PROTOCOL TITLE: An Open-Label Phase 2 Trial of Acalabrutinib plus Obinutuzumab in Patients with Untreated, Low Tumor Burden Follicular Lymphoma and Other Indolent Non-Hodgkin Lymphomas

WINSHIP PROTOCOL #: WINSHIP5186-20

COORDINATING CENTER: Winship Cancer Institute of Emory University

PRINCIPAL INVESTIGATOR:
Name: Jonathon B. Cohen, MD, MS
Department: Hematology and Medical Oncology
Telephone Number: 404-778-2214
Email Address: jonathon.cohen@emory.edu

CO-INVESTIGATORS:

Name: Jason Romancik, MD
Winship Cancer Institute of Emory University
Email Address: jromanc@emory.edu

STATISTICIAN:
Name: Jeff Switchenko
Research Assistant Professor
Department of Biostatistics & Bioinformatics, Rollins School of Public Health
Email Address: jswitch@emory.edu

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☒ **Study Exempt from IND Requirements per 21 CFR 312.2(b).**

REVISION HISTORY

Revision #	Version Date	Summary of Changes
N/A	N/A	N/A
1	9/8/22	Updated Appendix B - Drug Diary
2	11/15/23	Updated Acalabrutinib capsules to tablets

Table of Contents

1. Study Summary

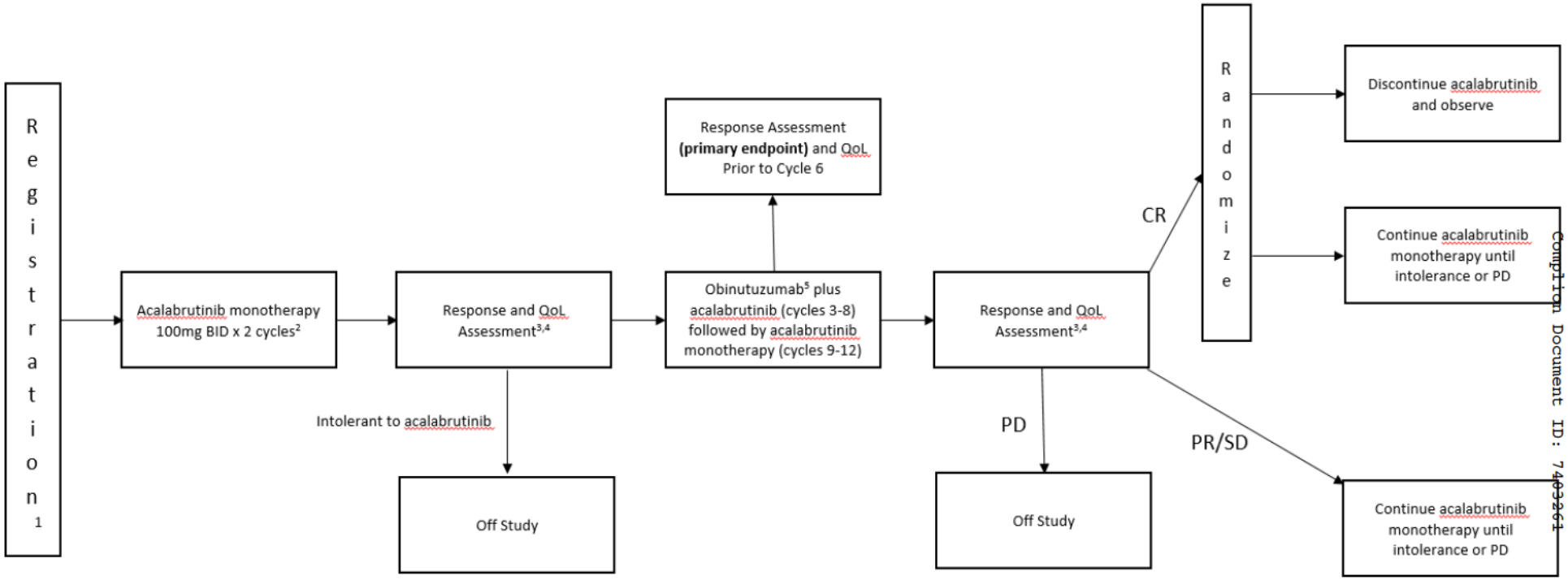
1.1 Synopsys

Title:	An Open-Label Phase 2 Trial of Acalabrutinib plus Obinutuzumab in Patients with Untreated, Low Tumor Burden Follicular Lymphoma and Other Indolent Non-Hodgkin Lymphomas
Study Description:	This research study is an open label, single arm, Phase II study, designed to evaluate the tolerability and efficacy of the combination acalabrutinib and obinutuzumab in subjects with previously-untreated, low-tumor burden follicular lymphoma and other indolent non-Hodgkin Lymphomas. We hypothesize that this combination will result in a higher complete response rate compared to what is historically seen with single-agent rituximab.
Objectives:	**Primary Objective**: • The primary objective is to determine if treatment acalabrutinib and obinutuzumab is effective in patients with untreated, low tumor burden follicular lymphoma and other indolent NHLs. **Secondary Objectives:** • Determine the CR rate for single agent acalabrutinib at the end of a single-agent run-in for patients with untreated low tumor burden FL. • Determine tolerability of acalabrutininb and obinutuzumab via assessment of patient-reported outcomes and conventional assessments • Assess duration of response and long-term outcomes including progression-free survival and rates of histologic transformation. • Assess the impact of early treatment with this regimen on health-related quality of life. **Exploratory Objective:** • Evaluate the impact of treatment discontinuation in patients who have achieved a complete response at the end of the induction phase.
Endpoints:	**Primary Endpoint:** • Complete response rate as of 6 months by the Lugano 2014 criteria **Secondary Endpoints:** • Overall response rate • CR rate for acalabrutinib monotherapy at end of single-agent run-in • 2-year progression free survival • 2-year rate of histologic transformation • Overall survival • Duration of Response • Time to next anti-lymphoma treatment • Quality of life assessments
Study Population:	The primary population of interest for this study is patients ≥ 18 years of age with follicular lymphoma (grade 1-3a) and a low tumor burden as defined by the GELF criteria (see Appendix 4). We will require at least 29 patients for our primary analysis using a Simon 2-stage design. In the 1st stage, 18 patients will be accrued. If there are 2 or fewer responses

	in those first 18 patients, the trial will stop. Otherwise, an additional 11 patients will be accrued for a total sample size of 29. We also plan to enroll up to 20 patients with other subtypes of indolent NHL and/or the following clinical scenarios: 1. Previously untreated follicular lymphoma (grade 1-3a) with a high tumor burden by GELF criteria who are unable or unwilling to receive standard front-line treatment approaches 2. Previously untreated marginal zone lymphoma, lymphoplasmacytic lymphoma, or any other indolent B-cell lymphoproliferative disorder with a low tumor burden by GELF criteria or who are unable/unwilling to receive more intensive front-line treatment 3. Previously untreated mantle cell lymphoma who would otherwise be appropriate candidates for watchful waiting OR who have symptomatic disease but are not candidates for or decline standard induction approaches. We will assess for preliminary evidence of efficacy of this treatment regimen in those lymphoma subtypes and/or clinical scenarios, and would consider a future amendment expanding one or more of those populations if an efficacy signal is identified. As a result, we will plan to enroll a total of 49 patients to the trial, at least 29 of whom will be patients with low tumor burden FL who are evaluable for the primary endpoint.
Phase:	Phase II
Description of Sites/Facilities Enrolling Participants:	Winship Cancer Institute of Emory University (Atlanta, GA).
Description of Study Intervention:	Following study consent and screening assessments, patients will enter the induction phase where treatment will be delivered in 28-day cycles. For cycles 1 and 2 patients will receive acalabrutinib monotherapy at the standard dose of 100mg orally twice daily. For cycles 3-8, patients will receive combination therapy with acalabrutinib and obinutuzumab. Obinutuzumab will be given on days 1, 8, and 15 of cycle 3, then on day 1 of cycles 4-8 (6 total cycles of obinutuzumab). After completing treatment with obinutuzumab, all patients will continue on acalabrutinib monotherapy for cycles 9 through 12. Patients who achieve a CR following cycle 12 will be randomized to either discontinue acalabrutinib or continue the medication until disease progression or intolerance. Patients with SD or PR after cycle 12 will continue acalabrutinib until intolerance or PD.
Study Duration:	The estimated time from when the study opens to enrollment until analysis of the primary outcome is 42 months. Patients in the follow-up phase who discontinue study therapy will be followed for 60 months or until the start of next anti-lymphoma treatment. Patients who continue acalabrutinib during the follow up phase will be treated on study until unacceptable toxicity, death, or start of the next anti-lymphoma therapy.

1.2 Schema

Acalabrutinib and Obinutuzumab in Low Tumor Burden Follicular Lymphoma and Other Indolent NHLs



1. Key Eligibility Criteria: Untreated FL with low tumor burden by GELF criteria; untreated FL with high tumor burden but patient unwilling or unable to receive chemotherapy; previously untreated MZL, lymphoplasmacytic lymphoma, or any indolent B cell lymphoproliferative disorder with low tumor burden.
2. 1 Cycle = 28 days
3. PET used for assessment of FL and MCL. Either PET or CT for MZL or other iNHL based on investigator preference. Repeat bone marrow assessment if initially positive and CR suspected.
4. QoL assessments with the Functional Assessment of Cancer Therapy – General (FACT-G) and Hospital Anxiety and Depression Scale (HADS) questionnaires will occur at baseline, prior to cycle 3, prior to cycle 6, and after cycle 12. After this, QoL will be assessed every 6 months x2 years then every 12 months x3 years.
5. Obinutuzumab dose 1,000mg on days 1, 8, and 15 of cycle 3 then 1,000mg on day 1 of cycles 4 through 8

1.3 Schedule of Assessments

Schedule of Assessments During Screening and Induction Phases

	Screening Phase	Induction Phase (28-day cycles)							
Treatment Cycle/Title:	Screening Visit[a]	Cycles 1 and 2		Cycle 3			Cycles 4 to 8	Cycles 9 to 12	End of Induction Visit
Day:	-28 to -1	1[b]	15[c]	1[b]	8	15	1[b]	1[b]	28(± 14) days after C12D1
Study Visit:	1	2,4	3	5		6	7 to 11	12 to 15	16
Administrative Procedures									
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Demographics and Medical History	X								
Prior and Concomitant Medication Review	X	Throughout							X
Acalabrutinib Administration		Throughout (twice daily)							X
Obinutuzumab Administration				X[l]	X[l]	X[l]	X		
Randomization									X[m]
Survival Status		Throughout							X
Clinical and Laboratory Procedures/Assessments									
Review Adverse Events		Throughout							X
Patient Reported Outcomes Questionnaire[d]		X[n]		X	X	X	X	X	X
Physical Examination	X	X	X	X		X	X	X	X
Vital Signs[e]	X	X	X	X		X	X	X	X
ECOG Performance Status	X	X	X	X		X	X	X	X
Quality of Life Assessments[f]	X			X			X[o]		X
Pregnancy Test – Urine or Serum β-HCG[g]	X	X		X			X	X	
Clinical Chemistry and Hematology[h]	X	X	X	X		X	X	X	X
Uric Acid	X			X					
HIV, HBsAg, HBcAb, HCV testing[i]	X								
Tumor Biopsy, Imaging, and Efficacy Measurements									
Tumor Imaging[j]	X[p]			X[q]			X[r]		X[s]
Bone marrow biopsy and aspirate	X[t]			X[u]			X[u]		X[u]
Tumor Biopsy[k]	X								

	Screening Phase	Induction Phase (28-day cycles)							
Treatment Cycle/Title:	Screening Visit[a]	Cycles 1 and 2		Cycle 3			Cycles 4 to 8	Cycles 9 to 12	End of Induction Visit
Day:	-28 to -1	1[b]	15[c]	1[b]	8	15	1[b]	1[b]	28(± 14) days after C12D1
Study Visit:	1	2,4	3	5		6	7 to 11	12 to 15	16

a) The screening period extends from Day -28 to Day 1. Subjects must be screened within 28 days prior to Cycle 1/Day 1. Screening visit can serve as baseline visit as long as labs and physical exam performed within 3 days of Cycle 1/Day 1.

b) During induction phase, day 1 study visits for cycles 2-12 must occur within ± 7 days, but obinutuzumab dose should be given ± 3 days. Patients should continue acalabrutinib during this time.

c) Cycle 1 Day 15 visit must occur ± 3 days. Cycle 2 Day 15 visit is not required for study purposes

d) Patient reported outcomes assessed via PRO-CTCAE administered at least monthly during induction phase

e) Assessment will include resting HR, BP, RR, and temperature.

f) Quality of life assessed using FACT-G and HADS questionnaires to be administered in person at study visit.

g) Only in women of child bearing potential

h) Includes complete blood count with differential, comprehensive metabolic panel, and LDH

i) If not already done within 6 months of signing informed consent

j) For follicular lymphoma and mantle cell lymphoma imaging assessment will be PET/CT; after cycle 12 can perform either CT neck/chest/abdomen/pelvis or PET/CT based on patient and investigator preference. For marginal zone lymphoma and other subtypes of indolent NHL, all imaging assessment can be either with PET/CT or CT neck/chest/abdomen/pelvis based on investigator preference.

k) Patients will either need a fresh biopsy or archived pathology reviewed at the treating center that confirms the diagnosis

l) If cycle 3 day 1 obinutuzumab is given as split dose, the full dose must be completed within 2 days. Weekly doses of obinutuzumab during cycle 3 must be given within ± 3 days

m) Patients with SD or PR following induction therapy will continue acalabrutinib until intolerance or progressive disease. Patients with CR following induction who are randomized to continue acalabrutinib will also continue until intolerance or progressive disease.

n) Assess PRO weekly during cycle 1

o) Perform QOL assessments at Cycle 6 day 1 visit

p) Up to 42 days between baseline imaging and initiation of study treatment is permitted

q) Within 7 days of cycle 3 day 1 – must be done before first obinutuzumab dose

r) Within 7 days before or after cycle 6 day 1

s) Within 7 days before end of induction visit

t) If bone marrow biopsy done within 12 months of ICF and no clinical suspicion for change in status, then this is optional

u) If marrow was previously involved, then repeat bone marrow biopsy at first suspicion of complete response

Windows for Disease Restaging:

Disease restaging will occur at the following time points:

- Within 7 days of Cycle 3, Day 1 (MUST occur before first dose of obinutuzumab)
- Within 7 days before or after Cycle 6, Day 1
- Within 7 days before the end of induction visit

