agent within 28 days of dosing.

**4.2.4** Subject is pregnant or breastfeeding (*Note*: breast milk cannot be stored for future use while the mother is being treated on study).

**4.2.5** Subject has active CSF involvement that requires ongoing intrathecal chemotherapy.

**4.2.6** Previous exposure to a BTK inhibitor.

**4.2.7** Subjects with severe hepatic insufficiency, as defined by Child-Pugh Score > 6 (Appendix C).

**4.2.8** Subject is receiving prohibited medications or treatments as listed in Section 5.3 of the protocol that cannot be discontinued/replaced by an alternative therapy. Subject requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer (please consult Section 5.3). Subjects may be eligible if they are medically able to discontinue CYP3A4 inhibitors/inducers at least 14 days before the first dose of study treatment.

**4.2.9** Subject requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 14 days of first dose of study drug. Subjects requires or is taking direct oral anticoagulants (e.g. apixaban, rivaroxaban, edoxaban, lovenox) within 7 days of first dose of study drug.

**4.2.10** Subjects receiving capsule form of acalabrutinib may not be taking proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who

switch to H2-receptor antagonists or antacids and subjects receiving tablet form of acalabrutinib are eligible for enrollment to this study.

**4.2.11** Subject is currently receiving any chemotherapy, anticancer immunotherapy. *Note*: Subjects receiving corticosteroids will be eligible, but corticosteroids are expected to be tapered off as soon as possible from a clinical standpoint.

**4.2.12** Subject has clinically significant cardiovascular disease such as ventricular dysfunction, symptomatic coronary artery disease, 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 (NYHA) Functional Classification (Appendix D) at screening. Subjects with controlled, asymptomatic atrial fibrillation during screening can enroll on study.

**4.2.13** Subject has familial short QT syndrome.

**4.2.14** Subject has a history of malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass that is likely to affect absorption.

**4.2.15** Subject has a known history of infection with HIV or any uncontrolled active significant infection (e.g., bacterial, viral or fungal).

**4.2.16** Subject has a known history of drug-specific hypersensitivity or anaphylaxis to acalabrutinib (including active ingredient or excipient components).

**4.2.17** Subject has active bleeding or history of bleeding diathesis (e.g., hemophilia or von Willebrand disease).

**4.2.18** Subject has a history of uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).

**4.2.19** Subject has a history of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of acalabrutinib.

**4.2.20** Subject had major surgical procedure within 28 days of first dose of acalabrutinib. *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 acalabrutinib.

**4.2.21** 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 before randomization and must be willing to undergo DNA PCR testing during the study. Subjects who are core antibody positive and viral load negative

must receive entecavir prophylaxis. Those who are HbsAg-positive or hepatitis B PCR positive will be excluded.

**4.2.22** Subjects who are hepatitis C antibody positive must have a negative polymerase chain reaction (PCR) result. Those who are hepatitis C PCR positive will be excluded.

**4.2.23** Evidence of disease (such as severe or uncontrolled systemic diseases, including uncontrolled hypertension and renal transplant) that, in the investigator's opinion, make it undesirable for the patient to participate in the study or that would jeopardize compliance with the protocol.

**4.2.24** History of or ongoing confirmed progressive multifocal leukoencephalopathy (PML).

**4.2.25** Received a live virus vaccination within 28 days of first dose of study drug.

**4.2.26** Any active significant infection (e.g., bacterial, viral or fungal, including subjects with positive cytomegalovirus [CMV] DNA polymerase chain reaction [PCR]).

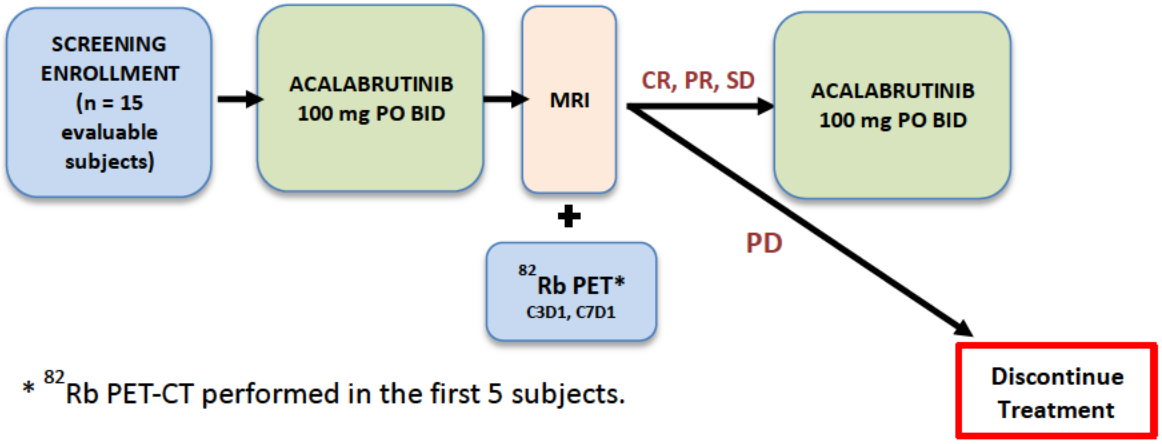
**4.2.27** Concurrent participation in another therapeutic clinical trial.

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

# 5.0 TREATMENT PLAN

## 5.1 Schema

**Figure 1 Study Schema**




LCCC 1841 is a multicenter open-label, single-arm, pilot study designed to investigate the antitumor effects of acalabrutinib in subjects with relapsed primary central nervous system (CNS) lymphoma, and relapsed secondary CNS lymphoma with no evidence of current systemic disease. $^{82}$Rb PET/CT will be performed at screening, at Cycle 3 Day 1 and at Cycle 7 Day 1 in the first 5 subjects at the University of North Carolina with parenchymal brain disease who consent to this testing. Subjects will continue on treatment until disease progression or discontinuation of treatment due to an adverse event. During the study, 15 evaluable subjects (per section 8.4) will be enrolled and treated. Up to 16 subjects (15 evaluable subjects) will receive acalabrutinib at the dose of 100 mg every 12 hours (**Table 1**).

**Table 1 Treatment dosage and administration**

| REGIMEN DESCRIPTION | | | | | |
|---|---|---|---|---|---|
| **Agent** | **Precautions** | **Dose** | **Route** | **Schedule** | **Cycle Length** |
| Acalabrutinib | Take acalabrutinib with or without food | 100mg | oral | Every 12 hours | 4 weeks (28 days) |

## 5.2 Toxicities and Dosing Delays/Dose Modifications

Any subject who receives at least one dose of acalabrutinib on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), version 5.0.

If a subject experiences a toxicity or other intolerable AE suspected to be at least possibly related to acalabrutinib treatment during the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE resolves or stabilizes to Grade ≤ 1 or baseline. Dose modifications for the following treatment-emergent toxicities are provided in **Table 2**. If/when treatment is resumed, the subject should proceed with the treatment schedule based on when the subject completed cycle 1 day 1; meaning that the schedule will not be paused when drug is held. If acalabrutinib is held for >14 consecutive days, then the subject should be permanently discontinued from study treatment and proceed to follow-up.

**Table 2. Acalabrutinib Dose Modifications**

| CTCAE Grade | Acalabrutinib Dose Modifications |
|---|---|
| **Hematologic Toxicities** | |
| *Neutropenia* | |
| Grade ≤ 3 | No dose modification is required |
| Grade 4, initial or second occurrence | Hold acalabrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level[1] |
| Grade 4, third occurrence | Hold acalabrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (100 mg QD)[1] |
| Grade 4, fourth occurrence | Discontinue acalabrutinib |
| *Thrombocytopenia* | |
| Grade 1 or 2 | No dose modification is required |
| Grade 4, or Grade 3 in presence of significant bleeding, initial or second occurrence | Interrupt acalabrutinib.<br><br>Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at 100 mg approximately every 12 hours. |
| Grade 4, or Grade 3 in presence of significant bleeding, third occurrence | Interrupt acalabrutinib.<br><br>Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at a reduced frequency of 100 mg once daily. |
| Grade 4, or Grade 3 in presence of significant bleeding, fourth occurrence | Discontinue acalabrutinib |
| **Nonhematologic Toxicities** | |
| *Nausea, Vomiting, or Diarrhea* | |
| Grade 1 or 2 | No dose modification is required |
| Grade ≥3, initial or second occurrence | Interrupt acalabrutinib. |

| | |
|---|---|
| | Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at 100 mg approximately every 12 hours |
| Grade ≥3, third occurrence | Interrupt acalabrutinib.<br><br>Once toxicity has resolved to Grade 1 or baseline level, acalabrutinib may be resumed at a reduced frequency of 100 mg once daily |
| Grade ≥3, fourth occurrence | Discontinue acalabrutinib |

[1] Neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines [38] and use must be recorded on the electronic case report form (eCRF).

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (e.g., once per week) until abnormalities have recovered to Grade ≤ 1. 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 investigator. 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 100 mg BID.

Treatment with acalabrutinib should be withheld for any unmanageable, at least possibly related study drug-related toxicity that is Grade ≥ 3 in severity. Consider the benefit-risk of withholding acalabrutinib for 3 to 7 days pre- and post-surgery depending on the surgery and the risk of bleeding (Refer to Section 6.1.6).

## 5.3 Prohibited and Concomitant Medications

CYP3A-mediated oxidation is the major route of metabolism of acalabrutinib in humans. CYP3A4/5 is the predominant CYP isoform responsible for metabolism of acalabrutinib. Therefore, additional strong or moderate inhibitors of CYP3A4 and strong and moderate inducers of CYP3A4 are prohibited.

A frequently updated P450 drug interaction table is available at: http://medicine.iupui.edu/clinpharm/ddis/.

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 at least 7 days before first dose of acalabrutinib.

Acalabrutinib is not a potent direct inhibitor of CYP3A4 and is not anticipated to be a perpetrator of drug interactions at the level of systemic inhibition of CYP3A4.

**For Subjects on Acalabrutinib Capsule Formulation**

Subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours 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. Use of proton-pump inhibitors during the study is also prohibited. It is recommended that subjects receiving proton pump inhibitors should switch to H2-receptor antagonists or antacids prior to enrollment to this study.

Although the effect of H2-receptor antagonists (such as 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.

**Vaccination Guidance**

Based on nonclinical data, no changes are recommended to standard of care practices with regard to vaccinations in subjects treated with acalabrutinib. As appropriate, vaccines consistent with standard practices for specific subject populations (eg, patients with CLL) should be used.

The patient handout in Appendix E should be provided to subjects to inform them of drugs to avoid taking while they are receiving study medications.

## 5.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Pregnancy
- Subject decides to withdraw from study treatment,
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator, or
- Subject is lost to follow up

## 5.5 Duration of Follow Up

All subjects will be followed every 3 months (±1 month) for survival for 5 years or until death, whichever occurs first, starting from time the subject discontinues study treatment. To document survival, subjects will either be contacted directly, or their medical record will be checked. Subjects removed from treatment prior to progression (e.g. due to adverse event(s) or withdraw from treatment) will have imaging scans (MRI) annually for 2 years or until death, whichever occurs first, from the time they discontinue study treatment.

## 5.6 Study Withdrawal

Subjects will be removed from protocol therapy and the PI notified when any of the criteria listed in section 5.4 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal should be obtained. While study participants are never required to provide a reason for their decision to withdraw, the subject should be asked if they are willing to share their reason for withdrawing, and if yes, the reason should be recorded in the eCRF.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

## 5.7 Off-Study Criteria

Subjects will be considered off study by any of the following criteria:

- Subjects have fulfilled all study activities including follow-up activities and no further data collection is needed
- Subject withdraws consent for treatment and any further data collection
- Death
- Lost to follow-up
- Subject starts a new anti-cancer therapy
- Situations in which the treating physician feels it is in the best interest for the subject to not continue in the study

# 6.0 DRUG INFORMATION

## 6.1 Acalabrutinib (CALQUENCE)

**Brief Description**: Acalabrutinib (also known as ACP-196 and/or Calquence®) is a selective, irreversible small molecule inhibitor of BTK.. Calquence® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL).

**Supplier:** AstraZeneca Pharmaceuticals LP, 2017; Wilmington, DE. A commercial supply of acalabrutinib will be supplied by AstraZeneca at no cost to the subject.

**Active ingredient:** acalabrutinib

### 6.1.1 How supplied:

Acalabrutinib capsules
Acalabrutinib capsules for oral administration, are supplied as opaque size 1 hard gelatin capsules, with a blue cap and yellow body, containing 100 mg acalabrutinib as the active ingredient.

The 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 Blue2).

| Pack Size | Contents | NDC Number |
|---|---|---|
| 60-count bottle | Bottle containing 60 capsules<br>100 mg, hard gelatin capsules with yellow body and blue cap, marked in black ink with 'ACA 100 mg' | 0310-0512-60 |

Acalabrutinib tablets
Acalabrutinib tablets for oral administration is supplied as an orange, oval, film-coated, and biconvex, containing 100 mg acalabrutinib as the active ingredient.

Inactive ingredients in the tablet core are low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.

The tablet coating contains copovidone ferric oxide yellow, ferric oxide red, Hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water, and titanium dioxide.

| Pack Size | Contents | NDC Number |
|---|---|---|
| 60-count bottle | Bottle containing 60 tablets with a child-resistant closure<br>100 mg, orange, oval, biconvex tablet, with debossment 'ACA100' on one side and plain on the reverse | 0310-3512-60 |

Additional information can be found at the CALQUENCE website.

**Full prescribing information for acalabrutinib capsules is available at:**
CALQUENCE CAPSULE prescribing information

**Full prescribing information for acalabrutinib tablets is available at:**
CALQUENCE TABLET prescribing information

### 6.1.2 Dosage and Administration:

The recommended dose is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity. Advise patients to swallow capsule or tablet whole with water. Advise patients not to open, break, dissolve, or chew the capsules or tablets. Acalabrutinib capsules and tablets may be taken without regard to food. If a dose is missed by more than 3 hours, it should be skipped, and the next dose should be taken at its regularly scheduled time. Extra capsules and tablets should not be taken to make up for the missed dose. If the drug is vomited within 3 hours of being taken, it may be re-taken at the discretion of the investigator.