Schedule of Assessments during Follow-Up Phase

Trial Period:	Patients continuing acalabrutinib	Patients Randomized to Observation		Patients who discontinue study therapy		
Treatment Cycle/Title:	Follow-up visits[a]	≤ 1 year from end of induction visit	>1 year from end of induction visit	Treatment Termination Visit	Safety follow-up Visit	Discontinuation Follow-up Visits[b]
Frequency:	Every 12 weeks ± 2 weeks[c]	Every 12 weeks ± 2 weeks	Every 24 weeks ± 4 weeks	Within 7 days last dose study drug	4 weeks ± 7 days last dose study drug	Every 12 weeks ± 2 weeks[d]
Prior and Concomitant Medication Review	X			X	X	
Acalabrutinib Administration	Continuous (twice daily)					
Survival Status	X	X	X	X	X	X
Review Adverse Events	X			X	X	
Patient-Reported Outcomes Questionnaire[e]	X			X	X	
Physical Examination	X			X	X	
Vital Signs[f]	X	X	X			
ECOG Performance Status	X	X	X	X	X	X
Quality of Life Assessment[g]	X[g]	X	X	X	X	X
Pregnancy Test – Urine or Serum β-HCG[h]	X					
Clinical Chemistry and Hematology[i]	X	X	X	X	X	X
Tumor Assessment[j]	X[k]	X[k]	X[k]			X[k]

Trial Period:	Patients continuing acalabrutinib	Patients Randomized to Observation		Patients who discontinue study therapy		
Treatment Cycle/Title:	Follow-up visits[a]	≤ 1 year from end of induction visit	>1 year from end of induction visit	Treatment Termination Visit	Safety follow-up Visit	Discontinuation Follow-up Visits[b]
Frequency:	Every 12 weeks ± 2 weeks[c]	Every 12 weeks ± 2 weeks	Every 24 weeks ± 4 weeks	Within 7 days last dose study drug	4 weeks ± 7 days last dose study drug	Every 12 weeks ± 2 weeks[d]

a. Patients who discontinue acalabrutinib for any reason (including disease progression) during the follow-up phase will start follow-up schedule for patients who discontinue study therapy.

b. Patients who discontinue study therapy will continue to be followed on study for follow-up of safety and survival unless they withdraw consent for further follow-up or start an alternative anti-lymphoma therapy.

c. There will be at most 12 weeks ± 2 weeks between study visits for patients who continue on acalabrutinib. If a patient is seen earlier than this interval, then the next follow-up visit can be scheduled 12 weeks from the time of that visit at the discretion of the treating physician.

d. Patients follow-up every 12 weeks ± 2 weeks from the last dose of study drug for 1 year then can decrease frequency of visits to every 24 weeks ± 4 weeks

e. Patient-reported outcomes assessed via PRO-CTCAE form administered in person at each study visit.

f. Assessment will include resting HR, BP, RR, and temperature.

g. Quality of life is assessed with the FACT-G and HADS questionnaires and will be conducted in person at study follow-up visits that correspond with scan review (i.e. every 6 months x2 years then every 12 months x 3 years). Patients who miss a follow-up visit will be contacted by telephone to complete QoL assessments. Patients who start a new treatment and those who stop following at the study site for other reasons will no longer be required to complete the QoL questionnaires.

h. For women of childbearing potential

i. Includes complete blood count with differential, comprehensive metabolic panel, and LDH

j. During follow-up phase tumor imaging can be with PET/CT or CT neck/chest/abdomen/pelvis based on patient and investigator preference for all disease types. Bone marrow biopsy to be performed at first suspicion of CR (if marrow previously involved) or if there is clinical concern for new marrow involvement.

k. During the follow-up phase tumor imaging will be obtained every 6 months (± 1 month) x2 years from the end of induction visit then every 12 months (± 1 month) x3 years. Patients who discontinue study therapy can continue with this imaging schedule if deemed appropriate by the treating physician.

2. Objectives (and Endpoints)

OBJECTIVES	ENDPOINTS
Primary	
The primary objective is to determine if treatment acalabrutinib and obinutuzumab is effective in patients with untreated, low tumor burden follicular lymphoma and other indolent NHLs.	• The primary efficacy endpoint is the complete response rate prior to cycle 6 of therapy by the Lugano 2014 criteria
Secondary	
• Determine the CR rate for single agent acalabrutinib at the end of a single-agent run-in for patients with untreated low tumor burden FL. • Determine tolerability of acalabrutininb and obinutuzumab via assessment of patient-reported outcomes and conventional assessments • Assess duration of response and long-term outcomes including progression-free survival and rates of histological transformation. • Assess the impact of early treatment with this regimen on health-related quality of life.	• Overall response rate • CR rate for acalabrutinib monotherapy at end of single-agent run-in • 2-year progression free survival • 2-year rate of histologic transformation • Overall survival • Duration of Response • Time to next anti-lymphoma treatment • Quality of life assessments
Tertiary/Exploratory	
• Evaluate the impact of treatment discontinuation in patients who have achieved a complete response at the end of the induction phase. • To assess the safety and efficacy of acalabrutinib and obinutuzumab in other subtypes of indolent NHL.	

3. Background

3.1 Study Rationale

Follicular Lymphoma and Other Indolent NHL with a Low Tumor Burden

Follicular lymphoma (FL) is the most common indolent non-Hodgkin lymphoma (NHL) diagnosed in the United States and Western Europe with an annual incidence of 3.4-5 cases per 100,000 and a median age of diagnosis of 65 years.[1-3] The majority of patients present with advanced (stage III or IV) disease that is currently incurable with existing therapies, though the prognosis for these patients has improved considerably in recent years with the introduction of new therapeutic agents. In fact, the median overall survival (OS) has not been reached for patients with FL who started treatment in the rituximab era.[4-7] However, FL is a biologically and clinically heterogeneous disease characterized by multiple remissions and relapses, and some patients will experience an aggressive clinical course. Up to 20% of patients will relapse within 24 months following first-line therapy, and this is associated with a particularly poor outcome with a 5-year OS rate of less than 50% and a high incidence of transformation to aggressive NHL.[8,9]

The treatment approach for patients with advanced-stage FL is often determined by tumor bulk. The Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria were developed to guide clinicians when making initial treatment decisions and includes an assessment of the size of lymph node and extranodal masses, presence of systemic symptoms, cytopenias, and risk of compression of surrounding structures.[10] For patients who are asymptomatic and have a low tumor burden at the time of diagnosis, a strategy of watchful waiting is frequently employed based on the results of early prospective trials that showed no survival advantage to early treatment with chemotherapy.[10-12] With this approach, the median time to first systemic therapy was 3 years. More recently, rituximab monotherapy has been compared to watchful waiting in low tumor burden FL in a phase 3 trial which showed that early treatment with rituximab significantly delays disease progression and the time until first treatment with chemotherapy and radiotherapy.[13] There was no OS benefit associated with early treatment with rituximab at a median follow-up of 46 months, but the estimated percentage of patients who did not need new to start new therapy at 3 years was 88% in the rituximab group compared to 46% in the watchful waiting group. In addition, patients treated with early rituximab showed significant improvements in quality of life (QoL) based on the Mental Adjustment to Cancer scale and the Illness Coping Styles assessments.

Similarly, the RESORT trial evaluated the efficacy of rituximab monotherapy in low tumor burden FL when given as an induction phase followed by randomization of responding patients to receive either maintenance rituximab vs. rituximab retreatment at time of progression.[14] Patients underwent restaging after the induction phase and the overall response rate (ORR) at this time point was 70.8% with a complete response (CR) rate of 11.8%. Patients treated on this trial also had a prolonged time to first cytotoxic therapy; at 3 years 95% of patients treated with maintenance rituximab and 84% of patients managed with rituximab retreatment were cytotoxic therapy free. Based on these data the use of rituximab monotherapy in low tumor burden FL is now considered an appropriate strategy, especially for patients who are uncomfortable deferring therapy or for whom delaying more intensive treatment is a priority.

The phase 2 BRIEF study attempted to improve the outcomes for patients with low tumor burden FL and a FLIPI score ≥ 2 by treating with 2 cycles of bendamustine and rituximab followed by rituximab maintenance for 2 years.[15] Patients on this trial had a 93% ORR and 2 year PFS of 85.4%, but there were three unexpected patient deaths during the maintenance phase so this treatment strategy is not recommended.

Non-follicular indolent NHLs such as marginal zone lymphoma (MZL), small lymphocytic lymphoma (SLL), and lymphoplasmacytic lymphoma/Waldenstrom's Macroglobulinemia (LPL/WM) are also associated with prolonged survival times but are also generally considered incurable in advanced stages. Similar to FL, the optimal treatment strategy in asymptomatic patients is not defined and many of these patients are also managed initially with watchful waiting. The RESORT trial included a subset of patients with indolent NHL who were also treated with rituximab monotherapy.[16] While the ORRs were lower for these patients compared to FL (22.8% for SLL and 52.1% for MZL), the patients enjoyed a prolonged time to first cytotoxic therapy of at least 6.3 years.

In recent years, a number of novel agents such as lenalidomide and the BTK inhibitors have been developed and are now used in the treatment of indolent B-cell NHLs. These agents are often well-tolerated but they have yet to be evaluated in the setting of low tumor burden indolent NHL to see if their use can improve upon the outcomes observed with the use of single-agent rituximab.

Health-Related Quality of Life and Patient-Reported Outcomes

Prior retrospective studies suggest that a diagnosis of indolent lymphoma and disease recurrences are associated with a negative psychological impact and a decrease in quality of life.[17,18] Elevated anxiety has also been documented in patients undergoing treatment for hematologic malignancies as well as in survivors of NHL.[19,20] A negative physical impact of cytotoxic chemotherapy has also been reported[17], whereas the use of newer agents such as rituximab allow for less toxic treatment for indolent lymphoma and may not have the same detrimental impact on quality of life that traditional chemotherapy does.[21] In the context of low tumor burden indolent NHL, the impact of treatment with rituximab monotherapy has been evaluated in two prospective clinical trials which also suggest that this treatment approach is not associated with any reduction in quality of life and may actually lead to improvements in some aspects of QoL.[13,22] The impact of the newer agents such as acalabrutinib and obinutuzumab on QoL and psychological distress in this patient population is not known.

The Functional Assessment of Cancer Therapy – General (FACT-G) is a questionnaire that evaluates physical, social, emotional, and functional well-being and has been validated to asses quality of life in non-Hodgkin Lymphoma patients.[23] The FACT-lym questionnaire was developed more recently and consists of the FACT-G plus 15 questions measuring symptoms or concerns specific to patients being treated for lymphoma. Several items in the lymphoma-specific subscale ask about systemic symptoms such as pruritus and night sweats that are likely not applicable to patients diagnosed with low tumor burden indolent lymphoma or those who are being followed on observation. For this reason, we will be using the FACT-G to make QoL assessments.

The Hospital Anxiety and Depression Scale (HADS) has been previously used in lymphoma patients and is comprised of anxiety and depression subscales that consist of seven items each. Total scores for each subscale range from 0 to 21 with higher scores representing greater anxiety or depression.

Patient-reported outcomes (PROs) allow for patients to self-report issues related to their physical and psychologic well-being and these assessments can help provide information about a patient's physical fitness and tolerance to treatment. Research has demonstrated that that integrating PROs into the care of patients with cancer has the potential to improve their care delivery and outcomes, including treatment tolerability, hospitalizations, and even survival.[24] The Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) is a tool to assess the patient's symptom burden that has been shown to be a valid and reliable assessment of symptomatic adverse effects for patients undergoing cancer treatment.[25,26] This tool will be incorporated in the scheduled assessments for patients who continue on treatment to determine how treatment with acalabrutinib and obinutuzumab impacts the overall symptom burden for patients on study therapy.

Rationale

The combination of obinutuzumab and acalabrutinib has not been evaluated to date in the treatment of FL and other indolent NHLs. Additionally, the use of novel agents like the BTK inhibitors has not been evaluated in patients with low tumor burden FL, which is a group of patients that has historically been managed either with watchful waiting or single-agent rituximab.

The combination of anti-CD20 monoclonal antibodies and BTK inhibitors have clinical activity in the treatment of FL. The combination of obinutuzumab and acalabrutinib has been evaluated in patients with CLL/SLL in the phase 3 ELEVATE-TN trial which demonstrated clinical efficacy of the combination in this setting without any new safety signals.[27]

Observation is considered the current standard of care for many patients who will be eligible for this study – with single-agent rituximab being a reasonable alternative for patients who are not comfortable with this approach. This is because no other therapeutic approach studied in this patient population thus far has resulted in an overall survival benefit, not because the current results for patients are satisfactory. Clinical trials using novel, chemotherapy-free approaches in this population to try and improve outcomes and QoL are warranted.

In this study, we aim to evaluate the safety and efficacy of obinutuzumab and acalabrutinib in the treatment of low tumor burden FL to see if we can improve upon the historical CR rate of 11.8% following induction therapy with single agent rituximab that was reported in the RESORT trial.[14] The inclusion and exclusion criteria (Section 9) were developed to identify patients who are at high risk for complications from study therapy; these patients will not be offered clinical trial enrollment and will instead be considered for standard of care approaches.

We will use the FACT-G, HADS, and PRO-CTCAE to assess the impact of early treatment with obinutuzumab and acalabrutinib on patient safety and health-related QoL to better assess the overall risk-benefit profile of this new treatment regimen. Finally, we are exploring the impact of treatment discontinuation in responding patients.

3.2 Clinical Experience

Bruton Tyrosine Kinase Inhibition In Follicular Lymphoma and Other Indolent NHLs
Bruton tyrosine kinase (BTK) is a non-receptor enzyme in the Tec kinase family that is expressed among cells of hematopoietic origin, including B-cells, myeloid cells, mast cells, and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration.[28-30] In addition, BTK-dependent activation of mast cells, myeloid cells, and other immunocytes in peritumoral inflammatory stroma has been shown to sustain the complex microenvironment needed for lymphoid and solid tumor maintenance.[31-33] Taken together, these findings suggest inhibition of BTK may offer an attractive strategy for treating B-cell neoplasms, other hematologic malignancies, and solid tumors.

BTK inhibition has been shown to have clinical activity in relapsed/refractory (R/R) FL based on the results of a phase 2 clinical trial which showed that ibrutinib monotherapy in this settings yields an ORR of 37.5%, a complete response CR rate of 12.5%, and a median PFS of 14 months.[34] Response rates were significantly higher among patients with rituximab-sensitive disease (ORR 52.6%) compared to those who were refractory to rituximab (ORR 16.7%). In patients with untreated FL, treatment with rituximab plus ibrutinib has an ORR of 82% and a CR rate of 27% in a phase 2 trial.[35] In a phase 1b trial of acalabrutinib ± rituximab, there were 13 patients with untreated FL who received combination therapy and had an ORR of 92% and a CR rate of 31%.[36]

BTK inhibition is also effective in treating other subtypes of indolent NHL. In a phase 2 trial evaluating ibrutinib monotherapy in R/R MZL, the ORR was found to be 48% with a CR rate of 3%.[37] At median follow-up of 19.4 months, the median duration of response was not reached, with 62% of responders alive and progression-free at 18 months. In previously untreated and relapsed LPL/WM, ibrutinib plus rituximab was compared to placebo plus rituximab in a phase 3 trial which showed a significantly higher major response rate with ibrutinib-rituximab compared to placebo-rituximab (72% vs. 32%, $p<0.01$) as well as a significantly higher rate of PFS at 30 months (82% vs 28%).[38]

The optimal duration of therapy for patients receiving BTK inhibitors is not well-established. Currently FDA labeled indications support indefinite treatment but it is not known whether continued therapy for responding patients is truly needed. In this study, we will randomize responding patients to discontinue or continue acalabrutinib treatment to identify the impact of continued treatment on response duration, patient reported quality of life, and toxicity.