Subjects should be instructed to store the drug product at home out of the reach of children.

### 6.1.3 Storage and Stability:

Acalabrutinib capsules and tablets are packaged in white, HDPE bottles and should be stored according to the storage conditions as indicated on the label. The storage condition for acalabrutinib capsules and tablets per USPI is 20°C-25°C (68°F-77°F) with excursions permitted to 15°C-30°C (59°F-86°F)

**Handling and Disposal**:

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

### 6.1.4 Risk Assessments

**Contraindications**
No contraindications are known for acalabrutinib.

**Important Identified Risks**
The following summarizes the important identified risks observed with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Package Insert.

*Hemorrhage*
Serious hemorrhagic events, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in clinical trials with acalabrutinib; some of these bleeding events resulted in fatal outcomes. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies.

The mechanism for hemorrhage is not well understood. Acalabrutinib may further increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies and patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3 to 7 days pre- and post-surgery depending on the surgery and the risk of bleeding (see Section 5.2). Please note that acalabrutinib should not be held for CSF sample collection via lumbar puncture.

*Infection*
Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections, 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 hepatitis B virus (HBV) reactivation, aspergillosis, and progressive multifocal leukoencephalopathy (PML) have occurred.

Consider prophylaxis in subjects who are at increased risk for opportunistic infections.

Subjects with infection events should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

*Cytopenias*
Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Subjects with cytopenias should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Subjects should be closely monitored as appropriate.

*Second Primary Malignancies*
Events of second primary malignancies, including non-solid tumors and skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer. Advise protection from sun exposure.

Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor.

*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. Monitor for symptoms of atrial fibrillation and atrial flutter (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) and obtain an ECG as clinically indicated. Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated

**Important Potential Risks**
There is one important potential risk for acalabrutinib monotherapy. Information related to this important potential risk is presented below. Additional details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Package Insert.

*Hepatotoxicity*

The mechanism underlying hepatotoxicity events of non-infectious etiology is currently unknown. Following a comprehensive review of hepatotoxicity events in the acalabrutinib clinical program, there was insufficient evidence to establish an association between hepatotoxicity events and acalabrutinib due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without

treatment for patients with transaminase elevations. There is limited evidence regarding hepatotoxicity of non-infectious etiology from literature for other BTK inhibitors.

# 7.0 CLINICAL ASSESSMENTS

## 7.1 Clinical Assessments

Clinical assessments will be performed as outlined in the Time and Events table.

### 7.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening and throughout the study as summarized in the Time and Events Table. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

### 7.1.2 Demographics

Demographic information (date of birth, gender, race and ethnicity) will be recorded at the screening visit.

### 7.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at the screening visit and a focused medical history on symptoms/toxicity will be performed thereafter.

### 7.1.4 Physical Examination

A complete physical examination including height (at screening only), weight, ECOG performance status, and vital signs (i.e., temperature and blood pressure) will be performed by either the investigator or a sub-investigator who is a physician at the screening and Cycle 1 Day 1 visits. Vital signs may be taken by appropriately qualified personnel.

Qualified staff (MD, NP, and PA) may complete the abbreviated physical exam at all other visits.

New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

### 7.1.5 Adverse Events

Events should be assessed per NCI-CTCAE criteria, version 5.0. Information regarding occurrence of adverse events will be captured. Duration (start and stop

dates), severity/grade, outcome, treatment and relation to study drug will be recorded in the electronic case report form (eCRF).

### 7.1.6 Performance Status

Performance status as defined by ECOG (Appendix F) will be assessed as outlined in the Time and Events.

### 7.1.7 Disease Assessments

Baseline disease assessment using MRI of brain should be obtained within 28 days prior to first dosing with acalabrutinib and then conducted at intervals as noted in the Time and Events Table. CT or PET-CT imagining will be performed at screening in order to confirm no evidence of systemic involvement of lymphoma. A prior scan showing no evidence of systemic involvement may be used as long as it is without the protocol windows described in the Time and Events Table. Eye exams will be performed per standard of care in subjects with noted ocular involvement detected via ophthalmologic exam during screening.

## 7.2 Laboratory Assessments

### 7.2.1 Hematology

Blood will be obtained and sent to the clinical site hematology lab for a complete blood count with white blood cell differential.

### 7.2.2 Serum Chemistry Profile

Blood will be obtained and sent to the clinical site chemistry lab for determination of sodium, potassium, chloride, $CO_2$, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase. LDH will be measured at screening.

### 7.2.3 Coagulation Test

International normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) will be performed during screening to ensure eligibility criterion 4.1.9 is met.

### 7.2.4 Pregnancy Test

A serum pregnancy test will be obtained from female subjects who are of childbearing potential within 72 hours prior to starting study treatment.

### 7.2.5 Hepatitis C Testing

Subjects will be tested for Hepatitis C at screening. Subjects who are hepatitis C antibody positive must have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.

### 7.2.6 Hepatitis B Prophylaxis

Subjects will be tested for Hepatitis B at screening. Subjects must either have hepatitis B core antibody negative OR if a subject is hepatitis B core antibody positive they must have their hepatitis B viral load checked. These subjects will be excluded if their viral load is positive. Subjects who are core antibody positive and viral load negative will be considered eligible but must receive entecavir prophylaxis.

## 7.3 Mini-Mental State Examination

Mental status and cognitive function will be evaluated using Mini-Mental Status Examination (MMSE) questionnaire (see Appendix G ).

## 7.4 Correlative Studies

Provision of Data to Correlative Scientists

**Identification and Role of the Study Coordinator as the Honest Broker**

The study coordinator will be in charge of collecting and maintaining all data points and data management. The study coordinator should have adequate training to enter, manage, and deidentify data. The study coordinator will provide a unique study number to each enrolled subject. All documentation and samples will be labeled with the unique study number. The correlative teams will only be provided this unique study ID number as opposed to any other patient identifiers. The clinical team will be the only people able to access identifiable data and the study coordinator will be a conduit to provide the de-identified data to the correlative team.

**Requests for a data**

Identifiable data will not be given out to any correlative investigators at any time. Multicenter and UNC correlative Investigators may ask the study coordinator for a specific data set, and the study coordinator will return a deidentified data set. This data may only be used for purposes of the study. Any use other than directly related to the study must be approved by the IRB of record. If there is a need for an investigator to access identifiable data during the study, then a new IRB application will need to be submitted from that investigator detailing the reasons needed to access that data. The study coordinator will also ensure that correlative results are not returned from the correlative team to the clinical team to dictate treatment or follow-up decisions unless this is specifically approved by the IRB of record and delineated in the clinical protocol.

### 7.4.1 Blood Pharmacokinetic Profile of Acalabrutinib

Standard plasma pharmacokinetic parameters of orally administered acalabrutinib will be characterized, including area under the plasma concentration versus time curve for acalabrutinib will be estimated using non-compartmental analysis.

### 7.4.2 Cerebrospinal Fluid Uptake of Acalabrutinib

Cerebrospinal fluid sample (3 – 4 mL) will be collected when possible after (2 +/- 1 hours) oral administration of acalabrutinib to characterize its uptake. Residual sample, if available, will be stored and may used for future research related to the study

### 7.4.3 Somatic Mutations in MYD88 and CXCR4

Tumor sample for MYD88 and CXCR4 testing will be collected prior to treatment to determine correlation of mutational status and response to treatment with acalabrutinib. Testing will only be carried out if there is sufficient tissue available. Residual sample, if available, will be stored and may used for future research related to the study.

### 7.4.4 Rubidium-82 Positron-Emission Tomography

$^{82}$Rb PET/CT will be performed at screening, at Cycle 3 Day 1 and at Cycle 7 Day 1 in the first 5 subjects at the University of North Carolina with parenchymal brain disease who consent to this testing. We will quantify the uptake by calculating SUV variables (SUVmax and SUVave of normal brain, subcutaneous fat, lung and mediastinal blood pool) and visually assessing (using the Brain Lymphoma Rubidium Visual Scoring Scale: Appendix H) the uptake at various time points at the tumor site. We will also drive various SUV-based and visual quantitative (similar to Deauville Score) scores by comparing the SUV and visual score of the tumor to the SUV and visual scores of normal structures captured on the images, e.g. lung, subcutaneous fat and aorta.

# 8.0 EVALUATIONS AND ASSESSMENTS

## 8.1 Time and Events Table

| Study Assessments | Screening[1] | Study treatment[1] (Cycle length = 28 days) | | | | | | End of Treatment[1] | Follow Up[19] |
|---|---|---|---|---|---|---|---|---|---|
| | | C1 D1 | C1 D8 | C2 D1 | C3 D1 | C4-7 D1 | C8-n D1 | | |
| Informed consent | × | | | | | | | | |
| Demographics | × | | | | | | | | |
| Medical history[2] | × | × | × | × | × | × | × | × | |
| Physical exam[3] | × | × | × | × | × | × | × | × | |
| Eligibility verification | × | | | | | | | | |
| ECOG performance status | × | × | | × | × | × | × | × | |
| ECG | × | | | | | | | | |
| Viral testing[4] | × | | | | | × | × | | |
| Hematology[5] | × | × | × | × | × | × | × | × | |
| Serum chemistry[6] | × | × | | × | × | × | × | × | |
| Coagulation tests[7] | × | | | | | | | | |
| Pregnancy test | ×[8] | ×[8] | | | × | ×[8] | ×[8] | × | |
| MRI of brain[9] | × | | | | × | ×[9] | ×[9] | | ×[9] |
| $^{82}$Rb PET-CT[10] | × | | | | × | ×[10] | | | |
| CT or PET/CT[11] | × | | | | | | | | |
| Ocular Exams[12] | ×[12] | ×[12] | | | | | | | |
| CSF sample via lumbar puncture[13] | | × | × | | | | | | |
| Acalabrutinib PO BID[14] | | × | | | | | | | |
| Subject diary review | | × | × | × | × | × | × | × | |
| Toxicity assessment[15] | × | × | × | × | × | × | × | × | ×[1] |
| Concomitant medication review | × | × | × | × | × | × | × | × | |
| Plasma PK assessment[16] | | | × | | | | | | |

| Study Assessments | Screening[1] | Study treatment[1] (Cycle length = 28 days) | | | | | | End of Treatment[1] | Follow Up[19] |
|---|---|---|---|---|---|---|---|---|---|
| | | C1 D1 | C1 D8 | C2 D1 | C3 D1 | C4-7 D1 | C8-n D1 | | |
| Correlative tumor sample testing[17] | | × | | | | | | | |
| MMSE[18] | × | | | | | ×[18] | ×[18] | × | |
| Survival[19] | | | | | | | | | × |

## Footnotes to Time and Events Table

1. All screening assessments should be completed within 28 days before initiating study therapy unless otherwise specified. If screening labs are performed within 72 hours of initiating study treatment on C1D1, they do not need to be repeated. Each scheduled visit should occur within ±3 days of the scheduled visit while the subject is receiving study treatment. The end of treatment visit should occur 30 days (±7 days) after discontinuing study therapy and all ongoing AEs should be followed until resolution or the condition has stabilized with no further change expected.

2. Relevant medical history will be recorded at the screening visit. Medical history focused on symptoms / toxicity will be performed thereafter. Medical history includes the collection of clinically significant AEs.

3. A complete physical exam should be conducted at screening i.e., baseline including height (baseline only) and weight. A targeted physical exam including weight should be conducted on Day 1 of each cycle. Vital signs (blood pressure, pulse and temperature) should be obtained at each visit.

4. HBV and HCV testing will be performed during screening. Subjects who are hepatitis B core antibody positive and viral load negative at baseline must receive entecavir prophylaxis. Additionally, these subjects must be monitored for hepatitis b reactivation every before beginning every 4$^{th}$ cycle (Cycles 4, 8…etc.).

5. Hematology should include complete blood count with white blood cell differential.

6. Serum chemistry will include sodium, potassium, chloride, $CO_2$, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase. LDH will be performed at screening only.

7. International normalized ratio (INR) or prothrombin time (PT) and activated partial thromboplastin time (aPTT) will be performed during screening to ensure eligibility criterion 4.1.9 is met.

8. Serum pregnancy test must be performed in female subjects of childbearing potential within 72 hours before initiating study treatment on day 1 of cycle 1. For subsequent cycles, a pregnancy test will be done on day 1 of odd cycles.

9. MRI of brain should be obtained at screening within 28 days prior to start of study treatment and while on treatment at C3D1 (±7 days), C5D1 (±7 days), C7D1 (±7 days), C10D1 (±7 days), C13D1 (±7 days), C19D1 (±7 days), C25D1 (±7 days), and then annually (±30 days) for up to five years, or as needed, if there are any clinical signs/symptoms of progression. Scans will be continued until disease progression. If a subject comes off treatment for any reason other than disease progression (e.g. adverse events or withdraw from treatment), then the subject will have an MRI of the brain annually (±30 days) for up to 2 years or until disease progression.

10. Rubidium PET-CT performed at screening, C3D1 (±7 days), and C7D1 (±7 days), in the first 5 subjects at the University of North Carolina who consent to the procedure.

11. CT or PET-CT imaging will be performed at screening in order to confirm no evidence of systemic involvement of lymphoma. A prior scan showing no evidence of systemic involvement can be utilized, as long as it is performed within 28 days of starting study drug.

12. Ocular exams will be performed during screening only if the subject has ocular symptoms or recommended per standard of care. Subjects with active ocular lymphoma will have ophthalmologic evaluation (exam or imaging) to confirm CR.

13. Cerebrospinal fluid sample (3 – 4 mL) will be collected at 2 hours (+/- 1 hour) after oral administration of acalabrutinib at Cycle 1 Day 1 and Cycle 1 Day 8. Subjects who cannot have CSF samples drawn may remain in the study.