Acalabrutinib (ACP-196)

Acalabrutinib is FDA approved for the treatment of R/R MCL based on the results of the phase 2, open-label monotherapy ACE-LY-004 study.[39] Subjects in this study received acalabrutinib 100mg BID continuously, in repeated 28-day cycles until disease progression or unacceptable drug-related toxicity, whichever occurred first. The ORR was 80.6%. A best response of CR was achieved in 42.7% of subjects and a best response of PR was achieved in 37.9% of subjects. The median duration of response was 25.7 months.

Acalabrutinib is now approved for use in treatment-naïve or relapsed CLL based on the results of the ELEVATE TN and ASCEND trials.[27] In ELEVATE TN, patients with untreated CLL were randomized to receive obinutuzumab plus acalabrutininb, acalabrutinib alone, or obinutuzumab plus chlorambucil. At median follow-up of 28 months, acalabrutinib plus obinutuzumab significantly prolonged PFS compared to obinutuzumab plus chlorambucil (median not reached vs. 22.6 months; HR 0.10, 95% CI 0.06-0.18, p<0.0001). The median PFS with acalabrutinib monotherapy was also not reached. The IRC-assessed ORR with acalabrutinib plus obinutuzumab was 94% with a 13% CR rate. The ORR for acalabrutinib monotherapy was 85% with 1 patient achieving a CR.

In the phase 3 ASCEND trial, patients with R/R CLL were randomized to receive either acalabrutinib monotherapy or investigator's choice of rituximab/idelalisib or rituximab/bendamustine.[40] At median follow-up of 16.1 months, acalabrutinib significantly prolonged IRC-assess PFS vs rituximab/idelalisib or rituximab/bendamustine (median not reach vs. 16.5 months; HR 0.31, 95% CI 0.20-0.49, p<0.0001). ORR was not significantly different between the two arms (81% vs. 75%).

For more details regarding the clinical efficacy of acalabrutinib, please refer to the Investigator's Brochure.

Obinutuzumab (GA-101)

Obinutuzumab is a CD20-directed cytolytic antibody monoclonal antibody that is delivered as an IV infusion. Obinutuzumab is approved in the US in combination with bendamustine followed by obinutuzumab monotherapy for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen. It is also approved for use in combination with chemotherapy followed by obinutuzumab monotherapy for up to two years in patients achieving at least a partial remission, for the treatment of adult patients with previously untreated stage II bulky, III, or IV follicular lymphoma.

Patients with indolent NHL who received obinutuzumab monotherapy had a response rate at the end of treatment that ranged from 28% (11/40 patients) to 58% (7/12 patients). Some patients in studies BO20999, BO21003, and JO21900 had rituximab-refractory disease but still achieved a CR by the end-of-treatment assessment.

The GADOLIN trial is an open-label, multicenter, randomized study including 321 patients with FL who had no response to or have progressed during or within 6 months of rituximab product or a rituximab product-containing regimen.[41] These patients were randomized to receive either bendamustine alone or bendamustine in combination with obinutuzumab. Patients who did not have disease progression at the end of 6 cycles of combination therapy then went on to have obinutuzumab monotherapy for 2 years. The primary objective of this study was to evaluate PFS as determined by an independent review committee (IRC). The median observation time was 21.1 months. The median PFS in the bendamustine arm was 13.8 months. Median PFS was not reached in the obinutuzumab plus bendamustine arm (HR = 0.48, 95% CI: 0.35-0.67; stratified log-rank test p-value < 0.0001).

The GALLIUM trial is an open-label, randomized study including 1202 patients with previously untreated, stage II bulky, II, or IV FL.[42] Patients were randomized 1:1 to receive either obinutuzumab or rituximab product in combination with chemotherapy (CHOP, CVP, or bendamustine) for 6-8 cycles. Patients with at least a PR to combination therapy received monotherapy with obintuzumab or rituximab product every two months until disease progression or for a maximum of 2 years. Efficacy was based on PFS per IRC. After a median follow-up of 34.5 months, a planned interim analysis showed that obinutuzumab-based chemotherapy resulted in a significantly lower risk of progression, relapse, or death than the rituximab based chemotherapy with an estimated 3-year PFS rate of 80% versus 73.3% (hazard ratio for progression, relapse, or death, 0.66; 95% CI, 0.51 to 0.85; p=0.001). ORR was similar between the two groups (88.5% in the obinutuzumab group and 86.9% in the rituximab group).

4. Study Intervention/Investigational Agent

4.1 Description

Acalabrutinib (ACP-196)
Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally bioavailable in humans and is suitable for formulating in tablets. 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). It is also under evaluation for the treatment of patients with other B-cell malignancies.

Mechanism of Action:
Acalabrutinib is a potent inhibitor of BTK in vitro and in vivo. Pharmacology models have been used to define kinase selectivity of acalabrutinib in comparison to other BTK inhibitors, and to investigate functional effects of on-target and off-target activities. Acalabrutinib shows improved selectivity for BTK compared with ibrutinib. Functional inhibition of non-target cells (eg, T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations.

Safety Pharmacology:
In vitro and in vivo safety pharmacology and toxicology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of acalabrutinib, refer to the Investigator Brochure.
Drug-Drug Interaction Potential:
For more detailed information on drug-drug interactions for acalabrutinib, refer to the Investigator Brochure. Please refer to Section 5.6 for guidance on drugs that may cause drug-drug interactions.

Obinutuzumab (GA-101)
Mechanism of Action:
Obinutuzumab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B lymphocytes. After binding to CD20, obinutuzumab mediates B-cell lysis through the

engagement of immune effector cells, directly activating intracellular death signaling pathways (direct cell death), and/or activation of the complement cascade. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis. Obinutuzumab is an antibody with a reduced fucose content so it induces greater ADCC activity than rituximab in vitro using human cancer cell lines. Obinutuzumab also demonstrated an increased ability to induce direct cell death when compared to rituximab. Obinutuzumab binds to FCγRIII using purified proteins with a higher affinity than rituximab. Obinutuzumab and rituximab bind with similar affinity to overlapping epitopes on CD20.

Safety Pharmacology:
In vitro and in vivo safety pharmacology studies with obinutuzumab have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of obinutuzumab, please refer to the current United States Package Insert (USPI).

Drug-Drug Interaction Potential:

For more detailed information on drug-drug interaction potential for obinutuzumab, refer to the USPI. Please refer to Section 5.6 for guidance on drugs that may cause drug-drug interactions

4.2 Drug/Device Handling

Premedications:

Acalabrutinib

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

Obinutuzumab

Patients may be premedicated with glucocorticoid, acetaminophen, and anti-histamine at the preference of the investigator in accordance with the package insert and/or institutional guidelines/practice. Please refer to the USPI for additional information.

Formulation, Packaging, and Storage

Acalabrutinib
The investigational product, acalabrutinib for oral administration, is supplied as orange, oval, film-coated, biconvex, debossed with 'ACA 100' on one side and plain on the other tablet. Inactive ingredients in the tablet core are low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet coating consists of copovidone, ferric oxide yellow, ferric oxide red, hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water and titanium dioxide.

Acalabrutinib maleate tablets are packed in white, HDPE bottles containing a silica gel desiccant and should be stored according to the storage conditions as indicated on the label. Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F)

Refer to the acalabrutinib Investigator Brochure for additional information regarding the drug product to be used in this trial.

Obinutuzumab

Obintuzumab 1000 mg/40 mL (25 mg/mL) single-dose vials containing preservative-free solution. (NDC 50242-070-01) are stable at 2°C to 8°C (36°F to 46°F). Protect obinutuzumab vials from light. Do not freeze. Do not shake.

For the diluted product, chemical and physical stability have been demonstrated in 0.9% NaCl at concentrations of 0.4 mg/mL to 20 mg/mL for 24 hours at 2°C to 8°C (36°F to 46°F) followed by 48 hours (including infusion time) at room temperature (≤ 30°C/86°F). Obinutuzumab does not contain antimicrobial preservatives. Therefore, care must be taken to ensure that the solution for infusion is not microbiologically compromised during preparation. The solution for infusion should be used immediately. If not used immediately, the prepared solution may be stored up to 24 hours at 2 to 8°C. No incompatibilities between obinutuzumab and polyvinyl chloride or polyolefin infusion materials have been observed in concentration ranges from 0.4 mg/mL to 20.0 mg/mL after dilution of obinutuzumab with 0.9% sodium chloride.

Refer to the Package Insert for additional information regarding the drug product to be used in this trial.

Administration of Study Drug

Acalabrutinib

Acalabrutinib tablet is administered orally twice daily. Whenever possible, it should be administered at the same time each day. The tablets should be swallowed intact with water. Acalabrutinib tablets should be swallowed whole with water. Subjects should not chew, crush, dissolve, or cut the tablets. Acalabrutinib can be taken with or without food.
If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the next dose. If it has been > 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

Patients must record administration of acalabrutinib (time and date of each dose, and missed doses) on the supplied patient journal.

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 5.6.

Obinutuzumab

Prepare the solution for infusion, using aseptic technique, as follows:

- Inspect visually for any particulate matter and discoloration prior to administration.
- Dilute into a 0.9% sodium chloride PVC or non-PVC polyolefin infusion bag. Do not use other diluents such as dextrose (5%).
- Withdraw 40 mL of obinutuzumab solution from the vial.
- Dilute 40 mL (1000 mg) into a 250 mL 0.9% sodium chloride infusion bag
- Mix diluted solution by gentle inversion. Do not shake or freeze.

- For microbiological stability, the diluted obinutuzumab infusion solution should be used immediately. Dilute under appropriate aseptic conditions. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours prior to use.
- The product can be administered at a final concentration of 0.4mg/mL to 4 mg/mL

Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix obinutuzumab with other drugs. No incompatibilities between obinutuzumab and PVC or non-PVC polyolefin bags and administration sets have been observed.

4.3 Accountability

The study drug provided for this study will be used only as directed in the study protocol. The Winship IDS (Investigational Drug Service) personnel will account for all study drugs. Drug accountability should be performed until the patient stops study treatment completely. Study site personnel will account for all study drugs received at the site.
Study drug supplies must be kept in an appropriate, secure locked area and stored in accordance with the conditions specified on the labels. The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug/s in a Drug Accountability Log.
The Drug Accountability Log may record specifics to study drug dispensation such as:
• Records of product delivery, inventory, temperature monitoring, destruction, and return.
• Dosages prepared, time prepared, doses dispensed.
• Doses and/or vials destroyed.
• The Drug Accountability Log may be reviewed by the monitor during site visits and at the completion of the study.

Patients will be asked to return all unused study treatment and packaging on a regular basis, at the end of the study or at the time of study treatment discontinuation.
The study drug supply will be disposed of per Winship's Investigational Drug Service (IDS) SOP.
Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or caregiver (collection of drug diary) will be captured in the Drug Accountability Form. This information must be captured in the source document at each patient visit.

The patient might be requested to maintain a medication diary of each dose of medication. The medication diary (Appendix B) will be returned to clinic staff at the end of each cycle.
Dose changes and interruptions of study drug must be specifically documented in the patient source documents and eCRF.

5. Procedures Involved

5.1 Study Design

This is an open-label phase II study of acalabrutinib in combination with obinutuzmab in patients with untreated, low tumor burden follicular lymphoma and other indolent NHLs. Tumor burden will be assessed based on the GELF criteria (Appendix E). Following study consent and screening assessments, patients will enter the induction phase where treatment will be delivered in 28-day cycles. For cycles 1 and 2, patients will receive acalabrutinib monotherapy at the standard dose of 100mg orally twice daily.

For cycles 3-8, patients will receive combination therapy with acalabrutinib and obinutuzumab. Obinutuzumab will be given on days 1, 8, and 15 of cycle 3 then on day 1 of cycles 4-8 (6 total cycles of obinutuzumab). After completing treatment with obinutuzumab, all patients will continue on acalabrutinib monotherapy for cycles 9 through 12.

Response will be assessed after cycle 2 (acalabrutinib monotherapy), after 3 cycles of the combination of obinutuzumab/acalabrutinib, and after cycle 12. After completing cycle 12, patients will enter the follow-up phase. Patients who are in CR after cycle 12 will be randomized to either discontinue acalabrutinib or to continue acalabrutinib monotherapy until intolerance or PD. All patients with PR or SD following cycle 12 will continue with acalabrutinib monotherapy until intolerance or PD. Patients with PD following cycle 12 will discontinue study treatment. Patients with PD at any time prior to the conclusion of cycle 12 *may* continue study therapy if they are felt to be benefitting by the treating physician, but no one with PD will continue therapy past cycle 12. The study will enroll 29 patients with follicular lymphoma for our primary analysis. The study will also enroll up to 20 patients with other histologic subtypes of indolent NHL in order to identify preliminary evidence of efficacy of this combination in those subtypes and/or clinical scenarios.

5.2 Study Parameters

Efficacy Parameters
Response to treatment will be assessed according to the Lugano Classification for response assessment in lymphoma[43] for patients with FL and based on the appropriate disease response criteria for non-follicular lymphoma. See Section 5.8 for a description of disease response and progression criteria.

Safety Parameters
The safety of acalabrutinib and obinutuzumab will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent AEs or abnormalities of laboratory tests; SAEs, AEs of special interest (AESI), or AEs leading to discontinuation of study treatment or death.

For consistency of interpretation, AEs and laboratory results will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Standard definitions for seriousness will be applied (see Section 17).

Patient-Reported Outcome and Health-Related Quality of Life Assessments
The impact of treatment with acalabrutinib and obinutuzumab on health-related quality of life and patient distress will be assessed using the FACT-G questionnaire, the Hospital Anxiety and Depression Scale (HADS), and the PRO-CTCAE. See section 5.8 for a description of QoL, depression/anxiety, and PRO assessments.

5.3 Dosing and Administration

Study treatment will be administered in 28-day cycles.

Acalabrutinib:
Acalabrutinib 100mg will be administered orally twice daily, every day starting on cycle 1 Day 1 and will continue through cycle 12 unless the patient develops intolerance to acalabrutinib or symptomatic/clinically significant disease progression.

After 12 cycle, patients who achieve CR will be randomized to either continue acalabrutinib at the same dose until intolerance or PD or discontinue the medication. Patients with a PR or SD after 12 cycles of treatment will continue acalabrutinib at the same dose until intolerance or PD.

Obinutuzumab:
Each dose of obinutuzumab is 1000mg administered intravenously according to institutional protocols and the USPI. Patients who are deemed to be at high risk for infusion-related reactions *may* receive the first dose of obinutuzumab as a split dose (100mg on day 1, 900 mg on day 2). This option is only available for the first dose of obinutuzumab. In this case, we would recommend that patients receive the day 1 dose at 25 mg/hr x 4 hours without titration of the infusion rate.