14. Acalabrutinib treatment will continue until the subject shows signs of disease progression, unacceptable toxicity, or withdraws from the study.

15. Toxicity assessment per NCI-CTCAE criteria, v.5.0.

16. Blood samples for pharmacokinetic analysis will be collected prior to acalabrutinib dosing and at 1, 2, and 4 hours after oral administration of acalabrutinib on Day 8 of Cycle 1. It is important to collect the time of last dose at each time point.

17. Testing of tumor sample for MYD88 and CXCR4 will be collected at baseline (Cycle 1 Day 1 prior to treatment initiation). Testing will only be carried out if there is sufficient tissue available. This may be from an archival sample or a fresh biopsy collection if collected per standard of care.

18. Mini-Mental State Examination (MMSE) is performed at screening, C7D1, and then every 6 months while on the study treatment. A final MMSE will be performed at the end of treatment visit.

19. From the time subjects discontinue study treatment, they will be followed for survival every 3 months (±1 month) for 5 years or until death, whichever comes first. To document survival, subjects will either be contacted directly, or their medical record will be checked.

## 8.2 Handling of Biospecimens Collected for Correlative Research

Biospecimens collected for this study will be stored in the Lineberger Comprehensive Cancer Center (LCCC) Tissue Procurement Facility (TPF), or if needed, in a secure off-site storage facility. All biospecimen samples will be obtained in accordance with procedures outlined in the LCCC1841 Study Laboratory Manual and stored in containers with controlled access. Each sample will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Information about the subject's disease will be linked to the specimens stored in the repository database. TPF-associated research staff, LCCC Bioinformatics staff who support the TPF database and the LCCC Data Warehouse, and researchers with IRB-approval for access to PHI for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the subject's participation in the clinical study may also be included. This information may be important for understanding how the subject's cancer developed and responded to treatment.

*Storage Time:*

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the subject to use tissue for other research purposes (e.g., TPF consent form was signed by the subject). Specimens will be stored for 10 years.
    - The investigator must agree to abide by policies and procedures of the TPF facility and sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF

facility (e.g., Use of leftover specimens will require a protocol outlining the research plan for biospecimen use).

*Compliance Statement*
Biospecimen collection for this study will be conducted in full accordance to all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

## 8.3 Assessment of Safety

Any subject who receives at least one dose of acalabrutinib on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAE v5.0.

## 8.4 Assessment of Efficacy

### 8.4.1 The International Primary CNS Lymphoma Collaborative Group Response Assessment Criteria [37]

Subjects who receive 1 cycle of acalabrutinib will be evaluable for efficacy. If a subject does not receive a full cycle of acalabrutinib they will not be evaluable and be replaced. The following criteria were developed on the basis of anatomic and radiographic definitions (**Table 3**). As additional radiographic, laboratory, or functional studies become more widely available and are demonstrated to have predictive value, they may be recommended as well.

**Table 3. Anatomic and Radiographic Endpoint Definitions**

| Endpoint Definitions | | | |
|---|---|---|---|
| **Endpoint** | **Response Category** | **Definition** | **Point of Measurement** |
| Overall survival | All patients | Death as a result of any cause | Entry onto trial |
| Event-free survival | All patients | Failure or death as a result of any cause | Entry onto trial |
| Progression-free survival | All patients | Disease progression or death as a result of PCNSL | Entry onto trial |
| Disease-free survival | CR, CRu | Time to relapse | First documentation of response |
| Response duration | CR, CRu, PR | Time to relapse or progression | First documentation of response |

*CR requires the following:*

(1) Complete disappearance of all enhancing abnormalities on gadolinium-enhanced MRI.

(2) No evidence of active ocular lymphoma as defined by absence of cells in the vitreous and resolution of any previously documented retinal or optic nerve infiltrates. Chronic changes of the retinal pigment epithelium in the setting of a prior retinal or optic nerve infiltrate does not preclude the definition of a CR. All patients with initial involvement of the eyes on baseline evaluation should have a detailed follow-up evaluation including dilated fundus examination and color photographs of the posterior pole of the eye. Repeat ophthalmologic evaluation is not required for patients without evidence of ocular lymphoma at baseline or interval development of ocular symptoms.

(3) At the time a CR is determined, the patient should have discontinued use of all corticosteroids for at least 2 weeks. Rare exceptions may be made for those patients receiving corticosteroids for another diagnosis (e.g., panhypopituitarism).

*CR/unconfirmed (CRu) includes those patients who fulfill the criteria for CR with the following features/limitations:*

(1) Any patient who fulfills all criteria for CR but continues to require corticosteroid therapy at any dose should be considered an unconfirmed CR. This is critical because corticosteroids may be oncolytic in treating occult tumor. In addition, corticosteroids may decrease gadolinium enhancement on MRI.

(2) Some patients will have a small but persistent enhancing abnormality on MRI related to biopsy or focal hemorrhage. It is often difficult to ascertain whether this represents a residual nidus of tumor or scar tissue. Adjunctive radiologic studies such as single-photon emission computed tomography or positron emission tomography may be helpful, but often the nature of these abnormalities may only be determined by observing the patient with serial scans. If the type of abnormality does not change or slowly involutes over time without therapy and corticosteroids, it is reasonable to categorize it as a CR.

(3) Patients with a persistent minor abnormality on follow-up ophthalmologic examination (persistent non-malignant cells in the vitreous, alteration of the retina/optic nerve that is not consistent with tumor infiltration) may be considered a CRu if this abnormality is unlikely to represent ocular lymphoma.

*Partial response (PR) requires all of the following:*

(1) A ≥50% decrease in the contrast-enhancing lesion seen on MRI as compared with baseline imaging.

(2) Corticosteroid dose is irrelevant to the determination of PR.

(3) Ophthalmologic examination should show a decrease in the vitreous cell count or retinal/optic nerve cellular infiltrate but may continue to show persistent malignant or suspicious cells. Color photos of the posterior pole of the eye should be obtained to document improvement in retinal/optic nerve infiltrates.

(4) No new sites of disease.

Stable disease is defined as less than a PR but is not progressive disease.

*Progressive disease requires the following:*

(1) A more than 25% increase in the contrast-enhancing lesion seen on MRI as compared with baseline or best response (comparison should be made to the smallest of multiple lesions).

(2) Progression of ocular disease as indicated by an increase in the vitreous cell count or progressive retinal or optic nerve infiltration.

(3) Appearance of any new lesion or site of disease (ocular, leptomeningeal or systemic) during or at the end of therapy.

*Relapsed disease (only applicable to patients with a prior CR, CRu) requires the following:*

(1) Appearance of any new lesion.

# 9.0 ADVERSE EVENTS

## 9.1 Definitions

### 9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Preplanned Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of a central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy. Unplanned diagnostic tests and procedures are not AEs; however, the sign/symptoms leading to them are AEs. Pre-existing conditions (unless they worsen) and abnormal lab values that are judged to be not clinically significant by the investigator are not AEs.