Obinutuzumab will be administered during cycles 3 through 8. There will be no obinutuzumab maintenance phase. Refer to the schedule of assessments (Section 1.3) for the dosing schedule.

5.4 Dose Modification

The investigator will decide whether any AE that occurs is related to either or both drugs and determine whether dose modification or discontinuation of one or both drugs is required per the guidance below.

Acalabrutinib

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib-related toxicity. If a subject experiences a treatment-related toxicity or other intolerable AE during the course of therapy, then acalabrutinib should be withheld, as necessary, until the AE returns to grade 1 or baseline.

Dose modifications for the following treatment-emergent toxicities are provided below:

- Grade 4 neutropenia (< 500/µL) for > 7 days (neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines [Smith 2006] and use must be recorded on the case report form [CRF]).
- Grade 3 thrombocytopenia in presence of significant bleeding.
- Grade 4 thrombocytopenia.
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

Drug Modification Actions for Acalabrutinib

Occurrence	Action
1st – 2nd	Hold acalabrutinib until recovery to Grade 1 or baseline; may restart at original dose level
3rd	Hold acalabrutinib until recovery to Grade 1 or baseline; restart at one dose level lower (100 mg QD)
4th	Discontinue acalabrutinib

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade 1. If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥ 4 weeks then the dose may be increased to the next higher dose level, at the discretion of the 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. Patients who re-escalate acalabrutinib treatment who again experience an AE requiring dose reduction may not re-escalate a 2nd time and should remain on the lower dose. The maximum dose of acalabrutinib is 100 mg BID.

Treatment with acalabrutinib should be withheld for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity.

Every attempt should be made to manage patients experiencing a grade ≤2 toxicity with aggressive supportive care as needed and to continue acalabrutinib therapy at full dose. However, patients experiencing a grade ≤2 hematologic or non-hematologic toxicity that doesn't resolve with supportive care may hold treatment until resolution to grade 1 or baseline or may reduce the dose to the next lowest dose level without an intermittent hold. Upon recovery to grade 1 or baseline, patients may be restarted at the full dose level *or* may receive one lower dose level based on investigator/patient preference.

Obinutuzumab:

No dose modifications of obinutuzumab are allowed. If a patient is unable to tolerate obinutuzumab in the assessment of the investigator, further doses may be held and the patient may continue to receive acalabrutinib on study at the discretion of the investigator.

Patients experiencing any of the following toxicities should have obinutuzumab held until resolution to grade 1 or baseline:

- Grade ≥3 febrile neutropenia
- Grade 4 neutropenia or thrombocytopenia
- Grade ≥ 3 infection

Management of Obinutuzumab Infusion Reactions:

If a patient experiences an infusion reaction of any grade during infusion, adjust the infusion as follows:

- Grade 4 (life-threatening): Stop infusion immediately and permanently discontinue obinutuzumab therapy.

- Grade 3 (severe): Interrupt infusion and manage symptoms. Upon resolution of symptoms, consider restarting obinutuzumab infusion at no more than half the previous rate (the rate being used at the time that the infusion reaction occurred) and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose. Permanently discontinue treatment if patients experience a Grade 3 infusion-related symptom at rechallenge.
- Grade 1–2 (mild to moderate): Reduce infusion rate or interrupt infusion and treat symptoms. Upon resolution of symptoms, continue or resume infusion and, if patient does not experience any further infusion reaction symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose.

Holding Study Therapy for Procedures
If the patient requires an invasive procedure during the course of the study, it is permissible to hold acalabrutinib for up to 7 days pre- and post-procedure. Holding obinutuzumab is not required in this setting and efforts should be made to deliver the obinutuzumab dose as scheduled if deemed appropriate by the investigator. If it is not possible to administer obinutuzumab within ± 3 days of the scheduled visit, then the dose of obinutuzumab can be omitted and the patient will be allowed to continue on study.

5.5 Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy will be required if a suitable alternative is not available.

Permitted Concomitant Therapy
All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. However, if a prohibited concomitant medication must be administered, the patient cannot continue study therapy. If it is a short-term treatment course (< 2 weeks) the patient may hold acalabrutinib during that time and restart when the course is completed. If the patient requires a longer course of treatment with an otherwise prohibited medication, then the patient must discontinue study therapy. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF. All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered up to 30 days after the last dose of trial treatment should be recorded. In general, concomitant medications and therapies deemed necessary for the supportive care (e.g. such as anti-emetics, anti-diarrhea) and safety of the patient are allowed:

Medications to prevent or treat nausea or vomiting.
Anti-diarrheal medications (e.g., loperamide) for patients who develop diarrhea.

Pain medication to allow the patient to be as comfortable as possible.
Hematopoietic colony-stimulating growth factors (e.g. G-CSF, GM-CSF, M-CSF), thrombopoietin mimetics or erythroid stimulating agents as per local or published guidelines; in case of anemia, thrombocytopenia or neutropenia, potential immune mediated etiology should be ruled out
Nutritional support or appetite stimulants (e.g. megestrol).
Oxygen therapy and blood products or transfusions.
Inactivated vaccines.

The patient must be told to notify the investigational site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including physical therapy, herbal/natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications.

Monitoring and Treatment for Hepatitis B Reactivation

Patients who are both HBsAg negative and hepatitis B core antibody (anti-HBc) positive may be included. These patients should have HBV DNA levels obtained monthly for at least 12 months after the last cycle of therapy by means of real-time PCR with the use of an assay that has a sensitivity of at least 10 IU/mL. Patients who are anti-HBc positive but with no evidence of active disease, including a negative HBsAg and undetectable HBV DNA should receive prophylaxis against hepatitis B reactivation as close to the beginning of therapy as possible and this should continue for at least 6 months after completion of study therapy.

If the HBV DNA assay becomes positive and is above the World Health Organization's cutoff of 100 IU/mL, study treatment should be discontinued and the patient should be treated (for at least 1 year after the last dose of obinutuzumab) with an appropriate nucleoside analogue and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume study treatment once HBV DNA levels decrease to undetectable levels.

If the HBV DNA assay becomes positive and is ≤ 100 IU/mL, the patient should be retested within 2 weeks. If the assay is still positive, treatment with study therapy must be discontinued and the patient should be treated with an appropriate nucleoside analogue (for at least 1 year after the last dose of obinutuzumab) and immediately referred to a gastroenterologist or hepatologist for management. Patients may resume study treatment once the HBV DNA levels decrease to undetectable levels.

If a patient's HBV DNA level exceeds 100 IU/mL while the patient is receiving antiviral medication, study treatment must be permanently discontinued.

Prohibited or Restricted Concomitant Therapy

- During the course of the study, patients must not receive other antineoplastic therapies (e.g. investigational drugs, devices, chemotherapy, immunotherapies) or any other therapies that may be active against cancer or modulate the immune responses. Radiation therapy should also not be administered while on study. If a patient requires treatment with radiation therapy, they will need to be removed from study therapy.
    - A short course of steroids is permitted for patients aside from those in the low tumor burden FL cohort. This course may be no more than 14 days and steroids must be discontinued (or tapered to ≤ 10mg prednisone or equivalent) no later than 3 days after

initiation of study treatment. The use of systemic steroid therapy is allowed for the treatment of infusion reactions and for prophylaxis against imaging contrast dye allergy, standard pre-medication for chemotherapy or replacement-dose steroids in the setting of adrenal insufficiency (provided this is ≤ 10mg/day prednisone or equivalent). If systemic corticosteroids are required for the control of infusion reactions, it must be tapered to non-immunosuppressive (doses ≤10 mg/day prednisone or equivalent) within 2 weeks, then study therapy must be discontinued. Concomitant therapy with inhaled steroids for asthma or COPD as well as topical steroids is permitted.

- The use of live vaccines is not allowed through the whole duration of the study. Inactivated vaccines are allowed. There are no prohibited therapies during the post-treatment follow-up period.
- Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited.

Avoid co-administration of strong CYP3A inhibitors (see Appdendix D) with acalabrutinib. Alternatively, if the inhibitor will be used short-term, interrupt acalabrutinib. After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of acalabrutinib. If the patient requires therapy with a strong CYP3A inhibitor for longer than 2 weeks, then study therapy must be discontinued. When acalabrutinib is administered with moderate CYP3A inhibitors, reduce acalabrutinib dose to 100 mg once daily. Avoid co-administration of strong CYP3A inducers with acalabrutinib. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily. It is not possible to produce an exhaustive list of medications that fall into these categories, so if in question, refer to the appropriate product label. For additional information on drugs with potential drug-drug interactions, refer to Section 5.6.

5.6 Drug-Drug Interactions

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin, decreased acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 3) should be avoided when possible.

5.7 Study Procedures

The schedule of events is provided in Section 1.3. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 4.2.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is

to ensure adequate **safety and tolerability assessments**. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

5.8 Description of Study Procedures

Informed Consent

The subject must read, understand and sign the ICF approved by the institutional review board or independent ethics committee (IRB/IEC), confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information, if required by local regulations.

The current standard of care for many patients who will be eligible to enroll in the trial is observation, though single-agent rituximab is a reasonable alternative in patients not comfortable with this treatment approach. Prior to signing informed consent, the investigator must discuss and offer them as reasonable alternatives to clinical trial enrollment. The investigator must also discuss that the purpose of this clinical trial is to investigate a new therapy that will hopefully improve on the outcomes seen with observation or single-agent rituximab, but there is no guarantee that this will be the case.

Medical History

Collect and record the subject's complete history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

Adverse Events

The accepted regulatory definition for an AE and important additional requirements for reporting SAEs are explained in Section 17.

Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 9. All screening procedures, unless otherwise indicated, should be completed within 28 days of the first dose of study drug.

ECOG Performance Status

The ECOG performance index is provided in Appendix A.

Physical Examination, Vital Signs, Height & Weight

Physical Exam

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and exam of other systems as clinically appropriate and consistent with routine care.

Symptom-directed physical exams will be done during the treatment period and at the safety follow-up (SFU) visits.

Vital Signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to

the assessment schedules. Vital signs on days of obinutuzumab infusions should be obtained and documented in the medical record consistent with standard of care infusion protocols at the treating institution.

Electrocardiogram

Resting 12-lead ECGs will be recorded as clinically indicated throughout the study. If clinically indicated, ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.
The Investigator or qualified Sub-Investigator will review all ECG interpretations and interval duration measurements for clinical significance. Any ECG interpretation deemed to be clinically significant will be reported as an AE.

Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. Urine or serum β-HCG testing will be performed at the screening visit and again on Day 1 of each treatment cycle for which a clinic visit is required. A urine or serum pregnancy test must also be obtained at each required study visit during the follow-up phase for patients who continue on acalabrutinib.

Hematology

For the purposes of this study, "hematology" laboratory tests should include total white blood cell count, hemoglobin, hematocrit, platelet count and a WBC differential.

Serum Chemistry

Clinical chemistry (serum or plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Potassium
Aspartate aminotransferase	Sodium
Bicarbonate	Total bilirubin[a]
Calcium	Total protein
Chloride	Urea or blood urea nitrogen, depending on local practice
Creatinine	

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin

Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing during screening and on study (see exclusion criterion #17).

Subjects who are anti-HBc positive should have quantitative PCR testing for HBV DNA performed during screening and monthly thereafter as per institutional practices. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and

a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. PCR testing should be performed when clinically indicated (eg, in the setting of rising transaminase levels).

Subjects with a known history of hepatitis C or who are hepatitis C antibody positive should be tested for HCV RNA performed during the screening phase. Patients who have completed treatment for HCV and have an undetectable HCV RNA may enroll on study.

Refer to Section 5.5 for more information regarding monitoring of subjects who are anti-HBc positive or who have a known history of HBV.

Health-Related Quality of Life Assessment

Health-related quality of life will be assessed using the Functional Assessment of Cancer Therapy – General (FACT-G) and Hospital Anxiety and Depression Scale (HADS)

The QOL assessment will be administered at the following time-points during the screening and induction phases:

- At the screening visit
- At the cycle 3 day 1 study visit
- At the cycle 6 day 1 study visit
- At the end of induction visit

During the follow-up phase, QOL assessments will be obtained every 6 months x2 years then every 12 months x3 years.

Patients who miss a follow-up visit will be contacted by telephone to complete QoL assessments. Patients who start a new treatment and those who stop following at the study site for other reasons will no longer be required to complete the QoL questionnaires.

See Appendices F and G for copies of the FACT-G and HADS questionnaires.

Patient-Reported Outcomes to Evaluate Symptomatic Toxicity

Patient-reported outcome data will be assessed using the PRO-CTCAE Measurement System that has been developed to evaluate symptomatic toxicity in patients on cancer clinical trials. The PRO-CTCAE will be administered electronically with a paper copy as a backup at the following time points:

During Screening and induction phases

- At the cycle 1 day 1 and cycle 1 day 15 visits. If feasible, attempt to administer weekly during cycle 1
- At the cycle 3 day 1, 8, and 15 visits
- At a minimum, administer at the day 1 visits for cycles 4 through 12
- At the end of induction visit

Follow-up phase

- For patients who continue on acalabrutinib during the follow-up phase, administer PRO-CTCAE at each scheduled study visit
- Administer the PRO-CTCAE at the Treatment Termination Visit and Safety follow-up visits for patients who discontinue study therapy for reasons other than being randomized to observation.

The PRO-CTCAE is for research data collection only. PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events. Study staff must clearly convey to the patient that the information regarding symptoms collected by the PRO-CTCAE self-report are for research purposes only and are not monitored by a physician. Study staff must advise patients to directly contact their clinical team per institutional standards for any new or concerning symptoms that develop between study visits. Patients will be advised to complete the questionnaires prior to the appointment and will take them to their clinic visit to be reviewed by the clinical team, and in cases where a self-identified AE on the PRO-CTCAE is evaluated by the clinical team, the grade and attribution can be assess by conventional methods as described in Section 17.

See Appendix H for a copy of the PRO-CTCAE form.

Tumor Assessments:

For all patients, pretreatment imaging is required within 42 days before the first dose of study drug.

For FL and MCL, a pretreatment PET/CT scan is required within 42 days before the first dose of study drug. On-treatment PET/CT scans will be done for tumor assessments as follows:

- Within 7 days of cycle 3 day 1 (scan must be obtained before the first dose of obinutuzumab)
- Within 7 days before or after cycle 6 day 1
- Within 14 days before or after the end of induction visit following cycle 12

During the follow up phase tumor imaging will be obtained every 6 months (+/- 1 month) x2 years then every 12 months (+/- 1 month) x3 years. During this phase imaging can be either PET/CT or CT neck/chest/abdomen/pelvis with contrast (unless contraindicated).

For MZL and other iNHL all imaging assessments, including pretreatment imaging, can be conducted with either PET CT or CT neck/chest/abdomen/pelvis with contrast (unless contraindicated) based on investigator preference according to the same schedule outlined above.

A bone marrow biopsy during the screening phase is not required if one was performed within 12 months of signing informed consent and there is no concern for a change in clinical status. A repeat bone marrow biopsy will be performed at first suspicion of CR if the marrow was previously involved but otherwise repeat bone marrow biopsies need only be completed as clinically indicated.