### 9.1.2 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 9.4 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

- Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.)
- Systemic or significant fungal infections

### 9.1.3 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the product (Acalabrutinib) is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by the product.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study product exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under

investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with product exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the product caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the product treatment group than in a concurrent or historical control group

### 9.1.4 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

### 9.1.5 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse study treatment-related experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

#### 9.1.5.1 Pregnancy

Pregnancy that occurs during the study in female subjects must also be reported as an SAE.

#### 9.1.5.2 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF.

If the associated AE fulfills serious criteria, Investigators should report the event to the Sponsor within 24 hours of learning of its occurrence using the SAE Reporting Form.

In the event of subject ingestion of more than the recommended acalabrutinib dosage, observation for any symptomatic side effects should be instituted, and vital signs, 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.

### 9.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued or the start of new anticancer therapy, whichever is earlier.

**Hy's Law**

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs.

Collected information should be recorded in the electronic case report forms (eCRF) for that subject. Please include a description of the event, its severity or toxicity grade per CTCAE(v5), onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

## 9.3 SAEs or Serious SARs

### 9.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued or the start of new anticancer therapy, whichever is earlier. Additionally, while the subject is on study, any serious adverse events that the investigator considers causally related to study drug(s) must additionally be reported.

### 9.3.2 Documentation and Notification

SAEs, Serious SARs, overdose, pregnancy, and any AEs of special interest (AESI) must be recorded in the SAE console within OnCore® for that subject within 24 hours of learning of its occurrence. Additionally, the Multicenter Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

### 9.3.3 AEs of Special Interest (AESI)

AESIs include ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.) as well as systemic or significant fungal infections (Section 9.1.2). If these adverse events occur in a subject exposed to acalabrutinib, then it must be reported to the sponsor expeditiously, irrespective of regulatory seriousness criteria or causality.

## 9.4 Adverse Event Reporting

### 9.4.1 IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Multicenter sites:

- For multicenter sites using a local IRB of record, please submit adverse events per local IRB policy.
- For multicenter sites relying on the UNC-IRB, an aggregated list of any SAEs that qualify as an Unanticipated Problem will be entered into OnCore® by the multicenter site and reported to the UNC IRB by the Multicenter Regulatory Associate using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem.

*Pregnancy*

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is receiving study treatment, or within 30 days of the subject's last dose of study treatment should be recorded as SAEs. The subject is to be discontinued immediately from study treatment and procedures.

For multicenter sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Multicenter Project Manager immediately (within 24 hours) via email. The Multicenter Project Manager will then report the event to the Funding Source (see requirements below). The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the UNC Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

### 9.4.2 Funding Source Reporting Requirements:

Serious adverse events, any cases of overdose, pregnancies, or adverse events of significant interest will be reported to AstraZeneca as soon as possible and no later than 1 business day of the Investigator and/or Institution receiving notification of any serious adverse event experienced by a subject participating in the study and receiving acalabrutinib. SAE report must be sent to the study sponsor at CPOMulticenter@med.unc.edu. The study sponsor (multicenter project manager) will then submit it to the AstraZeneca Product Safety mailbox,

AEMailboxClinicalTrialTCS@astrazeneca.com

SAEs that do not require expedited reporting to the Regulatory Authority/IRB/IEC still need to be reported to AstraZeneca as individual case reports on an ongoing basis.

Suspected Unexpected Serious Adverse Reactions (SUSARs) must be reported to Company at the same time these events are notified to the Regulatory Authority At the end of the Study a final unblinded summary line listing of all SAEs notified to the regulatory authority and/or Company during the Study, must be provided to the Company to enable reconciliation of safety information held by Company for its product(s).

Adverse Events (AEs) for malignant tumors reported during a study should be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important

Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

## 9.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual. These meetings will include the investigators as well as study coordinators, data coordinators, regulatory associates, clinical data management associates, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight of the Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of subjects treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

# 10.0 STATISTICAL CONSIDERATIONS

## 10.1 Study Design

As the first study of acalabrutinib in relapsed/refractory CNS lymphoma, LCCC1841 study is designed as an open label, single arm pilot study to provide preliminary data about its efficacy before proceeding to a larger two arm study. Furthermore, since this is a rare lymphoma, it would take an unreasonable amount of time and multiple centers would be needed to enroll an adequate number of subjects for a randomized phase 3 study.

The null hypothesis is: H0: ORR $\leq$ 50% vs H1: ORR $\geq$ 70% (i.e., 20% improvement). We plan to obtain 15 evaluable patients in this pilot study.

## 10.2 Sample Size, Accrual and Duration of Accrual

We plan to accrue up to 16 subjects to ensure planned (evaluable, in terms of status of overall response) sample size of 15. With 15 evaluable subjects, we reject the null hypothesis when we observe > 9 (10 or more) responders. This design gives power 72% with one-sided type 1 error 0.15. We will replace non-evaluable (e.g., loss to follow-up) cases by new subjects to guarantee planned sample size.

Accrual for this trial is expected to take approximately 24-36 months.

## 10.3 Data Analysis Plans

Analysis of efficacy will be conducted following pre-specified inference rule on rejecting the null hypothesis: H0: ORR <= 50%. Specifically, we will reject the null hypothesis if and only if there are >9 ORs in the 15 subjects. The main analysis is inferential because we frame it as a hypothesis-testing problem. We will also calculate 2-sided 95% clopper-Pearson confidence interval for ORR.

Secondary endpoints include PFS, CR, DoR, overall survival, and safety/toxicity. Analyses of secondary endpoints will be descriptive. Specifically, time-to-event outcomes like PFS, DoR, and OS will use analyzed using Kaplan-Meier method, and Kaplan-Meier survival curves will be provided. Categorical outcomes like CR, and safety/toxicity (different types of AEs) will be summarized using frequencies.

- For the primary outcome, ORR, there should be no missing data. We will replace non-evaluable cases with new subjects so that the total sample size of 15 evaluable subjects is guaranteed.
- There is only one test for the primary endpoint and hence there is no multiplicity issue.

Per exploratory endpoints:

[redacted]

# 11.0 STUDY MANAGEMENT

## 11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

## 11.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- The Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

## 11.3 Registration Procedures

All study subjects must be registered with the LCCC CPO Multicenter Office at the University of North Carolina. Affiliate site staff must email copy of informed consent documentation and completed New Subject Patient Registration Form to the assigned UNC Multicenter Project Manager (contact e-mail provided at SIM) and to CPOMulticenter@med.unc.edu (M-F 8:30AM – 5:00PM EST) or call 919-966-7359 to alert the UNC LCCC Multicenter Office of a potential patient. Upon verification of the Informed Consent documentation by the assigned Project Manager, a unique subject sequence number will be provided to the site study staff. Affiliate site staff must submit complete eligibility packets (institutionally-signed eligibility checklist and full source documentation confirming eligibility) via email to the assigned UNC Multicenter Project Manager and CPOMulticenter@med.unc.edu to begin review. All subjects must have final eligibility verified by the UNC Multicenter Project Manager on behalf of the UNC PI prior to starting treatment. Please allow a minimum of 24 hours for source to be reviewed and notification of subject eligibility released. A patient registration email will be sent to the site's study staff to officially confirm registration of the patient 'On-Study'. All subjects must maintain eligibility from the time of this notification through the beginning of treatment.