Efficacy evaluations prior to cycles 3 and 6 will not be used to remove any patient from therapy if patients are otherwise tolerating therapy and felt to be benefitting. Evidence of progressive disease following cycle 12 will result in discontinuation of therapy.

5.9 Assessment of Response to Treatment

Response assessment for patients with FL and MCL will be evaluated by PET/CT based on the *Lugano Classification* for response assessment in lymphoma, developed at the 2014 International Conference on Malignant Lymphoma (IMCL '14).[43] After the patient has completed 12 cycles of induction therapy, the response assessment can be conducted with either CT of the neck, chest, abdomen, and pelvis with IV contrast (unless contrast is contraindicated) or PET/CT based on patient and investigator preference.

The response assessment for patients with MZL or other indolent forms of NHL can be evaluated by either PET/CT or CT of the neck, chest, abdomen, and pelvis with IV contrast (unless contrast is contraindicated) based on the *Lugano Classification* criteria outlined for the imaging modality used.

For the small number of patients expected to enroll with a form of indolent NHL that does not have established response criteria, the choice of imaging modality used to reassess known sites of disease as well as determination of CR, PR, SD, or PD will be left to the discretion of the investigator.

If the bone marrow was previously involved, then a repeat bone marrow biopsy is required at first suspicion of CR and must have no morphologic evidence of disease to confirm CR.

The following are excerpts from the *Lugano Classification* for PET/CT- based response:

Complete Response

- PET/CT imaging with a score of 1-3 out of 5 using the Deauville Criteria. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within the spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake.
- No FDG-avid disease in bone marrow and bone marrow normal by morphology if involved at diagnosis.

Partial Response

- Score of 4 or 5 using the Deauville Criteria, but reduced uptake compared with baseline and residual mass(es) of any size.
- Residual uptake higher than uptake in normal marrow but reduced compared to baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.

Stable Disease

- Score of 4 or 5 using the Deauville Criteria, with no significant change in FDG uptake from baseline at interim or end of treatment
- No change in baseline marrow avidity

Progressive Disease

Score of 4 or 5 using the Deauville Criteria with an increase in intensity of uptake from baseline and/or new FDG-avid foci consistent with lymphoma.

The following are excerpts from the *Lugano Classification* for CT-based response:

Complete Response

- Target nodes/nodal masses must regress to ≤ 1.5cm in longest transverse diameter (LDi)
- No extralymphatic sites of disease

- All non-measured lesions must be absent and any organ enlargement must regress to normal

Partial Response

- ≥ 50% decrease in the sum of the product of the perpendicular diameters for multiple lesions (SPD) of up to 6 target measurable nodes and extranodal sites. When a lesion is too small to measure on CT, assign 5mm x 5mm as the default value. When no longer visible, 0 x 0 mm. For a node > 5mm x 5mm, but smaller than normal, use actual measurement for calculation
- Nonmeasured lesions must be absent/normal or regressed, but no increase
- Spleen must have regressed by > 50% in length beyond normal
- No new lesions

Stable Disease

- < 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met.
- No increase in nonmeasured lesions consistent with progression
- No increase in organ enlargement consistent with progression
- No new lesions

Progressive Disease – requires at least 1 of the following

- An individual node/lesion must be abnormal with: LDi > 1.5 cm and increase by ≥ 50% from PPD nadir and an increase in LDi or SDi from nadir of 0.5cm for lesions ≤ 2 cm or 1.0 cm for lesions > 2 cm.
- In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16cm. If no prior splenomegaly, must increase by at least 2 cm from baseline.
- New or clear progression of preexisting nonmeasured lesions.
- Regrowth of previously resolved lesions
- A new node > 1.5 cm in any axis
- A new extranodal site > 1.0cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma

5.10 Treatment Termination and Safety Follow-Up

Treatment Termination and Safety Follow-Up Visits

A treatment termination (TT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason (including disease progression) except for patients in CR who were randomized to discontinue acalabrutinib after the induction phase. The TT visit should be scheduled within 7 days of the last dose of study drug, if possible, and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit.

Each subject should be followed until the safety follow-up (SFU) visit at 4 weeks (+/- 7) days after his or her last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new anti-lymphoma therapy or demonstrates disease progression within this timeframe. For patients randomized to observation, the end of induction visit shall be used as the safety follow-up visit. Subjects who withdraw consent for

study treatment should still be encouraged to complete the SFU assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. If the TT visit and the SFU visit coincide, then these can be combined into 1 visit. The Schedule of Assessments (Section 1.2) describes the procedures required for the TT and SFU visits.

Follow Up for Progression and Survival
Each subject should be followed until the start of alternative anti-lymphoma therapy. If neither of these has occurred at the time of the 30-day SFU visit, discontinuation follow-up (DFU) visits should occur approximately every 12 weeks (+/- 2 weeks) for 1 year and thereafter every 6 months (+/- 1 month) until disease progression or next anti-lymphoma treatment. During this period, subjects will be followed per the schedule of activities (see Section 1.3).

Long-Term Follow-Up
Patients who initiate a subsequent anti-lymphoma therapy for any reason will no longer be required to complete study follow-up. However, when feasible we will identify the subsequent treatments received and will also follow the patient until death or until they are lost to follow-up. Patients will not be contacted directly but study staff may follow patients through the electronic medical record to assess subsequent treatments and survival, except in cases where a patient has revoked such consent.

5.11 Missed Evaluations

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

6. Data and Specimen Banking

Blood (tumor, bone marrow etc.) samples will be obtained and used for medical research by the investigators of this study. *Data and specimens from this study may be useful for other research being done by investigators at Emory or elsewhere. To help further science, Investigators may provide de-identified data and/or specimens to other researchers. Any information that could identify participants will not be included. If data or specimens are labeled with study ID, we will not allow other investigators to link that ID to identifiable information.*

Samples and data collected under this protocol may be used to study lymphoma. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking.

The results of some study tests and procedures will be used only for research purposes and will not be placed in subject's medical record. For this study, those items include: research blood collection.

7. Sharing of Results with Participants

In general, study staff will not provide any individual results to subjects (ex. outcome trial results or results from subject's samples studies). If something of urgent medical importance to the participating subjects will be found, the PI (or co-Is) will inform the subject, although we expect that this will be a very rare occurrence. Samples and data will only be used for research.

8. Study Timelines

8.1 Duration of therapy

Acalabrutinib

Acalabrutinib 100 mg will be administered orally twice daily, every day starting on Cycle 1 Day 1 and will continue through Cycle 12 (of a 28-day cycle) unless the patient develops intolerance to acalabrutinib or symptomatic/clinically significant progressive disease.

After 12 cycles, patients who achieve CR will be randomized to either continue acalabrutinib at the same dose until intolerance or PD or discontinue the medication and observe. Patients with a PR or SD after 12 cycles of treatment will continue acalabrutinib at the same dose until intolerance or progressive disease.

Obinutuzumab

Obinutuzumab will be administered Cycle 3 through Cycle 8. There will be no obinutuzumab maintenance phase. Refer to the schedule of activities (Section 1.3) for dosing schedule.

8.2 Duration of follow-up

The estimated time from when the study opens to enrollment until analysis of the primary outcome is 40 months. Patients in the follow-up phase who have discontinued study therapy will be followed for 60 months or until the start of next anti-lymphoma treatment. Patients who continue acalabrutinib during the follow up phase will be treated on study until unacceptable toxicity, death, or start of the next anti-lymphoma therapy.

Patient records may be reviewed until death to assess progression and survival. Survival information may be collected by clinic visit, email, or telephone after ending protocol treatment and until the study is terminated, the patient dies, or the patient is lost to follow-up.

A participant will be considered lost to follow-up if he fails to return for three scheduled visits and is unable to be contacted by the study site staff after three attempts at contact by phone.
The following actions must be taken if a participant fails to return to the clinic for a required study visit: The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

Reasons for removal of a subject from the study are:

- Subject's withdrawal of consent from study
- Decision by investigator
- Subject lost to follow-up
- Unacceptable toxicity
- Death

Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

Patients who have not initiated a new antineoplastic regimen will have the following assessments:
• Radiologic tumor assessments per the Schedule of Events (see Section 1.3)
• In case of a clinically significant AE, patient will be followed for safety until resolution or permanent sequelae of all toxicities attributable to study drug(s). If the patient discontinues study drug for a clinically significant AE, the patient will be followed until resolution of the AE or the event is considered to be stable and/or chronic.

9. Inclusion and Exclusion Criteria

Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1) Men and women ≥ 18 years of age.
2) Patients will need to have one of the following clinical scenarios:
   a) Previously untreated follicular lymphoma grade 1-3a with low tumor burden by GELF criteria (see Appendix E)
   b) Previously untreated follicular lymphoma grade 1-3a with high tumor burden by GELF criteria but who are unable or unwilling to receive standard front-line treatment approaches
   c) Previously untreated marginal zone lymphoma, lymphoplasmacytic lymphoma, or any other indolent B-cell lymphoproliferative disorder with low tumor burden by GELF criteria or who are unable/unwilling to receive more intensive front-line treatment.
   d) Previously untreated mantle cell lymphoma who would otherwise be appropriate candidates for watchful waiting OR who have symptomatic disease but are not candidates for or decline standard induction approaches.
3) Patients with previously untreated low tumor burden FL (criterion 2a) must have measurable and/or assessable disease defined as at least one involved lymph node or extranodal disease site that measures ≥ 1.5cm in greatest diameter.
4) Patients who meet inclusion criteria 2b, 2c, or 2d above are eligible as long as they meet one of the following criteria for measurable/assessable disease:
   a) At least one involved lymph node or extranodal disease site measuring > 1.5cm in greatest diameter
   b) Pathologically-confirmed bone marrow or peripheral blood involvement that can be reassessed for response
   c) Pathologically confirmed splenic or extranodal involvement with at least one known site of disease remaining after diagnostic biopsy that can be reassessed (ie, patients with splenic

marginal zone lymphoma who complete splenectomy and have no other detectable disease would not be eligible).

5) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (Appendix 2).
6) Woman of childbearing potential (WOCBP) and men enrolled on this protocol must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry for the duration of study participation, and for at least 2 days after the last dose of acalabrutinib or 18 months after the last dose of obinutuzumab, whichever is longer. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Refer to Section 13.5 for more details regarding reproductive status assessment.
7) Women of childbearing potential must have a negative serum or urine pregnancy test prior to starting therapy.
8) Willing and able to participate in all required evaluations and procedures in this study protocol.
9) Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

Exclusion criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1) The presence or history of histologically transformed or co-existing high-grade or aggressive non-Hodgkin lymphoma
2) Confirmed active or prior central nervous system disease
3) Prior receipt of lymphoma-directed therapy or prior antibody-based therapy (except for anti-microbial therapy for infection-associated marginal zone lymphoma such as hepatitis C or H pylori).
   (a) A short course of steroids is permitted for patients aside from those in the low tumor burden FL cohort. This course may be no more than 14 days and steroids must be discontinued (or tapered to ≤ 10mg prednisone or equivalent) no later than 3 days after initiation of study treatment.

   Patients in the low tumor burden FL cohort may *not* receive corticosteroids as an anti-lymphoma therapy at any time before starting treatment.
4) Prior malignancy (or any other malignancy requiring active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years **or** which will not limit survival to < 5 years.
5) Clinically significant cardiovascular disease such as symptomatic ventricular arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification. Note: Subjects with controlled, asymptomatic atrial fibrillation can enroll on study if deemed appropriate by the investigator.
6) Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease that would limit absorption of oral medication.
7) Known history of HIV or any active significant infection (eg, bacterial, viral, or fungal) within 14 days of cycle 1. Patients with uncomplicated viral or bacterial infections that are being managed with oral antibiotics and/or supportive care alone are eligible.

8) Known history of hypersensitivity or anaphylaxis to study drug(s) including active product or excipient components.
9) Active bleeding or history of bleeding diathesis (eg, hemophilia or von Willebrand disease).
10) Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).
11) Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
12) Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
13) Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists. Note: use of direct oral anticoagulants is permitted. Patients with a recent history of venous thromboembolism are permitted to enroll as long as they do not require treatment with a vitamin K antagonist.
14) History of significant cerebrovascular disease/event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug. Patients with a transient ischemic attack which has resolved and for which there are no ongoing symptoms are eligible.
15) Major surgical procedure within 28 days of first dose of study drug (not including a diagnostic procedure to make the lymphoma diagnosis). Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
16) Hepatitis B or C serologic status: subjects who are hepatitis B core antibody (anti-HBc) positive and who are hepatitis B surface antigen (HBsAg) negative will need to have a negative polymerase chain reaction (PCR) and must be willing to undergo DNA PCR testing during the study to be eligible. Those who are HBsAg positive or hepatitis B PCR positive will be excluded.
    Subjects who are hepatitis C antibody positive will need to have a negative PCR result to be eligible and have completed appropriate anti-viral treatment. Those who are hepatitis C PCR positive will be excluded. Anti-viral therapy for patients with hepatitis-C associated marginal zone lymphoma will not be considered a prior anti-lymphoma treatment.
17) Hematologic: ANC < 1,000/mcL, platelet count < 50,000/mcL (Unless felt to be related to underlying disease)
18) Hepatic: Total bilirubin ≥ 1.5x the upper limit of normal (ULN). Isolated bilirubin > 1.5x ULN is permitted if the direct proportion is <35%. AST/ALT > 2.5x ULN.
19) Creatinine clearance ≤ 40 mL/min/1.73m2
20) Breastfeeding or pregnant.
21) Concurrent participation in another therapeutic clinical trial.

10.Local Number of Participants

We will be recruiting up to 49 total patients. Patients will be registered after signing of the informed consent document and meeting all entry requirements.

11.Recruitment Methods

Investigators, nurses (CRNs), research coordinators (CRCs) and/or data managers review lists of patients with lymphoma and will determine if there are patients who might be eligible for a clinical trial. The CRN/CRC/data manager reviews accessible medical records to screen further for eligibility. The CRN/CRC reviews the eligibility with the physician.

Subjects will be identified by their treating physicians. Clinical care team at Winship will inform potential subjects about the known benefits and potential risks of a clinical trial as well as other available treatment options.

Some of the subjects recruited for this protocol will be patients being treated at Emory and under the care of one or more of the study investigators. Some potential subjects will be identified by their treating physician and referred to Emory for possible participation in the protocol.

No incentives are provided to patients for trial participation.

Study personnel will notify Winship Central Subject Registration (WCSR) by email at winshipcsr@emory.edu, once subject has been consented for a trial.
Email notification must be done within 24 hours after consent has been obtained and it will include scanned copies of:

- Signed patient consent form
- HIPAA authorization form
- Emory Research Management System (ERMS; *https://erms.emory.edu*) Enrollment Fax Cover

The WCSR will enter the subject into the OnCore Research Management System, which is the system of record for Winship Cancer Institute Clinical Trials.

Enrolling a subject requires careful screening and determination of eligibility.