## 11.4 Data Management and Monitoring/Auditing

The CPO Multicenter Office of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore™. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Multicenter personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by the multicenter study teams at participating institutions. The investigators at each site will allow monitors to

review all source documents supporting data entered into OnCore®. The Multicenter Clinical Data Management Associate can be reached at LCCC_OnCore@med.unc.edu.

All data will be monitored and source data will be verified on selected subjects. Queries will be issued on an ongoing basis on all subjects. Participating sites should respond to data queries within 14 days of receipt. The LCCC compliance committee or their designee will audit trial sites every twelve months while still enrolling or subjects are still on treatment. Participating sites must send source and regulatory documents to LCCC upon request, for remote monitoring and/or audit review.

## 11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

### 11.5.1 Emergency Modifications

UNC and multicenter investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For multicenter investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The multicenter institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the Multicenter Regulatory Associate).

### 11.5.2 Single Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper

regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

### 11.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs, please follow the guidelines below:

For Institutions Relying on UNC's IRB:
*Protocol Deviations***:** UNC or multicenter site personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies.

*Protocol Violations***:** Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

*Protocol Deviations*: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

*Protocol Violations*: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNC Multicenter Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the

subject and integrity of the data. Once your institution's IRB response is received, please forward to the Multicenter Regulatory Associate.

*Unanticipated Problems*: Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study personnel using the IRB's web-based reporting system.

Multicenter Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNC Multicenter Project Manager. The Multicenter Regulatory Associate will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

## 11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the amendment to their institution's IRB for approval. For multi-center studies, any multicenter site must submit their informed consent revisions to the Multicenter Regulatory Associate for review and approval prior to submission to their IRB.

## 11.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with an investigational product seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International

Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

## 11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, auditing and monitoring of trials will be conducted, and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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# 13.0 APPENDICES

## 13.1 Appendix A: Prohibited Medications or Those to Use with Caution

Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis. The most abundant circulating active metabolite in human is ACP-5862, which is formed by CYP3A-mediated oxidation. Strong inhibitors have the potential to increase plasma concentrations of acalabrutinib and decrease plasma concentrations of its active metabolites. Strong inhibitors of CYP3A enzymes are prohibited in this trial. Other drugs known to induce or inhibit CYP3A enzymes should be used with caution, or alternative treatments considered. ***Note****: this is not an exhaustive list and further details can be found at* https://drug-interactions.medicine.iu.edu/MainTable.aspx and at Expert Opin. Drug Metab Toxicol (2013) 9(6) 737-751. If a drug appears on more than one list follow the more conservative rule.

| CYP3A Inhibitors | |
|---|---|
| indinavir[a] | amiodarone |
| nelfinavir[a] | chloramphenicol |
| ritonavir[a] | boceprevir |
| clarithromycin[a] | ciprofloxacin |
| itraconazole[a] | delaviridine |
| ketoconazole[a] | diethyl-dithiocarbamate |
| nefazodone[a] | fluvoxamine |
| saquinavir[a] | gestodene |
| telithromycin[a] | imatinib |
| aprepitant[b] | mibefradil |
| erythromycin[b] | mifepristone |
| fluconazole[b] | norfloxacin |
| grapefruit juice[b] | norfluoxetine |
| verapamil[b] | starfruit |
| diltiazem[b] | telaprevir |
| cimetidine[c] | voriconazole |

[a]Strong inhibitor- causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
[b]Moderate inhibitor- causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
[c]Weak inhibitor- causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

| CYP3A Inducers | |
|---|---|
| efavirenz | phenobarbital |
| nevirapine | phenytoin |
| barbiturates | pioglitazone |
| carbamazepine | rifabutin |
| enzalutamide | rifampin |
| glucocorticoids | St. John's Wort |
| modafinil | troglitazone |
| oxcarbazepine | |

## 13.2 Appendix B: Cockcroft-Gault Equation

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

## 13.3 Appendix C: Child-Pugh Score

| Factor | **1 point** | **2 points** | **3 points** |
|---|---|---|---|
| Total bilirubin (µmol/L) | <34 | 34-50 | >50 |
| Serum albumin (g/L) | >35 | 28-35 | <28 |
| PT INR | <1.7 | 1.71-2.30 | >2.30 |
| Ascites | None | Mild | Moderate to Severe |
| Hepatic encephalopathy | None | Grade I-II (or suppressed with medication) | Grade III-IV (or refractory) |

| | **Class A** | **Class B** | **Class C** |
|---|---|---|---|
| Total points | 5-6 | 7-9 | 10-15 |
| 1-year survival | 100% | 80% | 45% |

## 13.4 Appendix D. New York Heart Association (NYHA) classification

| NYHA grading | | MET* |
|---|---|---|
| **Class I** | No limitations. Ordinary physical activity does not cause undue fatigue, dyspnoea or palpitations (asymptomatic LV dysfunction) | >7 |
| **Class II** | Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pectoris (mild CHF). | 5 |
| **Class III** | Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF) | 2 – 3 |
| **Class IV** | Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF). | 1.6 |

*MET (metabolic equivalent) is defined as the resting $VO_2$ for a 40-year-old 70kg man. 1 MET = 3.5mL $O_2$/min/kg body weight.

## 13.5 Appendix E. Patient Handout: Prohibited Medications

### PROHIBITED MEDICATIONS

One of the medications you are receiving during this clinical trial is acalabrutinib. Acalabrutinib interacts with some drugs that are processed by your liver. For this reason, it is very important to tell your study doctors about all the medicines you take before you start this study. It is also very important to tell them if you stop taking any of your usual medicines, or if you start taking a new medicine while you take part in this study. When you talk about your medicines with your study doctor, be sure to talk about **any** medicine you buy without a prescription (over-the-counter remedy), or anything that you buy from a health food store or grocery store (herbs, or supplements). You must also tell your other prescribers (doctors, physician's assistants, or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**.

- Acalabrutinib is processed by proteins in your liver by a group of proteins in the CYP3A family. Certain drugs can either increase (induce) or decrease (inhibit) the speed at which this processing occurs.
- Acalabrutinib must be used very carefully with other medicines that **induce** or **inhibit** liver processing.
- You and your healthcare providers must be careful about adding or removing any drugs that either induce or inhibit CYP3A processing.
- Your regular prescribers should look at this web site: http://medicine.iupui.edu/clinpharm/ddis/table.asp to see if any medicine they want to prescribe is on a list of drugs to avoid. Your study doctor may also have a list of medications for you to show your regular prescribers instead of, or in addition to, this website.
- Other medicines can be a problem with your study drugs.
    - You should check with your doctor or pharmacist before you use an over-the-counter medicine or supplement.
    - Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you.
    - Your study doctor's name is _____ and he or she can be contacted at _____.