Eligible patients will be enrolled on study centrally at Winship Cancer Institute by the Study Coordinator. When all required test results are available, complete the eligibility checklist and provide the checklist and the supporting documentation to the IRB approved investigator for review and sign-off. Once the investigator (sub-investigator, Co-Investigator) has signed the eligibility checklist, randomization and or enrollment may proceed. OnCore and ERMS must be updated to reflect eligibility and on treatment status.

Following enrollment, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator.

12. Withdrawal of Participants

Discontinuation from the study treatment with acalabrutinib and obinutuzumab does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

Patients may choose to discontinue the trial at any time, for any reason, and without prejudice to further treatment. The treatment termination visit (ie, end of treatment visit) will occur within 7 days of the last dose of the study drug. The safety follow-up visit will occur within 28 (+/- 7) days of the last dose of the study drug or before a new antineoplastic regimen has been initiated.

Reasons for discontinuing study intervention are:

- Completion of study therapy
- PD in the absence of clinical benefit as determined by the Investigator.
- Occurrence of a clinically significant AE found to be unacceptable or non-resolution of clinically significant AEs for > 6 weeks.
- Symptomatic deterioration.
- Noncompliance of the patient with protocol-mandated procedures based on the judgment and agreement of both the Investigator and study supporter.
- Continued participation is no longer in the patient's best interest in the opinion of the Investigator.
- Becomes pregnant or breastfeeding
- Withdrawal of consent.
- Discontinuation of the clinical trial by the study investigator

In the event of a patient's withdrawal, the Investigator will promptly notify the supporting sponsor and make every effort to complete the treatment termination and safety follow-up procedures specified in the Schedule of Events.

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF).

Subjects who sign the informed consent form but do not receive the study intervention may be replaced for the purposes of the primary endpoint. Subjects who sign the informed consent form, and are assigned and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced and will be considered non-responders in the intention to treat analysis.

Subjects who discontinue study therapy will continue to be followed on study for follow-up of safety and survival unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted.

13. Risks to Participants

13.1 Risks Associated with Acalabrutinib

Acalabrutinib monotherapy has demonstrated efficacy in subjects with relapsed/refractory MCL and in subjects with treatment naïve or relapsed/refractory CLL.

Based on review of the available safety and efficacy data for acalabrutinib as well as consideration of measures implemented in the acalabrutinib clinical development program to minimize potential risks to subjects, the overall benefit-risk assessment profile of acalabrutinib for the indication under investigation remains favourable for continuing clinical development and is justified by the perceived benefits that may be afforded to the patients.

More detailed information about the known and expected benefits and potential risks of acalabrutinib may be found in the Investigator's Brochure and Development Safety Update Report (DSUR).

Risk Assessment
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 Investigator's Brochure.

Hemorrhage
Serious hemorrhagic events, including fatal events, have occurred in clinical trials with acalabrutinib.

The mechanism for hemorrhage is not well understood. Patients receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary.

Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery.

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

Infections
Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequent reported Grade ≥3 infection was pneumonia (preferred term). 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 should be monitored for signs and symptoms of infection and treated as medically appropriate.

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

Cytopenias
Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anaemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as specified in the schedule of assessments and as medically appropriate.

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-melanoma skin carcinomas, have been reported in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer (basal cell carcinoma).

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 occurred in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, or a previous history of atrial fibrillation.

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. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator's Brochure.

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.

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 7-study integrated monotherapy population 'INT-7', which consisted of treated subjects in 5 acalabrutinib monotherapy studies (15-H-0016, ACE-CL-001, ACE-LY-002, ACE-LY-004, ACE-WM-001) and treated subjects in the acalabrutinib monotherapy treatment arms of 2 additional combination studies (ACE-LY-003 and ACE-MY-001). As of the 03 September 2017 data extraction date, the pooled INT-7 population represented 614 acalabrutinib-exposed subjects with a median exposure of 21.9 months (range, 0.03 to 42.4 months). Overall, the safety of monotherapy acalabrutinib in subjects with hematologic malignancies has been acceptable in the integrated analysis. An overview of AEs for this population is presented in Table 4-1.

TABLE 13-1. OVERVIEW OF TREATMENT-EMERGENT ADVERSE EVENTS OF THE INT-7 ALL MONOTHERAPY POPULATION

Adverse Event Category	N=614 n (%)
Any treatment-emergent adverse events	
Any grade	609 (99.2)
Grade ≥3	334 (54.4)
Any adverse event related to acalabrutinib	
Any grade	459 (74.8)
Grade ≥3	128 (20.8)
Any serious adverse events	256 (41.7)
Adverse events leading to study drug discontinuation	44 (7.2)
Grade 5 (fatal) adverse event	27 (4.4)

INT-7 studies include 15-H-0016, ACE-CL-001, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001.
Note: A subject with multiple severity grades for a given adverse event was counted once under the maximum severity.
Data as of 03 Sep 2017.

Almost all subjects (609 [99.2%]) had at least 1 AE, and about half (334 [54.4%]) had at least 1 Grade ≥3 AE. The most commonly reported AEs of any grade were headache (42.3%), diarrhea (40.4%), fatigue (24.6%), nausea (23.6%), contusion (23.5%), cough (22.1%), and upper respiratory tract infection (21.7). The most frequently reported Grade ≥3 AEs were neutropenia (10.4%), anemia (7.5%), pneumonia (6.5%), thrombocytopenia (3.7%), and hypertension (3.1%).

Treatment-related AEs were reported for 459 (74.8%) subjects, and 128 (20.8%) subjects had Grade ≥3 treatment-related AEs. The most frequently reported treatment-related AEs of any grade were headache (29.5%), diarrhea (17.4%), contusion (14.5%), nausea (9.3%), fatigue (7.5%), petechiae (7.5%), neutropenia (7.0%), arthralgia (5.9%), and dizziness (5.0%). The most frequently reported treatment-related Grade ≥3 AEs was neutropenia (6.8%).

For more comprehensive information on the safety profile of acalabrutinib, refer to the current Investigators Brochure.

13.2 Risks Associated with Obinutuzumab

The following summarizes significant risks with obinutuzumab based on obinutuzumab Contraindications and Warnings & Precautions. For additional information, please refer to obinutuzumab local prescribing information and package insert.

Contraindications
Obinutuzumab is contraindicated in patients with known hypersensitivity reactions (e.g., anaphylaxis) to obinutuzumab or any of the excipients, including serum sickness with prior obinutuzumab use.

Warnings and Precautions

- **Infusion Reactions**
  Obinutuzumab can cuase severe and life-threatening infusion reactions. 65% of patients with CLL experienced a reaction to the first 1000 mg of obinutuzumab infused. 38% of patients with R/R NHL and 60% of patients with previously untreated NHL experienced a reaction on Day 1 of obinutuzumab infusion. Premedicate patients with glucocorticoid, acetaminophen, and anti-histamine. Monitor patients closely during infusions. Interrupt or discontinue infusion for reactions. See package insert for further details.
- **Hypersensitivity Reactions Including Serum Sickness**
  Hypersensitivity reactions have been reported in patients treated with obinutuzumab. Signs of immediate-onset hypersensitivity include dyspnea, bronchospasm, hypotension, urticarial, and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported, with symptoms that include chest pain, diffuse arthralgias, and fever. Hypersensitivity reactions may be difficult to clinically distinguish from infusion related reactions. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped and treatment permanently discontinued.
- **Tumor Lysis Syndrome**
  Anticipate tumor lysis syndrome; premedicate with anti-hyperuricemics and adequate hydration especially for patients with high tumor burden, high circulating lymphocyte count or renal impairment. Correct electrolyte abnormalities, provide supportive care, and monitor renal function and fluid balance.
- **Infections**
  Fatal and serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. When obinutuzumab is administered with chemotherapy followed by obinutuzumab monotherapy, Grade 3 to 5 infections have been reported in up to 8% of patients during the combination therapy, up to 13% of patients during monotherapy, and up to 8% of patients after treatment. Monitor for infections during and after treatment.
- **Neutropenia**
  Severe and life threatening neutropenia, including febrile neutropenia, has been reported during treatment with obinutuzumab. Monitor patients with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Anticipate, evaluate, and treat any symptoms or signs of developing infection. Neutropenia can also be of late onset (occurring more than 28 days after completion of treatment and/or prolonged (lasting longer than 28 days).
- **Thrombocytopenia**
  Severe and life threatening thrombocytopenia has been reported during treatment with obinutuzumab in combination with chemotherapy. Fatal hemorrhagic events have been reported in patients with NHL and CLL treated with obinutuzumab in combination with chemotherapy, including during Cycle 1. Monitor platelet counts and for bleeding. Management of hemorrhage may require blood product support.
- **Immunization**
  The safety and efficacy of immunization with live or attenuated viral vaccines during or following obinutuzumab therapy have not been studied. Immunization with live virus vaccines is not recommended during treatment and until B-Cell recovery.

Adverse Events

For more information regarding the adverse events associated with the use of obinutuzumab, please refer to the USPI.

The GALLIUM trial evaluated the safety of obinutuzumab as compared to rituximab product in 1385 patients with previously untreated follicular lymphoma (86%) or marginal zone lymphoma (14%). Patients received chemotherapy (bendamustine, CHOP, or CVP) compared with either obinutuzumab (691 patients) or rituximab product (694), followed in responding patients by obinutuzumab or rituximab product monotherapy every two months until disease progression or for a maximum of two years. The chemotherapy was bendamustine in 59%, CHOP in 31%, and CVP in 10% of patients. Following combination therapy, 624 patients (90%) in the obinutuzumab arm and 612 patients (88%) in the rituximab product arm received monotherapy.

Serious adverse reactions occurred in 50% of patients on the obintuzumab arm and 43% of patients on the rituximab product arm. Fatal adverse reactions were reported during treatment in 3% in the obinutuzumab arm and 4% of the rituximab product arm, with infections and second malignancies being the leading causes. In the obinutuzumab arm, fatal infections occurred in 2% of patients compared to <1% in the rituximab product arm.

Throughout treatment and follow-up, the most common adverse reactions (incidence ≥20%) observed at least 2% more in the obinutuzumab arm included infusion related reactions, neutropenia, upper respiratory tract infection, cough, constipation, and diarrhea. Neutropenia, infusion related reactions, febrile neutropenia, and thrombocytopenia were the most common Grade 3 to 5 adverse reactions (incidence ≥5%) observed more frequently in the obinutuzumab arm.

During the monotherapy period, the common adverse reactions (incidence ≥10%) observed at least 2% more with obinutuzumab were upper respiratory tract infection (40%), cough (23%), musculoskeletal pain (20%), neutropenia (19%), and herpesvirus infection (13%).

Grade 3 to 4 abnormalities reported at least 2% more in the obinutuzumab arm were lymphopenia, leukopenia, neutropenia, thrombocytopenia, and hyperuricemia. Patients in the obinutuzumab arm, as compared to the rituximab product arm, had higher incidences of Grade 4 neutropenia (38% vs. 30%, respectively), Grade 4 lymphopenia (33% vs. 22%), and Grade 4 leukopenia (17% vs. 12%).

In the monotherapy phase, new-onset Grade 3 or 4 neutropenia was reported in 21% of patients in the obinutuzumab arm (Grade 4, 10%) and 17% of patients in the rituximab product arm (Grade 4, 9%).

Infusion Reactions

In GALLIUM, 72% of patients in the obinutuzumab treated arm experienced an infusion reaction (all grades). Symptoms may include hypotension, tachycardia, dyspnea, and respiratory symptoms (e.g. bronchospasm, larynx and throat irritation, wheezing and laryngeal edema). The most frequently reported symptoms include nausea, fatigue, chest discomfort, dyspnea, dizziness, vomiting, diarrhea, rash, hypertension, hypotension, flushing, headache, pyrexia, and chills. The incidence of Grade 3 to 4 infusion reactions for these patients was 12%. In cycle 1, the incidence of infusion reactions (all grades) was 62%) in the obiutuzumab treated arm with Grade 3 to 4 infusion reactions reported in 10%). The incidence of infusion reactions (all grades) was highest on Day 1 (60%) and decreased on Days 8 and 15 (9% and 6%, respectively).

During Cycle 2, the incidence of infusion reactions (all grades) in the obinutuzumab treated arm was 13% and decreased with subsequent cycles.

During obinutuzumab monotherapy treatment in GALLIUM, infusion reactions (all grades) were observed in 9% of patients.

Overall, 1% of patients in GALLIUM experienced an infusion reaction leading to discontinuation of obinutuzumab.

Hypersensitivity Reactions Including Serum Sickness
Hypersensitivity reactions have been reported in patients treated with obinutuzumab. Signs of immediate-onset hypersensitivity include dyspnea, bronchospasm, hypotension, urticarial, and tachycardia. Late-onset hypersensitivity diagnosed as serum sickness has also been reported with symptoms that include chest pain, diffuse arthralgia, and fever. Hypersensitivity reactions may be difficult to clinically distinguish from infusion related reactions. However, hypersensitivity very rarely occurs with the first infusion and, when observed, often occurs after previous exposure. If a hypersensitivity reaction is suspected during or after an infusion, the infusion must be stopped and treatment permanently discontinued. Patients with known hypersensitivity reactions to obinutuzumab, including serum sickness, must not be retreated.

Hepatitis B Reactivation
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with anti-CD20 antibodies such as obinutuzumab. HBV reactivation has been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HGsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

Progressive Multifocal Leukoencephalopathy
JC virus infection resulting in progressive multifocal leukoencephalopathy (PML), which can be fatal, was observed in patients treated with obinutuzumab. Consider the diagnosis of PML in any patient presenting with new onset or changes to preexisting neurologic manifestations.

13.3 Hepatitis B Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with acalabrutinib and obinutuzumab. Please refer to Section 5.5 for details on viral hepatitis screening and monitoring for this study.

13.4 Progressive Multifocal Leukoencephalopathy (PML)

Serious or life-threatening occurrence of PML may occur in subjects treated with acalabrutinib and obinutuzumab.
Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.
If PML is suspected, hold further study treatment (as applicable, based on risks in the Investigator Brochure or local prescribing information) until PML is excluded. A diagnostic evaluation may include (but is not limited to):

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

If PML is confirmed, permanently discontinue study treatment (as applicable, based on risks in the Investigator Brochure or local prescribing information).

13.5 Reproductive Toxicity

Acalabrutinib
The potential for acalabrutinib to be excreted in breast milk of nursing mothers is unknown. For results of acalabrutinib nonclinical reproductive toxicity studies, including definitive embryofetal development studies, please refer to the Investigator Brochure. Women of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib. For male subjects with a pregnant or non-pregnant WOCBP partner, no contraception measures are required.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this study, within 2 days after the last dose of acalabrutinib, or 18 months within after the last dose of obinutuzumab, whichever is longer. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 17.

Obinutuzumab
Obinutuzumab is likely to cause fetal B-cell depletion based on findings from animal studies and the drug's mechanism of action. There are no data with obinutuzumab use in pregnant women to inform a drug-associated risk. Monoclonal antibodies are transferred across the placenta. In animal reproduction studies, weekly intravenous administration of obinutuzumab to pregnant cynomolgus monkeys from day 20 of pregnancy until parturition which includes the period of organogenesis at doses with exposures up to 2.4 times the exposure at the clinical dose of 1000mg montly produced opportunistic infections and immune complex mediated hypersensitivity reactions. No embryo-toxic or teratogenic effects were observed in the monkeys.

Avoid administering live vaccines to neonates and infants exposed to obinutuzumab in utero until B-cell recovery occurs.

There is no information regarding the presence of obinutuzumab in human milk, the effects on the breastfed child, or the effects on milk production. However, low levels of obinutuzumab were present in the milk of lactating cynomolgus monkeys. Human IgG is known to be present in human breast milk. Published data suggests that antibodies in breast milk do not enter the neonatal and child circulations in substantial amounts.

Reproductive Status Assessment and Pregnancy Testing

- **Reproductive Status Assessment for Clinical Trials**
  - Investigator, Clinical Research Coordinator (CRC) or Clinical Research Nurse (CRN) will ensure that the subject has completed the Reproductive Status Assessment and Birth Control Form prior to determination of study eligibility.
  - Investigator is responsible for assessing and signing the Reproductive Status Assessment and Birth Control Form documenting if birth control is required by study protocol and whether the subject is a male or woman of child-bearing potential (WOCBP) or woman not of child-bearing potential.
  - Subjects will be considered not of child-bearing potential if:
    - Female who has had a hysterectomy or bilateral oophorectomy
    - Female who is post-menopausal. Females are considered post-menopausal when:
      - Age ≥ 55 years and on year or more of amenorrhea
      - Age < 55 years and one year or more of amenorrhea, estradiol <20 OR estradiol <40 with FSH >40 in women not on estrogen replacement therapy
      - Note: Amenorrhea following cancer therapy does not rule out child-bearing potential.
  - Source documents, e.g. OBGYN note, which document reproductive status will be filed in the subject's research record.
- **Pregnancy Test Verification on the Study Drug Orders**
  - The reproductive status assessment and the pregnancy test verification must be documented either on the pregnancy test section imbedded into the study drug order or on the sticker with pregnancy test language placed on the study drug order. Licensed medical professions such as Medical Doctor (MD), Pharmacy Doctor (Pharm.D.), Clinical Research Nurse (CRN), Registered Nurse (RN), Advanced Practice Providers (APP) will review this information to ensure accuracy, sign and date the appropriate reproductive status assessment box.
    If the subject is a WOCBP, the licensed medical profession will also review, sign and date the results of the most recent pregnancy test prior to study drug administration.
  - The pregnancy test must be done when required per protocol if subject is WOCBP. Contraceptive methods such as tubal ligation or spouse's successful vasectomy do not waive pregnancy test requirement.
  - The pregnancy test is not required if:
    - Subject is male
    - Not required per protocol

Subject is female that is not a WOCBP

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. 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 (IUD) or intrauterine hormone-releasing system (IUS)
- 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.

13.6 Other Risks

Additional blood draws - The physical risk of drawing blood is local pain and bruising at the site of venipuncture. Qualified phlebotomists or designee will draw blood samples. Care will be taken to obtain these specimens in a safe and hygienic manner. A small number of people experience lightheadedness or fainting. There is a slight risk of infection. To minimize these risks, attempts will be made to draw study blood samples at the same time as blood draws needed for routine clinical care are obtained. Repeated blood drawing may be associated with iron deficiency anemia.

Data security- Subjects will be asked to provide personal health information (PHI). All attempts will be made to keep this PHI confidential within the limits of the law. However, there is a chance that unauthorized persons will see the subjects' PHI. All records will be kept in a locked file cabinet or maintained in a locked room at the participating sites. Electronic files will be password protected behind an academic institutional firewall. Only people who are involved in the conduct, oversight, monitoring, or auditing of this study will be allowed access to the PHI that is collected. Any publications from this study will not use information that will identify subjects. Organizations that may inspect and/or copy research

records maintained at the participating sites for quality assurance and data analysis include groups such as the National Cancer Institute (NCI) and Food and Drug Administration (FDA).

14. Potential Benefits to Participants

There is no guarantee of benefit to subjects who enroll in this protocol.

15. Data Management and Confidentiality

15.1 Statistical considerations

This is a Phase 2, single-arm trial designed to assess the safety and efficacy of acalabrutinib and obinutuzumab in subjects with low tumor burden FL and other indolent NHLs. Analysis of the primary endpoint will be done prior to cycle 6 of the induction phase. Descriptive statistics will be used to summarize baseline demographic and disease characteristics.

Rationale for Sample Size
The primary population of interest for this study will be patients with FL who have a low tumor burden as defined by the GELF criteria (see Appendix 4). The primary endpoint for this study is the CR rate at 6 months (prior to cycle 6 of induction therapy). We will compare our CR rate to a historical control of 11.8% for single agent rituximab that was reported in the RESORT trial. In order to have a power of 80% to detect an improvement in the CR rate from 12% to 30%, we will require at least 29 patients for our primary analysis using a Simon 2-stage design. The null hypothesis that the true response rate is 12% will be tested against a 1-sided alternative. In the 1st stage, 18 patients will be accrued. If there are 2 or fewer responses in those first 18 patients, the trial will stop. Otherwise, an additional 11 patients will be accrued for a total sample size of 29. The PI or designee must provide the DSMC a report outlining the overall enrollment and path to decision to open the next enrollment cohort. DSMC approval is needed in order to move to the second stage of the study. The null hypothesis will be rejected if 7 or more responses are observed in 29 patients. This design yields a Type I error rate of 0.05 and power of 80% when the true response rate is 30%. We also plan to enroll up to 20 patients with other subtypes of indolent NHL or clinical scenarios documented above in order to identify preliminary evidence of efficacy of this treatment in those subtypes and/or clinical scenarios, and would consider a future amendment expanding one or more of those populations if an efficacy signal is identified. This 20 patient cohort will be pooled with the primary cohort for the safety analysis but will be analyzed separately from the primary patient population in terms of efficacy outcomes. As a result, we will plan to enroll a total of 49 patients to the trial, at least 29 of whom will be patients with low tumor burden FL who are evaluable for the primary endpoint.

Analysis Populations:
All efficacy analysis will be performed using the intention to treat population, which consists of all patients who complete the consent form and meet eligibility criteria. Subjects who receive any amount of study treatment shall be included in the safety analyses. The analysis of DOR will only include subjects who have achieved objective response.

Missing Data Handling
No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to pre-specified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation (and will be considered non-responders if they are lost to follow-up prior to their first scheduled response assessment).

Efficacy Endpoints
The primary efficacy endpoint is the complete response rate prior to cycle 6 of therapy.

Secondary endpoints include:

- Overall response rate
- CR rate for acalabrutinib monotherapy at end of single-agent run-in
- 2-year progression free survival
- 2-year rate of histologic transformation
- Overall survival
- Duration of Response
- Time to next anti-lymphoma treatment
- Quality of life assessments

Safety Endpoints
Safety endpoints include:

- Grade 3+ adverse events
- All grade adverse events
- Patient-reported adverse events per PRO-CTCAE assessments
- Rate of treatment discontinuation and frequency of completion of study therapy

Study Treatment Administration and Compliance
Descriptive information will be provided regarding the number of acalabrutinib doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose delay, reductions and interruptions.

For each subject, acalabrutinib compliance will be described in terms of the proportion of study drug actually taken.

Analysis of Primary Efficacy Endpoint
Complete response rate will be calculated, and a 95% confidence interval will be estimated using the Clopper-Pearson method. This analysis applies as well to overall response rate and CR rate for acalabrutinib monotherapy at end of single-agent run-in.

Subjects who ultimately do not receive study therapy due to reasons other than being ineligible or those who do not have a response assessment due to non-complaince or due to early treatment discontinuation shall be considered non-responders. Patients with clinically suspected PD should, if feasible, complete radiographic assessment to confirm this but if this is not feasible, patients who have clinical evidence of progression resulting in discontinuation shall be considered as having PD.

Analysis of Secondary Efficacy Endpoint

For subjects who achieve objective response, DOR is defined as the time from the first tumor assessment supports the response to the time of confirmed disease progression or death due to any cause, whichever occurs first. Subjects who are still alive and free from progression at the time of data cutoff date, lost to follow-up, have discontinued study, or have initiated other non-protocol anti-tumor therapy (NPT) will be censored at the last tumor assessment when subjects are progression-free. DOR will be estimated using Kaplan-Meier method. Approximate 95% CIs for median DOR will be computed using the Brookmeyer and Crowley method.

PFS is defined as the time from first dose to documented disease progression, or death from any cause, whichever occurs first. Data for subjects who are still alive and free from progression at the time of data cutoff date, lost to follow-up, have discontinued the study, or have initiated NPT will be censored on last assessment prior to aforementioned events (or, if no baseline/post-baseline tumor assessment, at the time of first dose plus 1 day). PFS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median PFS will be computed using the Brookmeyer and Crowley method. Patients who do not receive treatment will be excluded from the PFS analysis.

OS is defined as the time from first dose to death from any cause. Data for subjects who are still alive at the time of data cutoff date, lost to follow-up, have discontinued the study (or, if no post-baseline assessment, at the time of first dose plus 1 day). Duration of OS will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median OS will computed using the Brookmeyer and Crowley method.

Time to next anti-lymphoma treatment is defined as the time from the end of induction visit up to and including the date of initiation of next treatment for any reason. This includes any chemotherapy, antibody therapy, oral therapy, and radiation therapy. Time to next anti-lymphoma treatment will be estimated using Kaplan-Meier methodology. Approximate 95% CIs for median time to next anti-lymphoma treatment will be computed using the Brookmeyer and Crowley method.

QOL measures from the FACT-G obtained during treatment will be compared to the baseline values obtained at the screening visit using paired t-tests, McNemar's tests, or their nonparametric equivalents, where appropriate.

Categorical PRO-CTCAE variables will be summarized using frequencies and percentages, and numeric PRO-CTCAE variables will be summarized using mean, median, standard deviation, interquartile range (IQR), and range.

16.2 Data/specimens:

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Principal Investigator. The

study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Data and/or data forms will be submitted in the clinical management system - Online Collaborative Research Environment (ONCORE)- per Winship SOP 4.2 Data Completion Metrics.

All information in original records and certified copies of original records or clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial is considered source data. Source data are contained in source documents, which can be original records or certified copies of hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Case Report Forms (CRFs) - Source data may be collected in the source documents or entered directly onto the case report forms.

All documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence will be maintained for at least 2 years after the investigation is completed.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

Samples and data collected under this protocol may be used to study non-Hodgkin Lymphoma. Access to stored samples will be limited to IRB-approved investigators. Samples and data will be stored using codes assigned by the investigators or their designees. Data will be kept in password-protected computers. Only investigators will have access to the samples and data.

All stored samples will be maintained in the laboratory to which it was sent initially for analysis. Study participants who request destruction of samples will be notified of compliance with such request and all supporting details will be maintained for tracking

16.Provisions to Monitor the Data to Ensure the Safety of Participants

Definition of Adverse Events (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with non-Hodgkin Lymphoma that were not present before the AE reporting period.
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened**: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization**: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs. In addition, elective hospitalizations solely for TLS prophylaxis, and without occurrence of TLS or other AE during the hospitalization, also should not be reported as AEs or SAEs.
- **Diagnostic testing and procedures**: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (eg, routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.
- **Abnormal laboratory results that the investigator considers to not be clinically significant**: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Progression of underlying malignancy**: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.
  If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.
  Symptomatic deterioration may occur in some subjects. Symptomatic deterioration is when progression is evident in the subject's clinical symptoms and the investigator may elect not to

perform further disease assessments. If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

Adverse Events of Special Interest (AESI)

The following events are adverse events of special interest (AESIs) for subjects exposed to acalabrutinib, and must be reported to the supporter expeditiously irrespective of regulatory seriousness criteria or causality:

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

Obinutuzumab events of special interest are:

- TLS (serious and non-serious events)
- Second malignancies

Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

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

Adverse Events (AEs) for malignant tumors reported during a study should generally 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. For studies in Early Stage and Late Stage Immuno-Oncology and Oncology Studies: The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the

study is a criterion and that is being treated by the IP under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that – as part of normal, if rare, progression – undergo transformation (e.g., Richter's transformation of B cell chronic lymphocytic leukemia into diffuse large B cell lymphoma) should not be considered a new malignant tumor.

In addition to the definition above, any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

Elevations in liver biochemistry that meet Hy's Law criteria are reported as SAEs, using the important medical event serious criterion if no other criteria are applicable.

Special Situations
Special situations are other situations of relevance for monitoring the safety of Acerta/AZ products and which may or may not be associated with an AE. These special situations must be collected/received, even if no AE occurred:

- Exposure to product during pregnancy
- Exposure to product whilst breastfeeding
- Overdose
- Abuse
- Misuse
- Off-label Use
- Medication error
- Occupational exposure
- Lack of efficacy
- Drug interactions
- Unexpected benefit

Classification of an Adverse Event

Severity of Event

Definitions found in the CTCAE version 5.0 will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures

- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

Pregnancy

Investigators should report all pregnancies and pregnancies in the partners of subjects to the supporting Sponsor within 24 hours of the awareness date. The Principal Investigator should report any occurrences

to the IRB and the investigator should report any occurrences to the FDA per institutional and/or regulatory guidelines, and to Acerta/AZ per contractual guidelines.
Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib or 18 months after the last dose of obinutuzumab will be reported, followed to conclusion, and the outcome reported.
Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drugs. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Pregnancies in Female Partners of Male Patients
If the female partner of male patients become pregnant while receiving the study drug or within 6 months after the last dose of obinutuzumab or 30 days after the last dose of acalabrutinib, whichever is longer, a report should be completed and expeditiously submitted to the investigator. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. After the authorization has been signed, the investigator will submit a Pregnancy Report when updated information on the course and outcome of the pregnancy becomes available.

Congenital Anomalies/Birth Defects and Abortions
Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as a serious adverse events. Similarly, any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event.

Overdose
Clinical information relevant to overdose is not available. For results from nonclinical overdose studies in rats and dogs, please refer to the Investigator Brochure.
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 supporting Sponsor within 24 hours using the SAE reporting form. The Principal Investigator should report any SAEs to the IRB and to the FDA per institutional and/or regulatory guidelines, and to Acerta/AZ per contractual guidelines.

Acalabrutinib

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.

Obinutuzumab

There has been no experience with overdose in human clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of obinutuzumab and supportive therapy.

Adverse Event and Serious Adverse Event Reporting

The investigator is responsible for ensuring that all AEs, SAEs, and Special Situations that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF.

As described in Section 5.8, the PRO-CTCAE data is used for research purposes only and will not be used for the collection and reporting of AEs. Study staff must clearly convey to the patient that the information regarding symptoms collected by the PRO-CTCAE are not monitored by a physician and the patient must contact the clinical team directly for any concerning symptoms. In cases where a self-identified AE on the PRO-CTCAE is evaluated by the clinical team, the grade and attribution can be assess by conventional methods as described in this section.