| CYP3A Inhibitors | |
|---|---|
| **indinavir**[a] | amiodarone |
| **nelfinavir**[a] | chloramphenicol |
| **ritonavir**[a] | boceprevir |
| **clarithromycin**[a] | ciprofloxacin |
| **itraconazole**[a] | delaviridine |
| **ketoconazole**[a] | diethyl-dithiocarbamate |
| **nefazodone**[a] | fluvoxamine |
| **saquinavir**[a] | gestodene |
| **telithromycin**[a] | imatinib |
| **aprepitant**[b] | mibefradil |
| **erythromycin**[b] | mifepristone |
| **fluconazole**[b] | norfloxacin |
| grapefruit & grapefruit juice[b] | norfluoxetine |
| verapamil[b] | starfruit |
| diltiazem[b] | telaprevir |
| cimetidine[c] | voriconazole |

[a]Strong inhibitor- causes a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.
[b]Moderate inhibitor- causes a > 2-fold increase in the plasma AUC values or 50-80% decrease in clearance.
[c]Weak inhibitor- causes a > 1.25-fold but < 2-fold increase in the plasma AUC values or 20-50% decrease in clearance.

| CYP3A Inducers | |
|---|---|
| efavirenz | phenobarbital |
| nevirapine | phenytoin |
| barbiturates | pioglitazone |
| carbamazepine | rifabutin |
| enzalutamide | rifampin |
| glucocorticoids | St. John's Wort |
| modafinil | troglitazone |
| oxcarbazepine | |

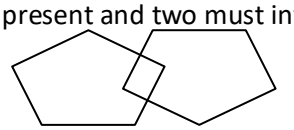
## 13.6 Appendix F. ECOG Performance Status

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. |
| 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). |
| 2 | In bed <50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol* 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

## 13.7 Appendix G: Mini-Mental State Exam

***Instructions:*** ***Ask the questions in the order listed. Score one point for each correct response within each question or activity.***

| Maximum Score | Patient's Score | Questions |
|---|---|---|
| 5 | | "What is the year? Season? Date? Day of the week? Month?" |
| 5 | | "Where are we now: State? County? Town/city? Hospital? Floor?" |
| 3 | | The examiner names three unrelated objects clearly and slowly, then asks the patient to name all three of them. The patient's response is used for scoring. The examiner repeats them until patient learns all of them, if possible. Number of trials: _____ |
| 5 | | "I would like you to count backward from 100 by sevens." (93, 86, 79, 72, 65, …) Stop after five answers.<br>Alternative: "Spell WORLD backwards." (D-L-R-O-W) |
| 3 | | "Earlier I told you the names of three things. Can you tell me what those were?" |
| 2 | | Show the patient two simple objects, such as a wristwatch and a pencil, and ask the patient to name them. |
| 1 | | "Repeat the phrase: 'No ifs, ands, or buts.'" |
| 3 | | "Take the paper in your right hand, fold it in half, and put it on the floor."<br>(The examiner gives the patient a piece of blank paper.) |
| 1 | | "Please read this and do what it says." (Written instruction is "Close your eyes.") |
| 1 | | "Make up and write a sentence about anything." (This sentence must contain a noun and a verb.) |
| 1 | | "Please copy this picture." (The examiner gives the patient a blank piece of paper and asks him/her to draw the symbol below. All 10 angles must be present and two must intersect.)<br>  |
| 30 | | TOTAL |

(Adapted from Rovner & Folstein)

## Instructions for administration and scoring of the MMSE

*Orientation (10 points):*

- Ask for the date. Then specifically ask for parts omitted (e.g., "Can you also tell me what season it is?"). One point for each correct answer.
- Ask in turn, "Can you tell me the name of this hospital (town, county, etc.)?" One point for each correct answer.

*Registration (3 points):*

- Say the names of three unrelated objects clearly and slowly, allowing approximately one second for each. After you have said all three, ask the patient to repeat them. The number of objects the patient names correctly upon the first repetition determines the score (0-3). If the patient does not repeat all three objects the first time, continue saying the names until the patient is able to repeat all three items, up to six trials. Record the number of trials it takes for the patient to learn the words. If the patient does not eventually learn all three, recall cannot be meaningfully tested.
- After completing this task, tell the patient, "Try to remember the words, as I will ask for them in a little while."

*Attention and Calculation (5 points):*

- Ask the patient to begin with 100 and count backward by sevens. Stop after five subtractions (93, 86, 79, 72, 65). Score the total number of correct answers.
- If the patient cannot or will not perform the subtraction task, ask the patient to spell the word "world" backwards. The score is the number of letters in correct order (e.g., dlrow=5, dlorw=3).

*Recall (3 points):*

- Ask the patient if he or she can recall the three words you previously asked him or her to remember. Score the total number of correct answers (0-3).

*Language and Praxis (9 points):*

- Naming: Show the patient a wristwatch and ask the patient what it is. Repeat with a pencil. Score one point for each correct naming (0-2).
- Repetition: Ask the patient to repeat the sentence after you ("No ifs, ands, or buts."). Allow only one trial. Score 0 or 1.
- 3-Stage Command: Give the patient a piece of blank paper and say, "Take this paper in your right hand, fold it in half, and put it on the floor." Score one point for each part of the command correctly executed.
- Reading: On a blank piece of paper print the sentence, "Close your eyes," in letters large enough for the patient to see clearly. Ask the patient to read the sentence and do what it says. Score one point only if the patient actually closes his or her eyes. This is not a test of memory, so you may prompt the patient to "do what it says" after the patient reads the sentence.

- Writing: Give the patient a blank piece of paper and ask him or her to write a sentence for you. Do not dictate a sentence; it should be written spontaneously. The sentence must contain a subject and a verb and make sense. Correct grammar and punctuation are not necessary.
- Copying: Show the patient the picture of two intersecting pentagons and ask the patient to copy the figure exactly as it is. All ten angles must be present and two must intersect to score one point. Ignore tremor and rotation.

***Sources:***

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- Folstein MF, Folstein SE, McHugh PR. "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
- Rovner BW, Folstein MF. Mini-mental state exam in clinical practice. *Hosp Pract*. 1987;22(1A):99, 103, 106, 110.
- Tombaugh TN, McIntyre NJ. The mini-mental state examination: a comprehensive review. *J Am Geriatr Soc*. 1992;40(9):922-935.

## 13.8 Appendix H: Brain Lymphoma Rubidium Visual Scoring Scale

Score 1: Uptake in lesion equal to or greater than uptake in normal brain but less than uptake in subcutaneous fat

Score 2: Uptake in lesion equal to or greater than uptake in the subcutaneous fat but less than uptake in the lung

Score 3: Uptake in lesion equal to or greater than uptake in lung but less than uptake in mediastinal blood pool

Score 4: Uptake in lesion equal to or greater than uptake in mediastinal blood pool

**In addition to visual scoring, we will calculate SUV in each lesion.**

## 13.9 Appendix I: Definition for Highly Effective Methods of Contraception

Highly effective methods of contraception (to be used during heterosexual activity) are defined as methods that can achieve a failure rate of <1% per year when used consistently and correctly. Women of childbearing potential who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib.

Such methods include:

- 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
- Intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy of a female subject's male partner (with medical assessment and confirmation of vasectomy surgical success)
- Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)

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

Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed during the entire period of risk associated with the study treatments as the subject's preferred and usual lifestyle. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

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.