Expectedness

Principal Investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Adverse Event Reporting

From the time of treatment allocation/randomization through 30 days following cessation of treatment or at documented disease progression (whichever is longer), all adverse events, that begin or worsen after informed consent, must be recorded by the investigator or designee at each examination on the Adverse Event case report forms/worksheets.

The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Conditions that were already present at the time of informed consent should be recorded in the Medical History page of the patient's CRF/worksheet.

Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 1 to 5 will be used to characterize the severity of the Adverse Event. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, death related to the AE corresponding respectively to Grades 1 - 5, will be used. Information about any deaths (related to an Adverse Event or not) will also be collected through a Death form (or

EOT/SEC/Survival Information in NOVDD). The occurrence of adverse events should be sought by non-directive questioning of the patient (patient) during the screening process after signing informed consent and at each visit during the study. Adverse events also may be detected when they are volunteered by the patient (patient) during the screening process or between visits, or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. The severity grade (CTCAE Grade 1-5)
2. Its duration (Start and end dates)
3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)
4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
5. Whether medication or therapy was given (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
6. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 9.2 and which seriousness criteria have been met (include for NCDS trials).
7. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

If the event worsens the event should be reported a second time in the CRF noting the start date when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4. For phase I studies any AE that constitutes a DLT should be reported like a grade 3 and 4 adverse event. All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome. Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.
Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded on the Adverse Events CRF.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or

medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

Serious Adverse Event Reporting

For the time period beginning with treatment initiation through 30 days following cessation of treatment, or until subject initiates new anticancer therapy, whichever is earlier. Any serious adverse event, or follow up to a serious adverse event, including death due to any cause whether or not related to the study drug, must be submitted on an SAE form and assessed by PI in order to determine reporting criteria to regulatory authorities, IRB, DSMC, or FDA .

All SAEs will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the adherence to be stable. Other supporting documentation of the event may be requested by the study PI and should be provided as soon as possible. All subjects with serious adverse events must be followed up for outcome.

Any additional information for the SAE including complications, progression of the initial SAE, and recurrent episodes must be reported as follow-up to the original episode. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one should be reported separately as a new event. Any SAEs experienced after the reporting period described above should only be reported to FDA/IRB if the investigator suspects a causal relationship to the study treatment.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess and record the relationship of each SAE to each specific study treatment (if there is more than one study treatment), complete the SAE Report Form, and submit the completed form. Each reoccurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the patient continued or withdrew from study participation.

All SAEs, secondary malignancies, Pregnancy, Overdose and other Special Situation reports, Adverse Events of Special Interest and Hy's Law reports are to be submitted to the AstraZeneca Product Safety mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com

Second and secondary malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported through **ONCORE.**
Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])

- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.
A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy).

Definition of unanticipated problems (UP) and reporting requirements

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or an outcome that meets **all** the following criteria: Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied; Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. This study will use the OHRP definition of unanticipated problems. Incidents or events that meet the OHRP criteria for UPs require the creation and completion of a UP report form. It is the site investigator's responsibility to report UPs to their IRB and to the DCC/study sponsor. The UP report will include the following information: Protocol identifying information: protocol title and number, PI's name, and the IRB project number; A detailed description of the event, incident, experience, or outcome; An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP; A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP. The investigator will make an assessment of whether the event constitutes an unanticipated problem posing risks to subjects or others (UP). This assessment will be provided to the Emory University IRB. If the Emory IRB determines an event is a UP it will notify the appropriate regulatory agencies and institutional officials.

The Data and Safety Monitoring Committee (DSMC)

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol as determined by CTRC, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP). The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry,

accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data. The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

17. Provisions to Protect the Privacy Interests of Participants

Participants will be assured of their voluntary participation in the study, their choice to answer or not answer any question, and the protocol for maintaining confidentiality.

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived.

18. Economic Burden to Participants

The study sponsor will pay for certain items and services the subject may receive in this study. Subjects will have to pay for the items or services for which the study sponsor does not pay. The sponsor will not pay for regular medical care. If subjects have insurance, Emory will submit claims to the insurance for

items and services that the sponsor does not cover. Emory will send in only those claims for items and services that it reasonably believes the insurance will pay and that the sponsor has not paid. The actual amount that participants have to pay depends on whether or not they have health insurance and whether or not that insurance will pay for any research study costs. Generally, insurance companies will not pay for items and services that are required just for a research study. Some insurance companies will not pay for regular medical treatment or treatment for complications if in a study. If subject do not have insurance, Emory will review that particular case as part of its program for low-income patient care. The standard policies of that program will apply. The program will figure out if subjects have to pay any costs for taking part in the study and what those costs will be

19. Consent Process

The initial informed consent discussion will occur in Winship Cancer Institute or the Emory Clinic.
At Winship Cancer Institute, the informed consent is an ongoing, interactive process rather than a one-time information session. The consent form document is designed to begin the informed consent process, which provides the patient with ongoing explanations that will help them make educational decisions about whether to begin or continue participating in the trial. The research team knows that a written document alone may not ensure that the patient fully understands what participation means. Therefore, the research team will discuss with the patient the trial's purpose, procedures, risks and potential benefits, and their rights as a participant. The team will continue to update the patient on any new information that may affect their situation.

Consent will be obtained prior to any research-driven procedures. The investigator will assess the patient's capacity during his/her encounters with him or her. The investigator will give the person providing consent adequate opportunity to read the consent document before it is signed and dated.

It will be explained to prospective participants that the study involves research, the purpose of the research, the expected duration of participation, as well as the approximate number of participants to be enrolled. The study procedures, and identification of research procedures v. non-research will also be thoroughly discussed. It will be explained to participants that participation is voluntary and that the subject may discontinue at any time.

Refusal to participate or withdraw will not involve a penalty or loss of benefits to which the participant is otherwise entitled. Refusal will in no way affect the participant's future are. The participant will also be told of the possible consequences of the decision to withdraw from the research, and procedures for orderly termination of participation.

Any significant new findings developed during the course of the research that may affect the participant's willingness to continue to participate will be provided. Also explained will be anticipated circumstances under which the subject's participation may be terminated by the investigator without the participant's consent.

Prospective participants will be provided with a description of any reasonably forseeable risks or discomforts as well as a description of any benefits to the participant or to others that might be reasons expected from the research. Alternative procedures or courses of treatment will also be thoroughly discussed.

Prospective participants will also be given detailed information describing the extent to which confidentiality of records identifying the participant will be maintained and what records may be examined by the research staff, IRBs, sponsor, their representatives, and possibly the FDA or OHRP.
Also communicated to the participant will be an explanation that emergency medical care will be arranged for a study-related illness or injury, and an explanation of whether funds are set aside to pay for this care and/or compensation, and if so by whom (e.g., sponsor, subject, insurer). The participant is told the source of the study's funding.

All participants will be told of any additional costs that may result from participation in the research.

Consent will be done in person or remotely through secured email, phone or by electronic consenting using one of the methods that is Emory LITS approved (e.g. DocuSign) when available. We will follow Emory's guidance on use of electronic informed consent.

Non-English-Speaking Participants

A certified translator/interpreter will be present during the consenting process and all questions and concerns will be answered by the treating physician.

A Short Form in that specific language will be used. A certified translator/interpreter will be present during the consenting process and this will be documented. We will use what's available on Emory IRB website. For the languages that are not available, we will have the short form translated to that language and submit the IRB for review and approval prior to use. Process to Document Consent in Writing: Winship SOP 2.1:"Obtaining Informed consent for Interventional clinical trial" will be followed.

Participants who are not yet adults (infants, children, teenagers)

N/A

Cognitively Impaired Adults

N/A

Adults Unable to Consent

Use of LAR, if applicable

20. Setting

The research will be conducted at Emory University. If non-Emory sites are added to this study in the future, the protocol will be amended to reflect this.

Potential participants will be identified in medical oncology clinics, multidisciplinary cancer clinic, surgical oncology clinics, multidisciplinary tumor board at Emory University.

21. Resources Available

Emory University was founded in 1836 and is a national center for teaching, research, and service. Emory University has been named as one of the nation's top 25 universities for more than a decade by the U.S.

News and World Report. Emory University research partners include the Georgia Institute of Technology, the University of Georgia, Morehouse School of Medicine, the US Centers for Disease Control and Prevention, Children's Healthcare of Atlanta, and the Georgia Clinical and Translational Science Alliance (GACTSA). Emory University researchers received $734 million from external funding agencies in fiscal year 2018, including approximately $441 million in funding from federal agencies, $359 million of this from the National Institutes of Health (NIH).

Winship Cancer Institute (Winship) is Georgia's first and only National Cancer Institute (NCI)-designated Comprehensive Cancer Center (P30CA138292) and is dedicated to the integration of innovative clinical and basic science research with outstanding patient care for the prevention, treatment and control of cancer. First designated in 2009, Winship's NCI designation was renewed in 2012 and 2016, achieving an "outstanding" rating. Winship earned the prestigious Comprehensive Cancer Center designation from the NCI in 2016, after demonstrating that its outstanding programs are reducing the cancer burden on the state of Georgia through research conducted in its laboratories, its clinical trial program, and its population-based science. The institutional support for Winship was rated as 'exceptional' by the review panel.

The **Winship Clinic Building C** houses the primary offices and clinical space for cancer services including the medical oncology, hematology, and surgical oncology clinics, the radiation oncology program, and the Winship Ambulatory Infusion Center. In summer 2017, Emory Healthcare completed the expansion of **Emory University Hospital Tower** on Clifton Road. This nine-floor facility adds 144 inpatient beds to the hospital, of which more than 80% are dedicated to cancer care. The hospital expansion also accommodates cancer patient-specific intensive care units, an expanded BMT Unit with peri-transplant clinics to facilitate continuity of care, and a 24-hour cancer urgent care center, which serves as both a triage facility and short stay treatment center for patients with cancer-related medical concerns.
The **Winship Phase I Unit**, on the fourth floor of the Emory University Hospital Tower, is the largest unit in Georgia dedicated to the earliest and most critical phase of new cancer therapy evaluation. There is space for 15 private treatment bays, four clinic rooms, its own lab for doing patient blood work, a dedicated secure medication room, computer workspace for research and other support staff, and a "fast track" bay with three chairs for rapid use in patients who, for example, might need only a research lab test done.

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APPENDIX A Performance Status Criteria

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

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

APPENDIX B Drug Diary

Study ID:

Acalabrutinib Pill Diary

Subject Initials: _____ Subject ID: _____ Cycle: _____

Instructions:

Planned Daily Dose: _____mg

REMINDERS:

1.

2.

Day:	Date:	Time: AM	PM	# of Tablets Taken	Comments:
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Patient Signature: _____

Date Signed: _____

Name of Medication:	Why did you take this medication?	Date Medication Started:	Date Medication Stopped:

Please record all medications taken during this cycle, including prescription medications and over the counter medications including vitamins and supplements.

If you have any questions, please call: _____

APPENDIX C Abbreviations and definition of terms

The following abbreviations and special terms are used in this study Clinical Study Protocol.

ADCC	Antibody-dependent cellular cytotoxicity
AE	adverse event
AESI	adverse events of special interest
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	aspartate aminotransferase
BID	twice per day (dosing)
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CD	cluster of differentiation (cell surface marker)
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practice
CIs	confidence intervals
CLL	chronic lymphocytic leukemia
COPD	chronic obstructive pulmonary disease
CR	complete response (remission)
CRF	case report form
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
CYP	cytochrome p450
DCR	disease control rate
DFU	Discontinuation follow-up
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

FACT-G	Functional Assessment of Cancer Therapy - General
FDA	Food and Drug Administration
FL	Follicular Lymphoma
G	obinutuzumab
GCP	Good Clinical Practice
GELF	Groupe d'Etude des Lymphomes Folliculaires
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
IEC	independent ethics committee
IND	Investigation new drug
IRC	Independent review committee
IRB	institutional review board
IV	intravenous or intravenously
JC virus	John Cunningham virus
LDH	lactate dehydrogenase
LPL/WM	Lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinemia
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MZL	Marginal Zone Lymphoma
NK	natural killer (cells)
NHL	Non-Hodgkin Lymphoma
ORR	overall response rate
OS	overall survival
PCR	Polymerase chain reaction
PFS	progression-free survival
PD	pharmacodynamic, pharmacodynamics, or progressive disease
PET	Positron emission tomography
P-gp	p-glycoprotein 1 (transporter)
PML	Progressive Multifocal Leukoencephalopathy
PR	partial response (remission)
PRO	Patient-reported outcome

PT	Prothrombin time
R/R	Relapsed/refractory
QD	once per day (dosing)
QT_c	corrected QT interval
QoL	Quality of life
RSI	Reference Safety Information
SAE	serious adverse event
SFU	Safety follow-up
SD	stable disease or standard deviation
SLL	Small lymphocytic lymphoma
SUSAR	suspected unexpected serious adverse reaction
TT	Treatment termination
ULN	upper limit of normal
USPI	United States package insert
WOCBP	Women of childbearing potential

APPENDIX D Known Strong in Vivo Inhibitors or Inducers of CYP3A

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[d]
boceprevir	carbamazepine[e]
clarithromycin[b]	phenytoin[e]
conivaptin[b]	rifampin[e]
indinavir	St John's wort[e]
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[c]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate by ≥ 5-fold.

b. In vivo inhibitor of P-glycoprotein.
c. Withdrawn from the United States market because of safety reasons.
d. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.
e. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Sponsor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers . Web link Accessed 11 June 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

APPENDIX E GELF Criteria

Involvement of >3 nodal sites, each with a diameter of >3cm	Any nodal or extranodal tumor mass with a diameter of 7cm
Presence of B symptoms	Risk of local compressive symptoms that may result in organ compromise
Cytopenias (leukocytes <1.0 x 10^9/L and/or platelets < 100 x 10^9/L	Leukemic Phase (>5.0 x 10^9/L malignant cells)
Splenomegaly (>16cm on CT scan)	Pleural effusion or peritoneal ascites

Data taken from reference [10]

APPENDIX F FACT-G (Version 4) Questionnaire

Below is a list of statements that other people with your illness have said are important.

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4

GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please m☐ this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some-what**	**Quit ea bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4

GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

APPENDIX G Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

APPENDIX H PRO-CTCAE FORM

NCI PRO-CTCAE™ ITEMS

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English
Form created on 2 February 2020

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ☒ in the one box that best describes your experiences over the past 7 days...

1.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

2.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

3.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA/DIARRHOEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

5.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

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6.	In the last 7 days, did you have any RASH?				
	○ Yes	○ No			

7.	In the last 7 days, how OFTEN did you have a HEADACHE?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEADACHE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did your HEADACHE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

8.	In the last 7 days, how OFTEN did you have ACHING MUSCLES?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ ITEMS

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10.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

11.	In the last 7 days, did you BRUISE EASILY (BLACK AND BLUE MARKS)?	
	○ Yes	○ No

12.	In the last 7 days, how OFTEN did you have NOSEBLEEDS?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NOSEBLEEDS at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

NCI PRO-CTCAE™ ITEMS

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English
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Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe