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DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: A Phase II study of BTK inhibitor acalabrutinib and PI3Kδ inhibitor umbralisib in combination with ublituximab (AU2) in patients with previously untreated mantle cell lymphoma (MCL)

CITY OF HOPE PROTOCOL VERSION: **IRB #20459** **Protocol Date: 03/06/2023**

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Clinical Trial Protocol

A Phase 2 Study of Acalabrutinib and PI3Kδ inhibitor Umbralisib in Combination with Ublituximab (AU2) in Patients with Previously Untreated Mantle Cell Lymphoma

Version Date:	03/06/2023
Protocol Version:	05
City of Hope #:	20459
Agents:	Acalabrutinib, Umbralisib, Ublituximab
IND Number:	153853
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Funding Support/ Industry partners:	AstraZeneca, TG Therapeutics
Industry Partner Protocol ID:	TG Therapeutics, Inc. tracking number U2-NTG-017
NCT Number:	NCT04783415
Participating Sites:	City of Hope (Duarte), Arizona Cancer Center, Roswell Park, Yale University School of Medicine
Short Title	Acalabrutinib, Umbralisib, and Ublituximab (AU2) for previously untreated MCL

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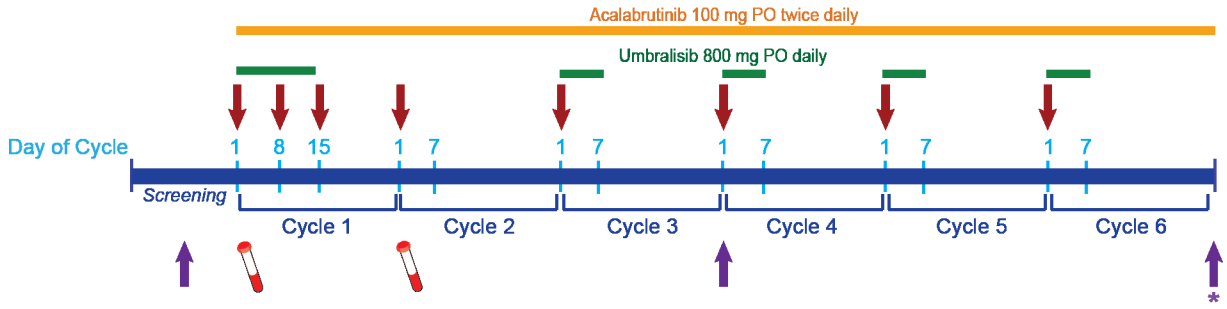
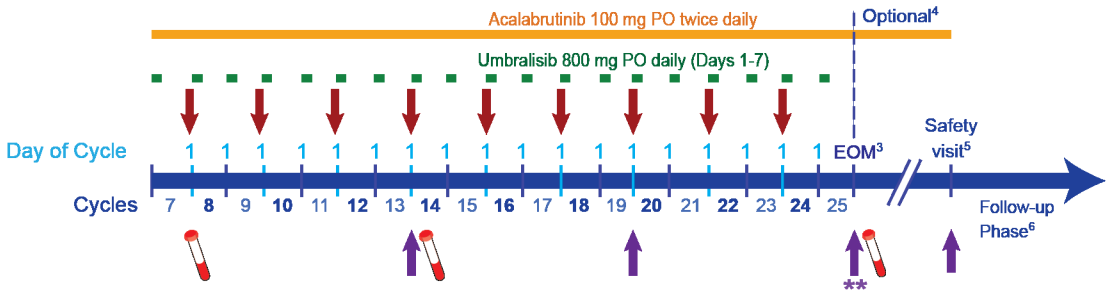
STUDY SCHEMA

Induction Phase (6 cycles)



Maintenance Phase (19 cycles)

Ublituximab every 2 cycles



Each cycle = 28 days

*** Participants with stable disease (SD) or better response (PR, CR) at the end of Induction will be eligible to proceed to Maintenance.**

**** And every 6 months thereafter until end of protocol therapy.**

[1] **Disease staging** will be by PET/CT (preferred) or CT (with Study PI's approval). Refer to Study Calendar and Section 11.1 for details.

[2] **Peripheral blood for correlative studies.** Blood will also be collected at time of relapse. Refer to Section 9.1.3 for additional details and a list of time points.

[3] **EOM** = End of maintenance. Visit to occur at the end of Cycle 25.

[4] **Participants may continue therapy** with acalabrutinib beyond 25 cycles of protocol therapy at the treating physician's discretion.

[5] **Safety visit** (within 30 days from last dose of protocol therapy).

[6] **Active Follow-up** will include staging after 6, 12, 18, and 24 months from last on-treatment scan, and will occur until disease progression or initiation of a new anti-lymphoma therapy. Refer to Section 5.8 and Study Calendar.

Each participant will be on study for a maximum of 6 years. Participants who continue therapy beyond 25 cycles with acalabrutinib for a total of 6 years of protocol therapy will only proceed with the safety follow-up visit; there will be no response/survival follow-up for these patients. Refer to Section 5.7.

PROTOCOL SYNOPSIS

Protocol Title

A Phase 2 Study of Acalabrutinib and PI3Kδ inhibitor Umbralisib in Combination with Ublituximab (AU2) in Patients with Previously Untreated Mantle Cell Lymphoma

Study Detail

Population/Indication(s):	Previously untreated Mantle Cell Lymphoma
Phase:	2
Sample Size:	Expected: 24; Maximum: 27
Estimated Accrual Duration:	2 years
Estimated Study Duration	7 years
Participant Duration:	5.5 years
Participating Sites:	• City of Hope Duarte, CA • Arizona Cancer Center • Roswell Park Cancer Institute • Yale University School of Medicine
Study Agents:	Acalabrutinib, Umbralisib, Ublituximab
Sponsor:	City of Hope
Industry Partners:	AstraZeneca, TG Therapeutics

Rationale for this Study

A combination of bendamustine and rituximab (BR) has become an accepted standard in frontline therapy of newly diagnosed MCL among patients who are poor candidates for intensive chemotherapy regimens and autologous stem cell transplantation. However, BR regimen is not curative, and the majority of patients ultimately relapse within 5 years. In addition, chemo-immunotherapy combinations have limited efficacy in MCL with aberrant *TP53* and/or complex karyotype (CK). Thus, achievement of a durable remission following upfront therapy of MCL remains an important goal in lymphoma therapeutics, and MCL with *TP53* aberrations and CK is a particular area of unmet need.

Emerging data indicate that upfront therapy with ibrutinib-rituximab combination is associated with 100% ORR in MCL. Therefore, BTK inhibitors combined with CD20-targeting agents are poised to be effective in upfront setting in MCL. However, patients who develop resistance to ibrutinib have dismal outcomes. Activation of the phosphoinotiside-3 kinase (PI3K) pathway has been implicated in resistance to chemotherapy and ibrutinib in MCL, and thus represents an actionable target in this disease. Idelalisib, a selective PI3Kδ inhibitor, has demonstrated single agent efficacy in relapsed/refractory MCL, albeit responses were short-lived. Moreover, additive or synergistic effects of the combination of ibrutinib and idelalisib have been reported in pre-clinical studies in lymphoid malignanices. Thus, combined targeting of BTK and PI3K may result in improved efficacy in MCL and prevent disease relapse, particularly when employed in the frontline setting.

Acalabrutinib is a next-generation BTK inhibitor that shows higher selectivity for BTK, while simultaneously lacking irreversible inhibition of other kinases. This higher target selectivity is expected to contribute to the improved safety profile over that of ibrutinib. Acalabrutinib is at least as efficacious as ibrutinib in MCL and it is expected to have fewer toxicities than ibrutinib.

Umbralisib is a highly-specific orally available dual inhibitor of PI3K-δ and casein kinase 1 epsilon (CK1ε) with nanomolar inhibitory potency. Umbralisib is currently being investigated in clinical trials in lymphoma. The first report suggested high tolerability of umbralisib, with decreased rates of colitis, pneumonitis and hepatic abnormalities compared to other PI-3Kδ inhibitors. The extended integrated safety follow-up results from 5 clinical trials using umbralisib that we presented at ASH 2017 confirmed a favorable tolerability. In addition, a triplet combination of umbralisib, ibrutinib and CD20-targeting antibody ublituximab was well tolerated, with umbralisib 800 mg daily becoming the RP2D in patients with relapsed B-cell malignancies.

Ublituximab is a glycolengineered chimeric monoclonal antibody engineered to optimally target the human CD20 antigen. A review of the adverse events observed to date for ublituximab indicates that several risks are associated with ublituximab infusions and treatment. Nevertheless, the risks associated with ublituximab therapy appear to be consistent with those

associated with existing CD20-directed therapy, and the proof of clinical activity of single agent ublituximab has been demonstrated in relapsed/refractory subjects with CLL and NHL, and subjects with MS. The potential benefits of ublituximab in subjects with CD20-positive B-cell lymphoproliferative disorders have been suggested from several nonclinical studies demonstrating a better *in vitro* ADCC activity compared with rituximab.

Based on the favorable safety profile reported with single agent ublituximab, subsequent combination studies were undertaken. Ublituximab has been evaluated in combination with lenalidomide, with ibrutinib, with bendamustine, with pembrolizumab, with venetoclax, and/or with umbralisib. To date, ublituximab in combination with these agents has been well tolerated. The combinations of ublituximab with ibrutinib, and of ublituximab with umbralisib have particularly displayed robust clinical activity in subjects with CLL, for which registration directed studies are ongoing.

We hypothesize that acalabrutinib in combination with the second-generation CD20-targeting antibody ublituximab and selective PI3Kδ inhibitor umbralisib (AU2) will demonstrate high efficacy and tolerability as frontline therapy in older/unfit MCL patients, and in patients with TP53 aberrations or complex karyotype.

Objectives

Primary Objective(s)

- Evaluate the anti-tumor activity of acalabrutinib, umbralisib and ublituximab (AU2) regimen as induction therapy in patients with treatment-naïve mantle cell lymphoma (MCL), as assessed by the complete response (CR) rate.

Secondary Objective(s)

- Evaluate the overall response rate (ORR) to AU2 in treatment-naïve MCL.
- Evaluate the progression-free survival (PFS), overall survival (OS) and duration of response (DOR) in patients with treatment-naïve MCL who received AU2.
- Evaluate the safety and tolerability of AU2 in patients with treatment-naïve MCL.

Exploratory Objective(s)

- Examine the T-cell populations and functionality in patients treated with AU2.
- Explore the predictive value of minimal residual disease (MRD) in MCL.
- Explore the mechanisms of resistance to AU2 therapy.

Study Design

This is a phase 2 study of BTK inhibitor acalabrutinib and PI3Kδ umbralisib in combination with ublituximab (AU2) in treatment-naïve MCL patients. Patients with previously untreated MCL ≥ 65 years; or ≥ 50 years and deemed ineligible for aggressive induction therapy or autologous stem cell transplant by the investigator, or unwilling to undergo such therapy; or ≥ 18 years with documented del(17p), or *TP53* mutation, or complex karyotype (CK) will be enrolled. As noted above, older patients with MCL do not have curative options, and current standard chemo-immunotherapy regimens (i.e., BR) are associated with a PFS of <4 years and significant toxicities. Furthermore, chemo-immunotherapy regimens are ineffective in patients high-risk MCL (*TP53* aberration and/or CK).

Participants will receive 6 cycles of Induction therapy (1 Cycle = 28 days) using the approved standard dose of acalabrutinib (100 mg PO, twice daily), and a previously demonstrated safe dose of umbralisib (800 mg PO, once daily, see schedule below) and ublituximab (900 mg IV, on Day 1, Day 8 and Day 15 of the first cycle, and Day 1 of each Cycle afterward).

Umbralisib will be administered daily for 14 days during cycle 1, followed by daily on days 1-7 with subsequent cycles. Maintenance therapy with anti-CD20 targeting antibodies has become standard approach post-induction in MCL, leading to improved OS [49, 50]. Participants with stable disease or better response at the end of Induction therapy will then receive 19 cycles of Maintenance therapy with the 3 agents, during which ublituximab (900 mg IV) will only be administered every 2 cycles. Participants may continue therapy with acalabrutinib beyond 25 cycles of protocol therapy at the treating physician's discretion.

The study will use a Simon's optimal two-stage design to evaluate the CR rate of the AU2 induction therapy. The first stage will accrue 9 patients. If there are 2 or fewer CR among 9 patients, the accrual will be terminated; if there are 3+ CR, the accrual will continue to second stage for a total of 24 patients. The study will require 10 or more CR in 24 patients to consider AU2 promising. The incidence of certain adverse events at least possibly related to study treatment will be monitored (see Section 12.4.2).

Evaluation Criteria and Endpoints

Primary Endpoint:

- Complete response (CR) rate at the end of induction therapy with AU2.

Secondary Endpoints:

- Overall response rate (ORR).
- Progression-free survival (PFS), overall survival (OS), and duration of response (DOR).
- Toxicity of AU2 regimen.

Exploratory Endpoints:

- T-cell populations, minimal residual disease, gene expression/mutation profiles.

Statistical Considerations

The primary endpoint is complete response (CR) rate after AU2 induction therapy. Secondary endpoints include toxicities, ORR to protocol treatment, PFS, OS, and DOR. The study sample size is based on the desire to discriminate a promising CR rate of 50% (alternative hypothesis) from a disappointing CR rate of 25% (null hypothesis). These response rates were chosen because 1) BR, a current standard, has been associated with an ORR of 80-90% and a CR rate of 40% [5, 7]; 2) In the phase 2 ACE-LY-004 trial in R/R MCL, treatment with acalabrutinib was associated with an ORR of 81% and a CR rate of 40% [39]. However, it is anticipated that this study will enroll a higher proportion of patients with high-risk MCL (*TP53* aberrations, CK) where BR is ineffective.

Simon's optimal two-stage design will be used. In the first stage, 9 evaluable patients will be accrued. If there are 2 or fewer CRs in these 9 patients, the study will be stopped. Otherwise, 15 additional evaluable patients will be accrued for a total of 24. The null hypothesis will be rejected and AU2 induction therapy will be considered promising if 10 or more CRs are observed in 24 evaluable patients. This design yields a 1-sided type I error rate of 0.05 and power of 0.8. When the CR rate is disappointing (25%), there is an 60% chance that the study will be terminated after the first stage.

Abbreviated Eligibility Criteria

Main Inclusion Criteria

- Histologically confirmed mantle cell lymphoma with documentation of monoclonal CD20+ B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1.
- Age ≥ 65 years; or ≥ 50 years and deemed ineligible for aggressive induction therapy or autologous stem cell transplant by the investigator, or unwilling to undergo aggressive induction; or ≥ 18 years with documented del(17p), or *TP53* mutation, or complex karyotype (CK) by cytogenetics and/or FISH studies.
- Requiring treatment for MCL, and for which no prior systemic anticancer therapies have been received (local radiotherapy not exceeding a total dose of 20 Gy at least 2 weeks prior the first dose of study therapy is allowed).
- Measurable disease by CT or PET/CT scan with one or more sites of disease ≥ 1.5 cm in longest dimension (including splenomegaly), or bone marrow involvement with or without malignant lymphocytosis.
- ECOG ≤ 2.
- Adequate hematological, renal, and hepatic function.
- Adequate coagulation.
- LVEF≥ 40%.
- Women of childbearing potential: negative serum pregnancy test.
- Agreement by females and males of childbearing potential to use a highly effective method of birth control or abstain from heterosexual activity for the course of the study through at least 2 days after the last dose of acalabrutinib for females, and at least 4 months after the last dose of ublituximab or umbralisib for both men and women.

Main Exclusion Criteria

- Subjects for whom the goal of therapy is tumor debulking before stem cell transplant.
- Chronic use of corticosteroids ≥20 mg/day (short-term use of steroids <14 days is allowed).
- Major surgical procedure within 28 days of start of protocol therapy. 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.
- Known history of hypersensitivity or anaphylaxis to study drug(s) including active product or excipient components.

- Concurrent participation in another therapeutic clinical trial.
- History of prior malignancy. Exceptions include malignancy treated with curative intent and no known active disease present for ≥ 2 years prior to initiation of protocol therapy; adequately treated non-melanoma skin cancer or lentigo maligna (melanoma in situ) without evidence of disease; adequately treated in situ carcinomas (e.g., cervical, esophageal, etc.) without evidence of disease; asymptomatic prostate cancer managed with “watch and wait” strategy.
- Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).
- Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.
- Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
- Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists.
- Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
- Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
- Known bleeding disorders (e.g., von Willebrand's disease or hemophilia).
- History of significant cerebrovascular disease/event, including stroke, myocardial infarction, or intracranial hemorrhage, within 6 months prior to start of protocol therapy.
- Known active central nervous system (CNS) involvement by lymphoma, including leptomeningeal involvement.
- Clinically significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class III or IV cardiac disease as defined by the New York Heart Association Functional Classification. Note: Subjects with controlled, asymptomatic atrial fibrillation can enroll on study.
- Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 6 months).
- History of or current progressive multifocal leukoencephalopathy (PML).
- Inability to swallow and retain an oral medication.
- Clinically significant uncontrolled illness, including active infection requiring antibiotics or antiviral agents.
- Live virus vaccines within 4 weeks of start of protocol therapy or planned administration of live virus vaccines during ublituximab therapy.
- Evidence of chronic active hepatitis B virus (HBV) or hepatitis C virus (HCV), or active cytomegalovirus (CMV) infection (See Section 3.2).
- Known history of human immunodeficiency virus (HIV) infection
- *Females only*: Pregnant or breastfeeding

Investigational Product Dosage and Administration

The treatment plan is as follows.

Induction phase:

Agent	Dose	Route	Schedule
Ublituximab	900 mg	IV	**Cycle 1**: Day 1, Day 8, and Day 15 **Cycles 2-6:** Day 1
Acalabrutinib	100 mg - Twice daily	Orally	Every day of each cycle
Umbralisib	800 mg - Once daily	Orally	**Cycle 1:** Days 1-14 **Cycle 2-6:** Days 1-7

Maintenance phase:

Agent	Dose	Route	Schedule
Ublituximab	900 mg	IV	**Every 2 cycles (Cycles 8, 10, 12, 14, 16, 18, 20, 22, 24)**, on Day 1, starting on Day 1 of Cycle 8
Acalabrutinib	100 mg - Twice daily	Orally	Every day of each cycle
Umbralisib	800 mg - Once daily	Orally	Days 1-7 of each cycle

Treatment will be administered on an *out-patient* basis (in-patient administration is allowed if deemed necessary by the Investigator).

Clinical Observations and Tests to be Performed

- Safety assessments (CBCs with differential, comprehensive chemistry panel, coagulation, ECHO/MUGA)
- Response assessments
- CT/PET/MRI scans
- Correlative tumor tissue, bone marrow and blood samples.

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AU2	Acalabrutinib, umbralisib, ublituximab regimen
BCR	B-cell receptor
BTK	Bruton tyrosine kinase
CFR	Code of Federal Regulations
CK	Complex Karyotype
COH	City of Hope
CR	Complete Response
CRA	Clinical Research Coordinator
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DLT	Dose Limiting Toxicity
DOR	Duration of response
DSMC	Data & Safety Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IDS	Investigational Drug Services
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
MCL	Mantle cell lymphoma
MRD	Minimal residual disease
NCI	National Cancer Institute
NGS	Next generation sequencing
OIDRA	Office of IND Development and Regulatory Affairs
ORR	Overall response rate
PD	Progressive Disease
PI	Principal Investigator
PI3K	Phosphoinositide 3-kinase
PMT	Protocol Management Team
PR	Partial Response
RNAseq	RNA sequencing
SAE	Serious Adverse Event
SD	Stable disease

1.0 OBJECTIVES

1.1 Primary Objective

- Evaluate the anti-tumor activity of acalabrutinib, umbralisib and ublituximab (AU2) regimen as induction therapy in patients with treatment-naïve mantle cell lymphoma (MCL), as assessed by the complete response (CR) rate.

1.2 Secondary Objectives

- Evaluate the overall response rate (ORR) to AU2 in treatment-naïve MCL.
- Evaluate the progression-free survival (PFS), overall survival (OS) and duration of response (DOR) in patients with treatment-naïve MCL who received AU2.
- Evaluate the safety and tolerability of AU2 in patients with treatment-naïve MCL.

1.3 Exploratory Objectives

- Examine the T-cell populations and functionality in patients treated with AU2.
- Explore the predictive value of minimal residual disease (MRD) in MCL.
- Explore the mechanisms of resistance to AU2 therapy.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

2.1.1 Mantle cell lymphoma (MCL)

MCL is a rare subtype of non-Hodgkin lymphoma (NHL) typically characterized by atypical small lymphoid cells with wide mantles around benign germinal centers [1]. The vast majority of patients present with stage IV disease that often includes lymphadenopathy, splenomegaly, bone marrow involvement, and gastrointestinal infiltration at the time of diagnosis [2]. The disease is twice as common in men as in women. Additionally, the risk of MCL is nearly 12-times greater for those aged 50–59 years compared to those <50 years. MCL is often characterized by a hallmark translocation t(11;14)(q13;q32), in which CCND1 is juxtaposed to the immunoglobulin heavy chain enhancer. This rearrangement manifests as an overexpression of cyclin D1 and is an important oncogenic driver promoting cell cycle deregulation [3]. MCL typically follows an aggressive clinical course with an overall poor prognosis. Intensive chemo-immunotherapy regimens remain the mainstay of treatment of newly diagnosed MCL. However, with an average age at diagnosis of 68 years, many patients are poor candidates for such therapy due to the presence of comorbidities. Despite high initial response rates, most patients eventually relapse and succumb to their disease [4].

2.1.2 Frontline immunotherapy for MCL

2.1.2.1 In older patients

A combination of bendamustine and rituximab (BR) has become an accepted standard in frontline therapy of newly diagnosed MCL among patients who are poor candidates for intensive chemotherapy regimens and autologous stem cell transplantation. In a prospective, multicenter, randomized trial which compared BR with R-CHOP as first-line treatment for patients with non-Hodgkin lymphoma (NHL), of a total of 549 patients, 94 (17%) carried a diagnosis of MCL [5]. Of these 94 patients, 46 received BR and 48 received R-CHOP. At a median follow up of 45 months, the median PFS was 35.4 months in the BR group *versus* 22.1 months in the R-CHOP group. Similar results were obtained in another large randomized study [6]. This improvement in PFS over R-CHOP, along with an acceptable side-effect profile, has made the BR regimen a popular first-line treatment option in treatment-naïve older MCL patients. A recent SWOG S1106 study demonstrated that BR may achieve high rate of minimal

residual disease (MRD) among patients with MCL [7]. *Despite these successes, BR regimen is not curative, and all patients ultimately relapse after a median of <3 years.*

2.1.2.2 In patients with TP53 and/or complex karyotype

Chemo-immunotherapy combinations have limited efficacy in MCL with aberrant *TP53* and/or complex karyotype (CK). In the Nordic trials, patients who had mutations in *TP53* did not benefit from intensive induction chemotherapy [8]. 50% of such patients relapsed by 1 year, and overall survival was 1.8 years. In a multicenter retrospective study, we have found that patients with CK similarly did not benefit from intensive induction chemotherapy, and had an OS of 3.5 years following low-intensity therapy such as BR [9]. *Thus, achievement of a durable remission following upfront therapy of MCL remains an important goal in lymphoma therapeutics, and MCL with TP53 aberrations and CK is a particular area of unmet need.*

2.1.3 Bruton tyrosine kinase (BTK) inhibition in B-cell malignancies

Chronic active B-cell receptor (BCR) signaling pathway has been implicated in the pathogenesis of B-cell neoplasia, including MCL [10]. Activation of Bruton tyrosine kinase (BTK) and its downstream targets plays a pivotal role in regulation of proliferation, survival and homing of malignant B-cells [11, 12]. Overexpression of BTK is commonly found in MCL and its pharmacologic targeting induces apoptosis *in vitro* [13]. Ibrutinib (Imbruvica) is a potent, orally bioavailable irreversible inhibitor of BTK that covalently binds the kinase active site at C481 residue. Ibrutinib received FDA approval in therapy of relapsed/refractory MCL based on the results of a phase II trial. 111 patients with MCL were treated with ibrutinib at 560 mg by mouth daily. 68% of patients achieved an objective response, and 21% entered complete response [14]. Among all patients, duration of response was limited to 13 months, and overall survival was less than 2 years [15]. However, patients who were exposed to fewer prior therapies derived increased benefit from BTK inhibition, with prolonged PFS and OS [16]. Furthermore, a combination of ibrutinib and rituximab resulted in further improvement of outcomes among patients with relapsed MCL, with median PFS of 43 months, thereby exceeding the expected efficacy of BR in this setting [17]. Emerging data indicate that upfront therapy with ibrutinib-rituximab combination is associated with 100% ORR in MCL.[18] *Therefore, BTK inhibitors combined with CD20-targeting agents are poised to achieve durable remissions in upfront setting in MCL*.

2.1.4 Resistance to ibrutinib

Patients with MCL who develop resistance to ibrutinib have dismal outcomes [19, 20]. A large retrospective cohort study of 114 patients who progressed on ibrutinib documented an overall survival of <3 months following cessation of the drug [20]. Mutations in BTK (C481S) and its downstream target PLCγ2 have been implicated in resistance to ibrutinib in CLL where they may account for the majority of resistant cases [21, 22]. In fact, emergence of BTK/PLCγ mutations typically pre-dates ibrutinib resistance in CLL [22]. By contrast, while such mutations are found in late ibrutinib failures in MCL, most patients relapse early in the course of therapy (within the first 6 months) and lack such mutations [20, 23]. Activation of the phosphoinotiside-3 kinase (PI3K) pathway has been implicated in resistance to chemotherapy and ibrutinib in MCL, and thus represents an actionable target in this disease [23, 24]. Idelalisib, a selective PI3Kδ inhibitor, has demonstrated single agent efficacy in relapsed/refractory MCL, albeit responses were short-lived [25].

Additive or synergistic effects of the combination of ibrutinib and idelalisib have been reported in CLL, MCL, and diffuse large B-cell lymphoma (DLBCL) cell lines [26, 27]. Combined inhibition of PI3K and BTK induced apoptosis of the DLBCL cell line TMD8, which was resistant to inhibition of either kinase alone [28]. Furthermore, acalabrutinib demonstrated enhanced efficacy when combined with PI3K inhibitor ACP-319 (no longer in development) in a CLL mouse model [29]. *Thus, combined targeting of BTK and PI3K may result in improved efficacy in MCL and prevent disease relapse, particularly when employed in the frontline setting.*

2.1.5 Umbralisib

Umbralisib (TGR-1202) is a highly-specific and orally available dual inhibitor of PI3K-δ and casein kinase 1 epsilon (CK1ε) with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K. With a dissociation constant (Kd) of 6.2 nM, umbralisib is a more selective inhibitor of PI3Kδ than idelalisib (1.2 nM) or duvelisib (0.047 nM) [30]. Moreover, umbralisib, unlike other p110-δ inhibitors (e.g., duvelisib and idelalisib), has a different chemical structure in which carbon and oxygen atoms replace the nitrogen atoms of the heterocyclic quinazolinone backbone [31]. Compared to other p110-δ inhibitors, this altered chemical structure is thought to not only reduce hepatotoxicity, but is also associated with conferring umbralisib with CK-1ε inhibitory potential [31, 32].

Umbralisib is currently being investigated in clinical trials in lymphoma. The first report suggested high tolerability of umbralisib, with decreased rates of colitis, pneumonitis and hepatic abnormalities compared to other PI-3Kδ inhibitors [33]. The extended integrated safety follow-up results from 5 clinical trials using umbralisib that we presented at ASH 2017 confirmed a favorable tolerability [34]. Furthermore, combinations of ibrutinib and umbralisib have not resulted in significant toxicities. In a Phase I trial of umbralisib and ibrutinib in patients with CLL and MCL, ibrutinib was used in standard doses (420 and 560 mg, respectively), while umbralisib dose was escalated from 400 to 800 mg (NCT02268851) [34, 35]. There were no DLTs at the RP2D of umbralisib 800 mg daily in combination with ibrutinib. This combination was highly efficacious in both CLL and MCL, with complete responses documented in both conditions. This study thus demonstrated favorable safety profile and high response rate of ibrutinib in combination with umbralisib in patients with relapsed/refractory MCL [35]. Similarly, a triplet combination of umbralisib, ibrutinib and CD20-targeting antibody ublituximab was well tolerated, with umbralisib 800 mg daily becoming the RP2D in patients with relapsed B-cell malignancies [36]. There is by now substantial precedence of use of umbralisib in upfront therapy of CLL, with the phase 3 UNITY-CLL trial fully accrued.

2.1.6 Acalabrutinib

Acalabrutinib (also known as ACP-196 and/or Calquence®) is a selective, irreversible small molecule inhibitor of BTK currently under clinical investigation. Acalabrutinib is an investigational product. 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). A detailed description of the chemistry, pharmacology, mechanism of action, efficacy, and safety of acalabrutinib is provided in the Investigator Brochure. Acalabrutinib is a next-generation BTK inhibitor that shows higher selectivity for BTK, while simultaneously lacking irreversible inhibition of activities of other kinases such as epidermal growth factor receptor (EGFR), interleukin-2-inducible T-cell kinase (ITK), and T cell X chromosome kinase (Txk), among others [37, 38]. This higher target selectivity is expected to contribute to the favorable safety profile [39]. In the phase 2 ACE-LY-004 trial consisting of 124 patients with MCL, administration of acalabrutinib (100 mg PO twice daily [bid]) was associated with an ORR of 81% (95% CI, 73%-87%), including a CR rate of 40% and a PR rate of 41%. The most common adverse events (AE) were primarily grade 1 or 2, with headache (38%), diarrhea (31%), fatigue (27%), and myalgia (21%). The most common grade 3 or worse AEs were neutropenia (10%), anemia (9%), and pneumonia (5%) [39]. Incidences of grade 3 and above atrial fibrillation and flutter, infection and bleeding complications were low in patients receiving acalabrutinib. Based on these findings, acalabrutinib received FDA approval in August 2017 for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy [40, 41]. Finally, emerging data suggest that the mechanisms of treatment resistance for acalabrutinib are similar to ibrutinib [42].

Thus, acalabrutinib is at least as efficacious as ibrutinib in MCL. However, given that acalabrutinib is a selective inhibitor of BTK, it is expected to have fewer toxicities than ibrutinib.

2.1.7 Ublituximab

Ublituximab (TG-1101) is a glycolengineered chimeric monoclonal antibody engineered to optimally target the human CD20 antigen. Ublituximab targeting of CD20 promotes antibody-dependent cell-mediated cytotoxicity (ADCC) of cells expressing this protein. Notably, ublituximab has a high affinity for FcγRIIIa (CD16) receptors, which is associated with eliciting greater ADCC than targeting by the other CD20 antibodies [43, 44]. Ublituximab targeting of CD20 is also associated with classical activation of the complement pathway (CDC), as well as induction of B-cell apoptosis.

Excluding the three Phase III studies that are being conducted under SPA (UTX-TGR-304, TG1101-RMS301, and TG1101-RMS302) and the three Phase II extension studies (UTX-TGR-204, UTX-TGR-501, and TG1101-RMS201E), as of 10 May 2019, over 1020 subjects have been exposed to ublituximab through ten Phase I or II clinical trials and one Phase III clinical trial (three of which are still enrolling).

Ublituximab exposure in oncology has ranged in dose from 450 mg to 1200 mg, both as induction (weekly infusions x 4 or 6 weeks) and maintenance (monthly through month 6 followed by quarterly). The maximum tolerated dose/exposure has not been established however the Phase II and III dose in oncology settings has been selected at 900 mg/infusion.

In oncology, the following adverse reactions have been observed: Infusion-related reaction was the most frequent drug-related AE in all studies, typically occurring during the first ublituximab infusion. Grade 3-4 neutropenia, rarely associated with a febrile episode, has been reported and usually resolved either spontaneously or in a few days with G-CSF therapy for oncology. Drug-related Grade 3 thrombocytopenia and worsening from slight to Grade 3-4 pancytopenia has also been reported although minimal. Asymptomatic, isolated, and transient Grade 2-3 drug-related elevated liver enzymes have been observed as well. Most subjects who experience ublituximab related adverse events may have a dose interruption or delay, and usually resume at the original dose.

A review of the adverse events observed to date for ublituximab indicates that several risks are associated with ublituximab infusions and treatment. Nevertheless, the risks associated with ublituximab therapy appear to be consistent with those associated with existing CD20-directed therapy, and the proof of clinical activity of single agent ublituximab has been demonstrated in relapsed/refractory subjects with CLL and NHL, and subjects with MS.

The potential benefits of ublituximab in subjects with CD20-positive B-cell lymphoproliferative disorders have been suggested from several nonclinical studies demonstrating a better *in vitro* ADCC activity compared with both rituximab [43] and ofatumumab. Moreover, the difference of activity was more pronounced when target cells expressed few CD20 molecules. Data from the completed Phase I study showed significant circulating lymphocyte depletion of up to 98% in subjects with relapsed/refractory CLL after at least one prior course of fludarabine. Moreover, 3 out of 18 (17%) evaluable subjects presented with a partial response after a 4-dose regimen of ublituximab and 5 out of 11 (45%) evaluable subjects after an 8-dose regimen.
The second single agent ublituximab Phase I study TGTX-1101-101 in subjects with relapsed/refractory B-cell lymphoma was completed. Of the 31 out of 35 subjects evaluable for efficacy, 14 out of 31 (45%) subjects have achieved an objective response. Responses were observed in both rituximab relapsed and rituximab refractory subjects, including subjects who had been exposed to several lines of rituximab therapy. The median time to response was 1.8 (range 1–11) months, with a median duration of response of 9.2 (range 1–24) months. Median PFS for all evaluable subjects was 7.7 (95% CI:4.5–16.2) months with a median PFS for the rituximab-refractory subjects of 4.7 (95% CI:1.9–16.2) months. Rapid and profound lymphocyte depletion was observed in subjects with the median time to a >50% reduction of 1 day (O'Connor et al., ASCO and EHA, 2014).

Based on the favorable safety profile reported with single agent ublituximab, subsequent combination studies were undertaken. Ublituximab has been evaluated in combination with lenalidomide, with ibrutinib, with bendamustine, with pembrolizumab, with venetoclax, and/or with umbralisib (TGR-1202). To date, ublituximab in combination with these agents has been well tolerated.

The combinations of ublituximab with ibrutinib, and of ublituximab with umbralisib have particularly displayed robust clinical activity in subjects with CLL, for which registration directed studies are ongoing.

We hypothesize that acalabrutinib in combination with the second-generation CD20-targeting antibody ublituximab and selective PI3Kδ inhibitor umbralisib (AU2) will demonstrate high efficacy and tolerability as frontline therapy in older/unfit MCL patients, and in patients with TP53 aberrations or complex karyotype.

2.2 Rationale for correlative studies

2.2.1 Minimal residual disease (MRD)

MRD is defined as the minimal traceable persistence of lymphoma cells following treatment. The ability to detect MRD positivity can facilitate better stratification of patients at higher risk of recurrence, as well as further aid in predicting upcoming clinical relapse [45]. This allows for better tailoring of treatments and helps to prevent or delay overt disease progression. Although numerous methods to monitor MRD have been reported, the allele-specific oligonucleotide (ASO) quantitative polymerase chain reaction (qPCR) method is currently the most sensitive and most commonly used approach. This approach is designed to detect immunoglobulin heavy chain (IGH) gene rearrangements, which are present in about 80-90% of MCLs [45]. While considered the gold standard for MRD assessment in MCL, ASO-qPCR requires design and testing of individual primers that are specific to the clonal rearrangement of the IGH gene, BCL-1/IGH rearrangement, or t(11;14) translocation. With the IGH-based marker present in approximately 70% of cases and a BCL-1/IGH marker observed in approximately 35–40% of cases (with some overlap between these two), an estimated 10–15% of MCL patients lack reliable markers for MRD [45, 46] To overcome these challenges, samples from participants may be evaluated using next-generation sequencing (NGS). This approach does not rely on specific primers and can also aid in identification of novel molecular markers associated with MCL [45].

2.2.2 Mechanisms of resistance

Increasing our understanding of the molecular mechanisms driving MCL is crucial to the development of new treatment strategies and identifying novel therapeutic targets. In addition to primary oncogenic drivers such as overexpression of cyclin D1 via t(11;14)(q13;q32) translocations, several other aberrant gene expression signatures are also associated with driving MCL [47]. BCR signaling is notable among these as it elicits several other downstream kinases (e.g., SYK, LYN, BTK) that are associated with promoting cell survival and facilitating increased resistance to treatments [48]. Likewise, aberrant activation of the NF-κB pathway is also associated with promoting increased resistance to treatment [47]. In this study, NGS will be used to evaluate gene expression (and mutations) from participant samples derived prior to and at time of relapse. Examination of cancer samples at these crucial time points will allow for novel identification of gene profiles that can be correlated with overall treatment outcomes; particularly, in the development of predictive markers of shortened PFS and therapy resistance.

2.3 Overview and Rationale of Study Design

This is a phase 2 study of BTK inhibitor acalabrutinib and PI3Kδ umbralisib in combination with ublituximab (AU2) in treatment-naïve MCL patients.

Patients with previously untreated MCL ≥ 65 years; or ≥ 50 years and deemed ineligible for aggressive induction therapy or autologous stem cell transplant by the investigator, or unwilling to undergo such therapy; or ≥ 18 years with documented del(17p), or *TP53* mutation, or complex karyotype (CK) will be enrolled.

As noted in the introduction, older patients with MCL do not have curative options, and current standard chemo-immunotherapy regimens (i.e., BR) are associated with a PFS of <4 years and significant toxicities. Furthermore, chemo-immunotherapy regimens are ineffective in patients high-risk MCL (*TP53* aberration and/or CK).

Participants will receive 6 cycles of Induction therapy (1 Cycle = 28 days) using the approved standard dose of acalabrutinib (100 mg PO, twice daily), and a previously demonstrated safe dose of umbralisib (800 mg PO, once

daily, see schedule below) and ublituximab (900 mg IV, on Day 1, Day 8 and Day 15 of the first cycle, and Day 1 of each cycle afterward).

Umbralisib will be administered daily on days 1-14 during cycle 1, followed by daily on days 1-7 with subsequent cycles. This intermitted dosing has been successfully employed with other PI3K inhibitors (ME-401; TIDAL study) and was associated with improved toxicity profile without a compromise in efficacy. This approach is particularly attractive in patients with previously untreated MCL who have an intact immune system and thus are at an increased risk of immune-mediated toxicities with PI3K inhibitors.

Maintenance therapy with anti-CD20 targeting antibodies has become standard approach post-induction in MCL, leading to improved OS [49, 50].

Participants with stable disease or better response at the end of Induction therapy will then receive 19 cycles of Maintenance therapy with the 3 agents, during which ublituximab (900 mg IV) will only be administered every 2 cycles.

Participants may continue therapy with acalabrutinib beyond 25 cycles of protocol therapy at the treating physician's discretion.

The study will use a Simon's optimal two-stage design to evaluate the CR rate of the AU2 induction therapy. The first stage will accrue 9 patients. If there are 2 or fewer CR among 9 patients, the accrual will be terminated; if there are 2+ CR, the accrual will continue to second stage for a total of 24 patients. The study will require 10 or more CR in 24 patients to consider AU2 promising.

3.0 ELIGIBILITY CRITERIA

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

Participants must meet all of the following criteria on screening examination to be eligible to participate in the study:

3.1 Inclusion Criteria

Informed Consent and Willingness to Participate

__1. Documented informed consent of the participant and/or legally authorized representative.

- Assent, when appropriate, will be obtained per institutional guidelines

Nature of Illness and Illness Related Criteria

__2. Histologically confirmed mantle cell lymphoma with documentation of monoclonal CD20+ B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1.

__3. Age ≥ 65 years; or ≥ 50 years and deemed ineligible for aggressive induction therapy or autologous stem cell transplant by the investigator, or unwilling to undergo aggressive induction; or ≥ 18 years with documented del(17p), or *TP53* mutation, or complex karyotype (CK) by cytogenetics and/or FISH studies.

__4. Requiring treatment for MCL, and for which no prior systemic anticancer therapies have been received (local radiotherapy not exceeding a total dose of 20 Gy at least 2 weeks prior the first dose of study therapy is allowed).

__5. Measurable disease by CT or PET/CT scan with one or more sites of disease ≥ 1.5 cm in longest dimension (including splenomegaly), or bone marrow involvement with or without malignant lymphocytosis.

__6. ECOG ≤ 2 (Appendix A).

Clinical Laboratory and Organ Function Criteria

__7. **Without bone marrow involvement**: ANC ≥ 1000/mm^3 **With bone marrow involvement**: ANC ≥ 500/mm^3 **NOTE:** Growth factor is not permitted within 7 days of ANC assessment unless cytopenia is secondary to disease involvement.	ANC:	Date:
__8. **Without bone marrow involvement**: Platelets ≥ 75,000/mm^3 **With bone marrow involvement**: Platelets ≥ 30,000/mm^3 **NOTE:** Platelet transfusions are not permitted within 7 days of platelet assessment unless cytopenia is secondary to disease involvement.	Plts:	Date:
__9. Total bilirubin ≤ 1.5 X ULN or ≤ 3X ULN for Gilbert's disease.	ULN: Bil:	Date:
__10. AST ≤ 2.5 x ULN	ULN: AST:	Date:
__11. ALT ≤ 2.5 x ULN	ULN: ALT:	Date:

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__12. Creatinine clearance of ≥ 30 mL/min per 24 hour urine test or the Cockcroft-Gault formula or $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$ (x 0.85 for females) **Or** $\text{CrCl (mL/min)} = \frac{(140\text{-age}) \times \text{actual body weight (kg)}}{0.8136 \times \text{serum creatinine (umol/L)}}$ (x 0.85 for females)	Serum Cr: Cr Clearance:	Date:
__13. **If not receiving anticoagulants**: International Normalized Ratio (INR) OR Prothrombin (PT) ≤ 1.5 x ULN **If on anticoagulant therapy**: PT must be within therapeutic range of intended use of anticoagulants	ULN: INR: PT:	Date:
__14. **If not receiving anticoagulants**: Activated Partial Thromboplastin Time (aPTT) ≤ 1.5 x ULN **If on anticoagulant therapy**: aPTT must be within therapeutic range of intended use of anticoagulants	ULN: aPTT:	Date:
__15. Left ventricular ejection fraction (LVEF) ≥ 40%	LVEF:	Date:
__16. **Women of childbearing potential (WOCBP)**: negative serum pregnancy test	Serum:	Date:

Contraception

__17. Agreement by females **and** males of childbearing potential* to use a highly effective method of birth control or abstain from heterosexual activity for the course of the study through at least 2 days after the last dose of acalabrutinib for females, and at least 4 months after the last dose of ublituximab or umbralisib, whichever comes later, for both men and women. Highly effective methods of birth control are defined in Appendix K.

* Childbearing potential defined as not being surgically sterilized (men and women) or have not been free from menses for > 1 year (women only).

3.2 Exclusion Criteria

Prior and concomitant therapies

__1. Chronic use of corticosteroids ≥20 mg/day (short-term use of steroids <14 days is allowed).

__2. Major surgical procedure within 28 days of start of protocol therapy. 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.

__3. Known history of hypersensitivity or anaphylaxis to study drug(s) including active product or excipient components

__4. Concurrent participation in another therapeutic clinical trial.

Other illnesses or conditions

__5. Subjects for whom the goal of therapy is tumor debulking before stem cell transplant.

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__6. History of prior malignancy. Exceptions include malignancy treated with curative intent and no known active disease present for ≥ 2 years prior to initiation of protocol therapy; adequately treated non-melanoma skin cancer or lentigo maligna (melanoma in situ) without evidence of disease; adequately treated in situ carcinomas (e.g., cervical, esophageal, etc.) without evidence of disease; asymptomatic prostate cancer managed with "watch and wait" strategy.

__7. Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).

__8. Requires treatment with proton pump inhibitors (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Subjects receiving proton pump inhibitors who switch to H2-receptor antagonists or antacids are eligible for enrollment to this study.

__9. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.

__10. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists.

__11. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.

__12. Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.

__13. Known bleeding disorders (e.g., von Willebrand's disease or hemophilia).

__14. History of significant cerebrovascular disease/event, including stroke, myocardial infarction or intracranial hemorrhage, within 6 months prior to start of protocol therapy.

__15. Known active central nervous system (CNS) involvement by lymphoma, including leptomeningeal involvement.

__16. Clinically significant cardiovascular disease such as symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class III or IV cardiac disease as defined by the New York Heart Association Functional Classification. Note: Subjects with controlled, asymptomatic atrial fibrillation can enroll on study. See Appendix B.

__17. Unstable angina (angina symptoms at rest), new-onset angina (begun within the last 6 months).

__18. History of or current progressive multifocal leukoencephalopathy (PML).

__19. Inability to swallow and retain an oral medication.

__20. Clinically significant uncontrolled illness, including active infection requiring antibiotics.

__21. Live virus vaccines within 4 weeks of start of protocol therapy or planned administration of live virus vaccines during ublituximab therapy.

__22. Evidence of chronic active Hepatitis B (HBV, not including patients with prior hepatitis B vaccination; or positive serum Hepatitis B antibody) or chronic active Hepatitis C infection (HCV), or active cytomegalovirus (CMV). If HBc antibody is positive, the subject must be evaluated for the presence of HBV DNA by PCR. If HCV antibody is positive, the subject must be evaluated for the presence of HCV RNA by PCR. (See Appendix J: Hepatitis B serologic test results). If the subject is CMV IgG or CMV IgM positive, the subject must be evaluated for the presence of CMV DNA by PCR. Subjects with positive HBc antibody and negative HBV DNA by PCR are eligible. Subjects with positive HCV antibody and negative HCV RNA by PCR are eligible. Subjects who are CMV IgG or CMV IgM positive but who are CMV DNA negative by PCR are eligible. Patients with a prior known history of hepatitis B and those with a positive anti-HBc with negative HBsAg at screening must be able to receive antiviral agents effective against hepatitis B.

__23. Known history of human immunodeficiency virus (HIV) infection.

Patient MRN (COH Only)	Patient Initials (F, M, L):
Institution:	

__24. *Females only*: Pregnant or breastfeeding

__25. Any other condition that would, in the Investigator's judgment, contraindicate the patient's participation in the clinical study due to safety concerns with clinical study procedures.

Noncompliance

__26. Prospective participants who, in the opinion of the investigator, may not be able to comply with all study procedures (including compliance issues related to feasibility/logistics).

Eligibility Confirmed* by (Choose as applicable):	**Print Name**	**Signature**	**Date**
☐ Site PI			
☐ Authorized study MD			
☐ Study Nurse			
☐ Study CRA/ CRC			
☐ Other:_____			
*Eligibility should be confirmed per institutional policies.			

4.0 PARTICIPANT ENROLLMENT

NOTE: Sites must meet activation requirements prior to enrolling participants.

4.1 Pre-Enrollment Informed Consent and Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility will be done only after obtaining written informed consent. Studies or procedures that are performed for clinical indications (not exclusively to determine study eligibility) may be used for baseline values and/or to determine pre-eligibility, even if the studies were done before informed consent was obtained.

The informed consent process is to be fully documented (see Section 17.4), and the prospective participant must receive a copy of the signed informed consent document. Screening procedures are listed in Section 10.0 (Study Calendar).

4.2 Participant Enrollment

4.2.1 COH DCC Availability and Contact Information

Eligible participants will be registered on the study centrally by the Data Coordinating Center (DCC) at City of Hope.

DCC staff are available **between the hours of 8.00 am and 5.00 pm PST, Monday through Friday (except holidays)**.

- E-mail: DCC@coh.org

4.2.2 Slot verification and reservation

A designated study team member should email the DCC to verify current slot availability, and to reserve a slot for a specific prospective subject (provide DCC with subject initials), including a tentative treatment date. Slots can only be held for a limited time, at the discretion of the study PI.

The DCC should be notified of cancellations of prospective participants holding slots as soon as possible.

4.2.3 Registration Process

Allow up to 24 hours for the DCC to review eligibility. To register a participant the subsequent procedure is to be followed:

1. The study team should contact the DCC via email to provide notification regarding the pending registration and communicate desired timeline of the registration, especially if it must be completed promptly to meet the registration window.
2. The study team will email a **Complete Registration Packet** to the DCC, which consists of a copy of the following documents:
    - Registration Cover Sheet (Appendix D)
    - Completed eligibility checklist (printed from Section 3.0 of the protocol) with required signature(s)
    - Source documents that support all eligibility criteria listed in the eligibility checklist
    - Signed Informed Consent
    - Signed HIPAA authorization form (if separate from informed consent)
    - Signed subject's bill of Rights (California only)
3. In some cases, the DCC may request additional documentation prior to registration. Please refer to the Work Instruction – Reviewing Packets and Registering Subjects for more information. A copy of this work instruction can be provided by the DCC, upon request.
4. When all source documents are received, the DCC will review to verify eligibility, working with the study team to resolve any missing required source elements. Any missing documents may delay review and

registration. A participant failing to meet all protocol eligibility requirements will not be registered and the study team will be immediately notified.

5. Once eligibility is confirmed, the DCC will send a Confirmation of Registration Form and signed Eligibility Checklist, including the Subject Study Number and cohort assignment to:
    - The study team: Site Lead Investigator, treating physician/ sub-investigator, protocol nurse, CRC and pharmacy (as needed).
    - The COH Study PI and COH study team designees (including but not limited to study monitor(s) and statistician(s)).
6. Upon receipt of the Confirmation of Registration Form, COH study team will register the patient in OnCore. The DCC will register non-COH patients in OnCore.

4.3 Screen Failures and Registered Participants Who Do Not begin Study Treatment

Notify the DCC immediately if the participant screen fails after registration or if the participant does not start treatment.

For non-COH sites, the reason for screen failure will be documented in the registration coversheet (Appendix D) and submitted to the DCC.

Issues that would cause treatment delays should be discussed with the Study Principal Investigator.

5.0 TREATMENT PROGRAM

5.1 Treatment Program Overview

This is a multicenter, open-label, single cohort, phase 2 study of BTK inhibitor acalabrutinib and PI3Kδ umbralisib in combination with ublituximab (AU2) for patients with previously untreated mantle cell lymphoma (MCL).

The trial consists of an Induction phase (6 cycles), followed by a Maintenance phase (19 cycles) for a total of 25 cycles of protocol therapy. Participants with stable disease (SD) or better response at the end of Induction will be eligible to proceed to Maintenance. At the end of Maintenance, participants may be allowed to continue therapy with acalabrutinib per treating physician's decision. For both Induction and Maintenance, each cycle will be 28 days.

Please refer to the Study Schema for additional details.

Participants who end protocol therapy will undergo follow-up (Section 5.7). Windows for all assessments and treatments are detailed in Section 10.

5.2 Cycle Definition

In the absence of a delay due to toxicity, each treatment cycle lasts 28 days with a ± 3 day window during Induction and 28 days with a ± 7 day window during Maintenance.

During the Induction phase (Cycles 1-6), Day 1 of each cycle is defined as the first day of administration of ublituximab.

During the Maintenance phase (Cycles 7-25), ublituximab is administered every 2 cycles (every 8 weeks) starting on Day 1 of Cycle 8, and each cycle is defined as 28 days.

5.3 Treatment Plan

The treatment regimen and schedule are as follows:

Induction phase:

Agent	Dose	Route	Schedule
Ublituximab	900 mg	IV	**Cycle 1**: Day 1, Day 8, and Day 15 **Cycles 2-6:** Day 1
Acalabrutinib	100 mg - Twice daily	Orally	Every day of each cycle
Umbralisib	800 mg - Once daily	Orally	**Cycle 1:** Days 1-14 **Cycles 2-6:** Days 1-7

Maintenance phase:

Agent	Dose	Route	Schedule
Ublituximab	900 mg	IV	**Every 2 cycles (Cycles 8, 10, 12, 14, 16, 18, 20, 22, 24)**, on Day 1, starting on Day 1 of Cycle 8
Acalabrutinib	100 mg - Twice daily	Orally	Every day of each cycle
Umbralisib	800 mg - Once daily	Orally	Days 1-7 of each cycle

Treatment will be administered on an *out-patient* basis (in-patient administration is allowed if deemed necessary by the Investigator).

5.4 Agent Administration

5.4.1 Required Premedications

- Patients should be premedicated prior to all ublituximab infusions. Pre-medications should include an antihistamine (diphenhydramine 50 mg or equivalent), and a corticosteroid (dexamethasone 10-20 mg or equivalent).
    - If pre-medications are administered IV: start the ublituximab infusion 30 minutes after conclusion of the last pre-medication infusion
    - If pre-medications are administered orally: start the ublituximab infusion 45-60 minutes after ingestion of the oral pre-medications
    - Adjusting antihistamine and corticosteroid doses, adjusting the timing of administration and/or additional pre-medications may be used at investigator discretion for additional prophylaxis against infusion related reactions
    - Use of oral acetaminophen 650 mg (or equivalent) should be restricted to patients who experience fever or pyrexia during week 1 dosing, or as clinically warranted
- After cycle 6, if use of a corticosteroid is of clinical concern, please contact the Principal Investigator.
- Use of anti-pneumocystis and antiviral prophylaxis is required for subjects receiving umbralisib. Refer to Section 5.10 for guidelines.
- Prophylaxis with an antiviral agent effective against hepatitis B is required in subjects with a prior known history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening.
  Promptly consult clinicians with an expertise in managing subjects with a prior history of hepatitis B regarding monitoring and consideration of options for hepatitis B antiviral therapy for prophylaxis/ treatment.

5.4.2 Ublituximab

Ublituximab will be administered as an intravenous infusion through a dedicated line. **Do not** administer as an IV push or bolus. Do not mix ublituximab with, or administer as an infusion with, other medicinal products.

The first infusion of ublituximab (Cycle 1, Day 1) will be administered over a target period of 4 hours. Ublituximab infusions on Cycle 1, Days 8 and 15 will be administered over a target period of 3 hours. For all subsequent ublituximab infusions, infusion time may be reduced to approximately 90 minutes.

Since infusion-related hypotension may occur, consider holding antihypertensive medications 12 to 24 hours prior to and throughout infusion of ublituximab. Decision to withhold antihypertensive medication is at investigator discretion.

Medication and resuscitation equipment must be available per institutional guidelines prior to ublituximab administration for the emergency management of potential anaphylactic reactions.

5.4.3 Acalabrutinib

Acalabrutinib will be administered as a 100 mg tablet taken orally approximately every 12 hours. The tablets should be swallowed intact with water without being crushed, dissolved, broken, or chewed. 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 participant 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.

As acalabrutinib is metabolized by CYP3A, participants should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer). Otherwise, subjects should maintain their regular diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.4.4 Umbralisib

Umbralisib should be taken at approximately the same time each day within 30 minutes of starting a meal. Subjects should be instructed to swallow the tablets whole and should not chew or crush them.

If a dose of umbralisib is missed, it should be taken as soon as possible on the same day. If it is missed for a period of greater than 12 hours, it should not be replaced. If vomiting occurs, no attempt should be made to replace the vomited dose.

5.5 Assessments and Special Monitoring

For a detailed list of all study procedures including timing and windows, see Section 10.

Note: Initiate a new cycle after all procedures/safety assessments have been completed.

5.5.1 Special Monitoring

- *Infusion reactions*
  - Infusion related reactions including severe reactions have been reported with ublituximab administration.
  - If such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions.
  - Refer to Section 5.10 for management guidelines.
- *Infections*

- Participants receiving umbralisib are at risk for infection, including pneumocystis, herpes, aspergillus, cytomegalovirus (CMV), and respiratory syncytial virus (RSV), as well as various bacterial infections. Use of anti-pneumocystis and antiviral prophylaxis is required for subjects receiving umbralisib.
- Participants receiving acalabrutinib are at risk for infection (bacterial, viral, or fungal).
- Refer to Section 5.10 for guidelines.

- *Tumor lysis syndrome (TLS)*
  - A TLS laboratory assessment (serum chemistry) will be performed during cycle 1 (see Section 10.0).
  - Refer to Section 5.10 for guidelines.
- *Hepatitis B reactivation*
  - In addition to mandatory prophylaxis with an antiviral agent effective against hepatitis B (Section 5.4.1), monitor subjects with a prior history of hepatitis B and those with a positive anti-HBc with negative HBsAg at screening closely as clinically indicated based on liver tests and any observed signs/ symptoms such as jaundice, abdominal pain, dyspepsia, dark-colored urine often accompanied by lighter-than-normal colored stools, nausea, vomiting or fatigue.
  - Refer to Section 5.10 for guidelines when there is an increase in liver enzymes while on study.

5.6 Duration of Therapy and Criteria for Removal from Protocol Therapy

Participants will receive protocol therapy until one of the below criteria are met:

- Confirmed Disease progression per 2014 Lugano classification
- Completed protocol therapy
- Participant is deemed intolerant to protocol therapy because of toxicity, despite dose modification/ delay
  - **Note:** If one agent is discontinued due to toxicity, then the participant may continue to receive the other study agents
- General or specific changes in the patient's condition which render the patient unacceptable for further treatment in the judgment of the investigator
- Withdrawal of consent for further protocol therapy (See Section 17.5)

Once participants meet criteria for removal from protocol therapy, the participant should then proceed to follow-up assessments (Section 5.7).

Documentation of the reason for discontinuing protocol therapy and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.7 Follow-Up

Following completion of protocol therapy, participants will enter follow-up.

Follow-up is comprised of:

- **Safety Follow-up**- 30 days post-last dose of protocol therapy.
  - **Note** the period for safety follow-up will be extended until stabilization or resolution for all reportable AEs (per the agreement of the Study PI) and accompanying follow-up safety report.
- **Response Follow-up**- for those who have yet to have disease progression and have not initiated a new anti-lymphoma therapy.

- **Survival Follow-up**- for all participants who have progressed OR completed Active Response Follow-Up OR initiated a new anti-lymphoma therapy. It will entail (a) Disease status (for those who have yet to progress) (b) Vital status (all participants).

Assessment time points and windows are detailed in Section 10.

Note: if a participant continues therapy beyond 25 cycles with acalabrutinib for a total of 6 years of protocol therapy, the participant will only proceed with the safety follow-up visit; there will be no response/survival follow-up.

5.8 Duration of Study Participation

Study participation may conclude when any of the following occur:

- Completion of study activities (treatment and follow-up)
- Withdrawal of consent (See Section 17.5)
- Patient decided to proceed with autologous transplantation
- Participant is lost to follow-up. All attempts to contact the participant must be documented.
- At the discretion of the investigator for safety, behavioral, study termination or administrative reasons

Documentation of the reason for discontinuing study participation and the date effective should be made in the Electronic Health Record/medical record and appropriate eCRF.

The COH DCC and the Study PI should be promptly notified of the change in participant status.

5.9 Prohibited and Concomitant Therapies/Medications

5.9.1 Allowed concomitant medications

If concomitant therapy must be added or changed, including over-the-counter medications or alternative therapies, the reason and name of the agent/therapy should be recorded in the eCRF and documented in the Electronic Health Record/medical record.

Concurrent glucocorticoid therapy as long as started for at least 7 days prior to study entry (<20 mg per day of prednisone or equivalent) is allowed as clinically warranted.

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

5.9.2 Precautionary and Prohibited medications/ therapies

This is not intended to be an exhaustive list; the investigator should consider each concomitant medication and potential for drug-drug interactions.

- Prohibited from **Day 1 of protocol therapy until end of protocol therapy** (last day of study agent or decision to end study agent(s) whichever occurs later).
  - Herbal and natural remedies
  - Other investigational therapy
  - Other concurrent systemic anti-cancer therapy: chemotherapy, biological response modifiers, hormone therapy, surgery, palliative radiation therapy, or immunotherapy.
  - Live vaccines.
  - Systemic corticosteroid therapy at a daily dose ≥20 mg prednisone or equivalent. Patients may be using topical or inhaled corticosteroids.

- **Guidelines for co-administration with acalabrutinib:**
  - Warfarin or equivalent Vitamin K antagonists are prohibited in patients on acalabrutinib as they may increase the risk of hemorrhage.
  - Co-administration of acalabrutinib and a proton pump inhibitor should be avoided.
  - Co-administration of acalabrutinib with a strong or moderate CYP3A inhibitor may increase acalabrutinib plasma concentrations resulting in increased toxicity. Use of strong or moderate CYP3A inhibitors should be avoided.
  - Conversely, co-administration of acalabrutinib with a strong CYP3A inducer should be avoided as this may decrease acalabrutinib concentrations.

Refer to Appendix E for examples.

Refer to Section 8.2.6 for appropriate acalabrutinib dose adjustments if co-administration with a CYP3A inhibitor or inducer is required.

If treatment with a gastric reducing agent is required, consider using a H2-receptor antagonist (e.g. famotidine) or an antacid (e.g. calcium carbonate).

- If receiving antacids, acalabrutinib dosing should be separated by at least 2 hours.
- If receiving H2-Receptor Antagonists, acalabrutinib should be taken 2 hours before taking a H2-receptor antagonist.

5.10 Supportive care

With the exception of prohibited therapies (Section 5.9.2), participants should receive prophylactic or supportive as clinically indicated per institutional policies.

Blood products and growth factors

- *Platelet and/or red blood cell supportive growth factors or transfusions*
  - Permitted when applicable
- *Colony stimulating factors (CSFs)*
  - Per investigator's discretion and institutional practice.

Anti-emetic prophylaxis

- Routine anti-emetic prophylaxis regimen should be administered per institutional standards.

Corticosteroids

- *Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption)*
  - Permitted
- *Systemic corticosteroids*
  - permitted if <20 mg/day prednisone or equivalent.
- *Brief course of corticosteroids (< 14 days)*
  - Permitted for prophylaxis (e.g. contrast dye allergy)
  - Permitted for treatment of non-autoimmune conditions (e.g, delayed-type hypersensitivity reaction caused by contact allergen)

Management of infusion related reactions

Symptomatic infusion reactions, despite premedication, may be treated at the discretion of the treating physician, including but not limited to: oral acetaminophen 650 mg (or equivalent), corticosteroids, antihistamines, oxygen, and bronchodilators.
If an infusion related reaction (IRR) is observed at any time during the ublituximab treatment, the treating investigator may reduce the infusion rate at their discretion.

The following are recommended infusion rate reduction/delay guidelines for patients who experience severe infusion related reactions that result in treatment interruption. Final decision for infusion rate reduction/delay or discontinuation resides with the treating investigator.

- **1st or 2nd Infusion Interruption:**

Hold infusion and closely monitor subject. Institute symptomatic medical management until resolution of IRR symptoms.
Following the judgment of the Investigator and, provided the patient is stable, the infusion may be resumed at no more than half the previous rate.
If the patient does not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment cycle dose (see Infusion Rate Recommendations for Ublituximab Administration below).

- **3rd Infusion Interruption (same day):**

Discontinue infusion for that day – monitor patient for resolution of all symptoms. Patient should have all vital signs completed as well as any other standard of care procedures completed as warranted by the Investigator prior to release of patient from study site.
Any remaining diluted investigational product should be discarded.

If an ublituximab infusion is discontinued, the next scheduled dose should be administered according to the protocol dosing schedule.

Infusion Rate Recommendations for Ublituximab Administration:

Cycle 1 Day 1 infusion over 4 hours

Cycle 1	Ublituximab Dose	Total volume to be infused	Infusion rate			
			T0 to T30'	T30' to T1H	T1H to T2H	T2H to T4H
Day 1	900 mg	500 mL	10 mL/H	20 mL/H	85 mL/H	200 mL/H

Cycle 1 Day 8 & 15 infusions over 3 hours

Ublituximab Dose	Total volume to be infused	Infusion rate		
		T0 to T1H	T1H to T2H	T2H to T3H
900 mg	500 mL	50 mL/H	150 mL/H	300 mL/H

Cycle 2 and remaining infusions over 90 minutes

Ublituximab Dose	Total volume to be infused	Infusion rate	
		T0 to T30min	T30min to T90min
900 mg	500 mL	200 mL/H	400 mL/H

Moderate CYP3A4/5 inhibitors or inducers, and proton pump inhibitors

- Closely monitor for AEs when administered concomitantly with acalabrutinib. Refer to Appendix E for examples.

Prophylaxis and management of infections

- Subjects receiving umbralisib are required to start prophylactic treatment with pneumocystis jiroveci pneumonia (PJP) and antiviral therapy on or prior to Day 1 of Cycle 1. Choice of PJP and anti-viral

prophylaxis is per investigator discretion and institutional standard of care, with the following as recommendations:

- Anti-viral Prophylaxis: Valtrex 500 mg daily or Acyclovir 400 mg BID or equivalent.
- PJP Prophylaxis: Dapsone 100 mg daily or Bactrim DS 1 tab M-W-F or equivalent.
- Final choice of PJP and anti-viral prophylactic therapy is per investigator discretion.
- If anti-viral or anti-bacterial prophylaxis is not tolerated, alternate to a different prophylactic agent, reduce the dose or modify the schedule for the prophylactic agent, or discontinue prophylaxis at investigator discretion.

- For patients receiving acalabrutinib, consider prophylaxis in patients who are at increased risk for opportunistic infections per institutional standards.

- Participants with documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the Investigator, per institutional standards.

Tumor lysis syndrome (TLS) prophylaxis and management

- Performed per institutional standards
  For patients that are considered at risk for TLS [e.g. bulky disease (a single mass with a diameter > 10cm), or WBC count>50,000/µL, or high uric acid (≥ 7 mg/dL) at baseline], allopurinol (300 mg po daily, dose adjusted per renal function) may be given. If a diagnosis of TLS is established, monitoring and multi-disciplinary management will be per institutional practice.

Hepatitis B reactivation

- For patients with a prior history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening who experience an increase in liver enzymes while on study, hold ublituximab immediately and assess for active hepatitis B infection.
  - If negative for hepatitis B, ublituximab may be resumed.
  - If reactivation of hepatitis B is confirmed, institute hepatitis B antiviral treatment. Ublituximab may be resumed at investigator discretion once hepatitis B infection has resolved, with continued monitoring as described in Section 5.5.1.

6.0 ANTICIPATED ADVERSE EVENTS

6.1 Ublituximab

The Investigator's Brochure (IB) is the primary source for safety information. The ublituximab IB includes a summary of adverse event data and discussion on potential risks that have been observed or may be predicted to occur with this study drug. Refer to the most recent IB, which is updated periodically, for current information on ublituximab.

The following adverse events were observed in subjects treated with single agent ublituximab and were considered at least possibly related to study medication. The preliminary safety data as of May 1, 2018 is provided for a total of 117 subjects exposed to single agent ublituximab with a maximum follow up of 2+ years.

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** neutropenia, thrombocytopenia
- **General Disorders and Administration Site Conditions:** pyrexia
- **Injury, Poisoning and Procedural Complications:** infusion related reaction
- **Nervous System Disorders:** headache

Common (≥ 2 - < 10%)

- **Blood and Lymphatic System Disorders:** anemia, pancytopenia
- **Gastrointestinal Disorders:** diarrhea, abdominal pain, nausea, oral pruritus
- **General Disorders and Administration Site Conditions:** fatigue, asthenia, chills, oedema peripheral, pain
- **Hepatobiliary Disorders:** cytolytic hepatitis
- **Infections and Infestations:** herpes zoster
- **Investigations:** aspartate aminotransferase increased, blood bilirubin increased, gamma-glutamyltransferase increased
- **Musculoskeletal and Connective Tissue Disorders:** muscular weakness
- **Nervous System Disorders:** dysgeusia
- **Respiratory, Thoracic and Mediastinal Disorders:** throat irritation, throat tightness
- **Skin and Subcutaneous Tissue Disorders:** pruritus, hyperhidrosis
- **Vascular Disorders:** hypertension

Amendment dated 12-30-20 added the potential risk of hepatitis B reactivation as a rare (less than 0.1%) but serious risk with ublituximab.

6.2 Acalabrutinib

Please refer to the investigator brochure and package insert for additional details.

Information provided in Tables 6.2.1 and 6.2.2 is based on Acalabrutinib IB V 10.0 (Feb 2021).

Adverse drug reactions observed in clinical studies with 1079 subjects receiving acalabrutinib monotherapy in hematological malignancies are summarized in Table 6.2.1. The median duration of exposure to acalabrutinib monotherapy treatment across the pooled dataset was 28.5 months (range, 0.0 to 65.3 months).

Table 6.2.1: Adverse drug reactions for acalabrutinib

Body System	Adverse Reaction	No. (%) of Subjects (n=1079)	
		All Grades	Grade ≥ 3
Blood and lymphatic system disorders	Leukopenia	202 (18.7)	174 (16.1)
	Neutropenia	187 (17.3)	169 (15.7)
	Anemia	159 (14.7)	84 (7.8)
	Thrombocytopenia	102 (9.5)	52 (4.8)
Cardiac disorders	Atrial fibrillation/flutter	59 (5.5)	15 (1.4)
Gastrointestinal disorders	Diarrhea	407 (37.7)	32 (3.0)
	Nausea	239 (22.2)	12 (1.1)
	Constipation	160 (14.8)	1 (0.1)
	Vomiting	157 (14.6)	9 (0.8)
	Abdominal Pain	151 (14.6)	10 (0.9)
General disorders and administration site conditions	Fatigue	248 (23.0)	19 (1.8)
	Asthenia	64 (5.9)	8 (0.7)
Infections and infestations	Infection	770 (71.4)	217 (20.1)
Metabolism and nutrition disorders	Tumor lysis syndrome*	5 (0.5)	4 (0.4)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	372 (34.5)	22 (2.0)
	Arthralgia	230 (21.3)	8 (0.7)
Neoplasms begnin, malignant and unspecified	Second primary malignancy	160 (14.8)	55 (5.1)
	Non-melanoma skin malignancy	93 (8.6)	8 (0.7)
	SPM excluding non-melanoma skin	81 (7.5)	49 (4.5)
Nervous system disorders	Headache	404 (37.4)	11 (1.0)
	Dizziness	151 (14.0)	2 (0.2)
Respiratory, thoracic and mediastinal disorders	Epistaxis	85 (7.9)	3 (0.3)
Skin and subcutaneous tissue disorders	Bruising	376 (34.8)	0
	Rash	227 (21.0)	6 (0.6)
Vascular disorders	Hemorrhage / Hematoma	158 (14.6)	26 (2.4)

* One case of drug-induced tumor lysis syndrome was observed in the acalabrutinib arm of Study ACE CL 309.

Table 6.2.2 lists all serious adverse drug reactions for acalabrutinib that have occurred more than once in clinical studies. These adverse events are considered "expected" for regulatory purposes. All life-threatening and fatal SADRs are considered unexpected.

Table 6.2.2: Serious adverse drug reactions considered expected for acalabrutinib

Body System	Adverse Reaction	No. (%) of Subjects All Grades (N = 1079) n (%)
Blood and lymphatic system disorders	Anemia	20 (1.9)
	Febrile neutropenia	16 (1.5)
	Neutropenia	2 (0.2)
	Thrombocytopenia	4 (0.4)
Cardiac disorders	Atrial fibrillation	13 (1.2)
Gastrointestinal disorders	Abdominal Pain	12 (1.1)
	Constipation	2 (0.2)
	Diarrhea	9 (0.8)

	Gastrointestinal hemorrhage	4 (0.4)
	Nausea	2 (0.2)
	Vomiting	4 (0.4)
General disorders and administration site conditions	Asthenia	2 (0.2)
	Fatigue	4 (0.4)
Infections and infestations	Acute sinusitis	3 (0.3)
	Aspergillus infection	2 (0.2)
	Bacteremia	2 (0.2)
	Bronchitis	3 (0.3)
	Cellulitis	11 (1.0)
	Clostridium difficile infection	2 (0.2)
	Diverticulitis	4 (0.4)
	Epiglottitis	2 (0.2)
	Gastroenteritis	4 (0.4)
	Gastroenteritis viral	2 (0.2)
	Herpes zoster	3 (0.3)
	Infection	2 (0.2)
	Influenza	6 (0.6)
	Kidney infection	2 (0.2)
	Lower respiratory tract infection	12 (1.1)
	Lung infection	9 (0.8)
	Neutropenic sepsis	3 (0.3)
	Parainfluenzae virus infection	2 (0.2)
	Pharyngitis	2 (0.2)
	Pneumonia	67 (6.2)
	Pneumonia fungal	2 (0.2)
	Pneumonia influenzal	2 (0.2)
	Pneumonia streptococcal	2 (0.2)
	Pseudomonas infection	2 (0.2)
	Respiratory tract infection	10 (0.9)
	Rhinovirus infection	2 (0.2)
	Salmonellosis	2 (0.2)
	Sepsis	18 (1.7)
	Septic shock	4 (0.4)
	Sinusitis	2 (0.2)
	Skin infection	2 (0.2)
	Upper respiratory tract infection	12 (1.1)
	Urinary tract infection	19 (1.8)
	Urosepsis	4 (0.4)
Metabolism and nutrition disorders	Tumor lysis syndrome	3 (0.3)
Musculoskeletal and connective tissue disorders	Back pain	2 (0.2)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Basal cell carcinoma	5 (0.5)
	Glioblastoma multiforme	2 (0.2)
	Lung adenocarcinoma	5 (0.5)
	Malignant melanoma	5 (0.5)
	Metastases to meninges	3 (0.3)
	Myelodysplastic syndrome	3 (0.3)
	Neuroendocrine carcinoma of the skin	2 (0.2)
	Prostate cancer	5 (0.5)

	Prostate cancer metastatic Renal cell carcinoma Squamous cell carcinoma Squamous cell carcinoma of skin	2 (0.2) 3 (0.3) 2 (0.2) 5 (0.5)
Nervous system disorders	Dizziness Hemorrhage intracranial Headache	2 (0.2) 2 (0.2) 2 (0.2)
Vascular disorders	Hematoma	3 (0.3)

Contraindications

No contraindications are known for acalabrutinib.

Warnings and Precautions

Table 6.2.3 summarizes the experience with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator's Brochure.

Table 6.2.3: Important identified risks for acalabrutinib

Important potential risks	Description
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-solid tumors and skin carcinomas, have occurred 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 and Flutter	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.

6.3 Umbralisib

The Investigator's Brochure (IB) is the primary source for safety information. The umbralisib IB includes a summary of adverse event data and discussion on potential risks that have been observed or may be predicted to occur with this study drug. Refer to the most recent IB, which is updated periodically, for current information on umbralisib.

The following adverse events were observed in subjects treated with single agent umbralisib and were considered at least possibly related to study medication. The preliminary safety data as of May 1, 2018 is provided for a total of 136 subjects exposed to single agent umbralisib with a maximum follow up of 5+ years.

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** neutropenia
- **Gastrointestinal Disorders:** nausea, diarrhea, vomiting
- **General Disorders and Administration Site Conditions:** fatigue

Common (≥ 2% - < 10%)

- **Blood and Lymphatic System Disorders:** anemia, thrombocytopenia, leukocytosis, lymphocytosis
- **Ear and Labyrinth Disorders:** tinnitus
- **Eye Disorders:** vision blurred
- **Gastrointestinal Disorders:** constipation, abdominal pain, abdominal distension, dyspepsia, colitis, dry mouth
- **General Disorders and Administration Site Conditions:** pyrexia, edema peripheral
- **Infections and Infestations:** pneumonia, oral candidiasis
- **Injury, Poisoning and Procedural Complications:** contusion
- **Investigations:** weight decreased, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased
- **Metabolism and Nutrition Disorders:** decreased appetite, dehydration, hyperglycemia, hypokalemia, hypophosphatemia

- **Musculoskeletal and Connective Tissue Disorders:** muscle spasms, pain in extremity
- **Nervous System Disorders:** dizziness, headache, dysgeusia, tremor
- **Psychiatric Disorders:** insomnia
- **Respiratory, Thoracic and Mediastinal Disorders:** cough
- **Skin and Subcutaneous Tissue Disorders:** rash maculo-papular, alopecia, night sweats, pruritus, rash

6.4 Ublituximab plus umbralisib

The Investigator's Brochure (IB) is the primary source for safety information. Refer to the most recent IB, which is updated periodically, for current information on ublituximab and umbralisib.

The following adverse events were observed in subjects treated with the combination of ublituximab + umbralisib and were considered at least possibly related to one or both of the study medications. The preliminary safety data as of May 1, 2018 is provided for a total of 75 subjects exposed to ublituximab + umbralisib with a maximum follow up of 3+ years.

Very Common (≥ 10%)

- **Blood and Lymphatic System Disorders:** anemia, neutropenia
- **Gastrointestinal Disorders:** diarrhea, nausea, vomiting
- **General Disorders and Administration Site Conditions:** fatigue
- **Injury, Poisoning and Procedural Complications:** infusion related reaction
- **Metabolism and Nutrition Disorders:** decreased appetite

Common (≥1% - < 10%)

- **Blood and Lymphatic System Disorders:** thrombocytopenia
- **Cardiac Disorders:** cardiac failure congestive
- **Ear and Labyrinth Disorders:** ear congestion, ear discomfort
- **Eye Disorders:** conjunctival pallor, conjunctivitis, corneal edema, vision blurred
- **Gastrointestinal Disorders:** abdominal discomfort, abdominal distension, abdominal pain, constipation, dyspepsia, flatulence, gastrooesophageal reflux disease, haematochezia, salivary hypersecretion, stomatitis
- **General Disorders and Administration Site Conditions:** asthenia, chills, face edema, infusion site pain, local swelling, edema peripheral, pyrexia, systemic inflammatory response syndrome
- **Hepatobiliary Disorders:** hyperbilirubinemia
- **Immune System Disorders:** hypogammaglobulinemia
- **Infections and Infestations:** bronchitis, cellulitis, clostridium difficile colitis, enterocolitis infectious, oral candidiasis, oral herpes, otitis media, pneumonia, pneumonia streptococcal, rhinovirus infection, sepsis, sepsis syndrome, sinusitis, skin infection, upper respiratory tract infection, urinary tract infection
- **Injury, Poisoning and Procedural Complications:** wound
- **Investigations:** alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, computerized tomogram thorax abnormal, immunoglobulins decreased, weight decreased
- **Metabolism and Nutrition Disorders:** dehydration, failure to thrive, hyperglycemia, hyperuricemia, hypokalemia, hypophosphatemia
- **Musculoskeletal and Connective Tissue Disorders:** joint swelling, muscle spasms, muscular weakness, myalgia, pain in extremity
- **Nervous System Disorders:** dizziness, dysgeusia, headache, lethargy, sinus headache, somnolence
- **Psychiatric Disorders:** agitation, anxiety

- **Renal and Urinary Disorders:** micturition urgency, renal failure, renal failure acute
- **Reproductive System and Breast Disorders:** scrotal cyst, semen discoloration
- **Respiratory, Thoracic and Mediastinal Disorders:** choking, cough, dysphonia, dyspnea, epistaxis, hypoxia, oropharyngeal pain, pneumonitis, productive cough, sinus congestion
- **Skin and Subcutaneous Tissue Disorders:** alopecia, cold sweat, dermatitis acneiform, dermatitis bullous, dry skin, ecchymosis, pruritus, rash, maculo-papular, rosacea, urticaria
- **Vascular Disorders:** hypertension

7.0 DOSE DELAY / MODIFICATION GUIDELINES

7.1 Dose Delays/ Modification

- Toxicities will be graded using the NCI CTCAE v 5.0.
- Baseline values are from the last values obtained prior to treatment.
- Both acalabrutinib and umbralisib may be dose reduced for toxicity. If a toxicity occurs, both drugs (as well as ublituximab) may be interrupted until resolution to Grade 1, to baseline, or as noted in Table 7.1.1. Following that, either or both oral agents may be dose reduced based on suspected attribution. General guidelines for recommended dose delays and modifications are provided below.
- No reduction in the dose of ublituximab is permitted. If Grade 4 anaphylaxis is observed at any point during ublituximab treatment, permanently discontinue ublituximab treatment and intervene as per investigator discretion.
- All study drugs may be delayed for a maximum of 8 weeks to allow recovery of toxicities as specified in the tables below.
- If one of the study drugs is discontinued for toxicity, patient may continue therapy with the other study drugs.
- When treatment interruption is required for toxicity, all drugs are held. If ublituximab is suspected to be the primary reason for a recurrent toxic event, it may be discontinued only in consultation with the Study PI.

Table 7.1.1 Recommended Dose Modifications

NCI-CTCAE Grade	Dose Delay and/or Modification
Hematologic Adverse Event	
Neutropenia	
Grade ≤ 2 neutropenia	Provide supportive care as warranted. Maintain current dose and schedule of acalabrutinib. Maintain current dose of umbralisib. If applicable, maintain full dose and schedule of ublituximab.
Grade 3 neutropenia	Provide supportive care as warranted. Maintain current dose and schedule of acalabrutinib. Maintain current dose of umbralisib. For recurrent or persistent Grade 3 neutropenia unresponsive to maximum supportive care:

	• If toxicity is suspected to be related to umbralisib by the investigator (e. g. based on timing of toxicity occurrence during the cycle), reduce umbralisib to next lower dose level. If the lowest dose level of umbralisib is reached, reduce acalabrutinib to the next lower dose level. • If toxicity is suspected to be related to acalabrutinib by the investigator (e. g. based on timing of toxicity occurrence during the cycle), reduce acalabrutinib to the next lower dose level. For recurrences, umbralisib may be dose reduced. If applicable, maintain full dose and schedule of ublituximab.
Grade 4 neutropenia or occurrence of neutropenic fever or infection	Provide supportive care as warranted. • If toxicity is suspected to be related to umbralisib by the investigator (e. g. based on timing of toxicity occurrence during the cycle): 1st occurrence: - Delay umbralisib until Grade ≤ 1 or baseline and, if present, neutropenic fever or infection is resolved; thereafter, resume umbralisib at current dose. - If grade 4 neutropenia lasts longer than 7 days (despite holding umbralisib), interrupt acalabrutinib until Grade ≤ 1 or baseline and, if present, neutropenic fever or infection is resolved; thereafter, resume acalabrutinib at current dose level. 2nd occurrence (despite maximum supportive care): - Same as for 1st occurrence, but resume umbralisib at next lower dose level (dose reduction). 3rd occurrence (despite maximum supportive care): - Delay umbralisib and acalabrutinib until Grade ≤ 1 or baseline and, if present, neutropenic fever or infection is resolved; thereafter, resume umbralisib and acalabrutinib at next lower dose level. 4th occurrence (despite maximum supportive care): - Discontinue umbralisib. - If grade 4 neutropenia lasts longer than 7 days (despite umbralisib discontinuation), discontinue acalabrutinib. If applicable, delay ublituximab until Grade ≤3 and, if present, neutropenic fever or infection is resolved; thereafter, resume ublituximab at full dose and schedule.

	• If toxicity is suspected to be related to acalabrutinib by the investigator (e. g. based on timing of toxicity occurrence during the cycle), delay acalabrutinib until Grade ≤ 1 or baseline, thereafter, resume acalabrutinib at current dose level. For recurrences, acalabrutinib and/or umbralisib may be dose reduced. If applicable, delay ublituximab until Grade ≤3 and, if present, neutropenic fever or infection is resolved; thereafter, resume ublituximab at full dose and schedule.
Thrombocytopenia	
Grade ≤3 thrombocytopenia	Provide supportive care as warranted. Maintain current dose and schedule of acalabrutinib. Maintain current dose of umbralisib. If applicable, maintain full dose and schedule of ublituximab.
Grade 3 thrombocytopenia with bleeding, or Grade 4 thrombocytopenia	Provide supportive care as warranted. • If toxicity is suspected to be related to umbralisib by the investigator (e. g. based on timing of toxicity occurrence during the cycle): 1st occurrence: - Delay acalabrutinib and umbralisib until Grade ≤ 1 or baseline; thereafter, resume both acalabrutinib and umbralisib at current dose level. 2nd occurrence: - Same as for 1st occurrence, but resume umbralisib at next lower dose level (dose reduction). 3rd occurrence: - Same as for 1st occurrence, but resume both umbralisib and acalabrutinib at next lower dose level (dose reduction). 4th occurrence: - Discontinue both acalabrutinib and umbralisib. Delay ublituximab until Grade ≤3; thereafter, resume ublituximab at full dose and schedule.

	• If toxicity is suspected to be related to acalabrutinib by the investigator (e. g. based on timing of toxicity occurrence during the cycle), delay acalabrutinib until Grade ≤ 1 or baseline, thereafter, resume acalabrutinib at current dose level. For recurrences, acalabrutinib and/or umbralisib may be dose reduced. Delay ublituximab until Grade ≤3; thereafter, resume ublituximab at full dose and schedule.
Pulmonary toxicity (pneumonitis) & Related Infections*	
Grade 1 or 2	Provide supportive care as warranted. Maintain current dose and schedule of acalabrutinib. Delay umbralisib. Upon complete resolution, restart umbralisib at next lower dose level. If recurrence after re-challenge, discontinue umbralisib. Hold ublituximab. Upon resolution, resume ublituximab at full dose and schedule. If recurrence after re-challenge, discontinue ublituximab.
Grade ≥3	Provide supportive care as warranted. Discontinue umbralisib. Hold acalabrutinib and ublituximab until complete resolution. Restart at acalabrutinib current dose level and ublituximab at full dose and schedule. If 2nd occurrence, discontinue all drugs
*** For sinopulmonary infections clearly not related to immune-mediated pneumonitis, umbralisib may be continued at investigator's discretion. While pneumonitis has been minimal with umbralisib, it is a reported adverse event associated with other PI3K delta inhibitors. Use of anti-pneumocystis and anti-herpetic viral prophylaxis is required prior to the start of therapy.**	
Diarrhea and/or Colitis	
Diarrhea Grade ≤2	Provide supportive care as warranted. Maintain current dose and schedule of acalabrutinib. If tolerable, maintain current dose of umbralisib. Otherwise, delay umbralisib until ≤ grade 1. Resume umbralisib at current dose level. **NOTE**: If persistent grade 2 diarrhea despite supportive care, delay umbralisib until ≤ grade 1; thereafter, resume umbralisib at next lower dose level.

	If recurrence after rechallenge, delay umbralisib until ≤ grade 1; thereafter, resume umbralisib at current dose. If applicable, maintain full dose and schedule of ublituximab. If intolerable or persistent grade 2 diarrhea despite supportive care, delay ublituximab until ≤ grade 1; thereafter, resume ublituximab at full dose and schedule.
Diarrhea Grade ≥3	Provide supportive care as warranted. 1st occurrence: - Delay acalabrutinib and umbralisib until Grade ≤ 1; thereafter, resume both acalabrutinib and umbralisib at current dose level. 2nd occurrence (despite supportive care): - Same as for 1st occurrence, but resume umbralisib at next lower dose level (dose reduction). 3rd occurrence (despite supportive care): - Same as for 1st occurrence, but resume both umbralisib and acalabrutinib at next lower dose level (dose reduction for both). 4th occurrence (despite supportive care): Discontinue both acalabrutinib and umbralisib. Delay ublituximab until ≤ grade 2 (or until ≤ grade 1 for recurrence after rechallenge); thereafter, resume ublituximab at full dose and schedule. If toxicity is suspected to be related to acalabrutinib rather than umbralisib by the investigator, delay acalabrutinib until Grade ≤ 1 or baseline, thereafter, resume acalabrutinib at current dose level. For recurrences, acalabrutinib and/or umbralisib may be dose reduced.
Colitis (all Grades)	Provide supportive care as warranted. Delay umbralisib and interrupt acalabrutinib. Treat with supportive care and after resolution of colitis, resume acalabrutinib at current dose level and umbralisib at next lower dose level. Upon second occurrence: - Discontinue umbralisib. - Interrupt acalabrutinib.

	- Treat with supportive care and after resolution of colitis, resume acalabrutinib at next lower dose level. Delay ublituximab until resolution to grade ≤1; thereafter, resume ublituximab at full dose and schedule.
Liver Toxicity (ALT/SGPT, AST/SGOT, Bilirubin, Alkaline Phosphatase)	
Reversible liver toxicity (transaminase elevation) has been seen on study and could be attributed to both umbralisib and acalabrutinib. Thus, any cases of grade ≥3 toxicity should be discussed with the study PI.	
Grade 1	Maintain current dose and schedule of acalabrutinib. Maintain current umbralisib dose. Assess concomitant medications and risk factors*. Monitor labs every 1-2 weeks. Maintain full dose and schedule of ublituximab***, if applicable.
Grade 2	Delay acalabrutinib, umbralisib and ublituximab***. Assess concomitant medications and risk factors*. Monitor labs at least weekly until toxicity fully resolved (Grade 0). Once resolved: o Restart acalabrutinib and umbralisib at current dose level. o Restart ublituximab*** at full dose and schedule. If 2nd occurrence of liver toxicity Grade 2: In addition to above measures, begin supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent per investigator discretion) **. Once fully resolved (to Grade 0): o Restart umbralisib at next lower dose level. o Restart acalabrutinib at current dose. o Restart ublituximab*** at full dose and schedule. o Taper prednisone by 10 mg per week until off. If liver toxicity recurs again to Grade 2, treat as a Grade ≥3 recurrence.
	Delay acalabrutinib, umbralisib and ublituximab***. Assess concomitant medications and risk factors*. Begin/continue supportive care (prednisone 0.5-1.0 mg/kg/day or equivalent per investigator discretion) **.

Grade ≥3 Discuss with the study PI.	Monitor labs at least weekly until toxicity fully resolved (Grade 0). Once resolved: o Restart acalabrutinib at current dose level. o Restart umbralisib at 400 mg po daily. o Restart ublituximab*** at full dose and schedule. o Taper prednisone by 10 mg per week until off. If 2nd occurrence of liver toxicity Grade ≥3: Discontinue umbralisib. Hold acalabrutinib and ublituximab until resolved (Grade 0). Thereafter, resume acalabrutinib at current dose level and restart ublituximab*** at full dose and schedule; however, if liver toxicity is strongly suspected to be related to acalabrutinib, treat as 3rd occurrence below. If 3rd occurrence of liver toxicity to Grade ≥3, discontinue acalabrutinib and resume umbralisib at 400 mg po daily and ublituximab*** at full dose and schedule once toxicity resolves (to Grade 0). If toxicity does not recur, umbralisib may be escalated by one dose level after a full cycle of therapy. Re-introduction of acalabrutinib may be attempted after 3 full cycles of therapy in absence of additional liver toxicity, after discussion with the study PI. In those circumstances, acalabrutinib should be given on days 8-28 of each cycle and liver function tests (AST, ALT, bilirubin) checked within 14±7 days after the first dose of acalabrutinib, and as needed thereafter. If liver toxicity recurs to grade ≥3, acalabrutinib should be permanently discontinued. If 4th occurrence of liver toxicity Grade ≥3 (while on umbralisib), permanently discontinue umbralisib. Re-introduction of acalabrutinib may be attempted after 3 full cycles of therapy in absence of additional liver toxicity, after discussion with the study PI. In those circumstances, liver function tests (AST, ALT, bilirubin) should be checked within 14±7 days after the first dose of acalabrutinib, and as needed thereafter. If liver toxicity recurs to grade ≥3, acalabrutinib should be permanently discontinued.

* Assess for disorders of lipids and glucose, thyroid disorders, alcohol use, viral infections, etc.

**Supportive Care – Aggressive management of lipid, glucose, other metabolic disorders, viral infections, etc.

Important: Before initiating steroids, check for viral hepatitis or CMV infection.

*** For patients with a prior history of hepatitis B and for those with a positive anti-HBc with negative HBsAg at screening who experience an increase in liver enzymes while on study, hold ublituximab immediately and assess for active hepatitis B infection. If negative for hepatitis B, ublituximab may be resumed. If reactivation of hepatitis B is confirmed, institute hepatitis B antiviral treatment.

Ublituximab may be resumed at investigator discretion once hepatitis B infection has resolved, with continued monitoring.	
All Other Non-Hematological Adverse Events	
Grade ≤2	Provide supportive care as warranted. Maintain current dose and schedule of acalabrutinib. Maintain current dose of umbralisib. If applicable, maintain full dose and schedule of ublituximab.
Grade ≥3	Provide supportive care as warranted. 1st occurrence: - Delay acalabrutinib and umbralisib until Grade ≤ 1 or baseline; thereafter, resume both acalabrutinib and umbralisib at current dose level. 2nd occurrence (despite supportive care): - Same as for 1st occurrence, but resume umbralisib at next lower dose level (dose reduction). Investigator discretion may be used to maintain current dose of umbralisib if toxicity appears to be attributable to acalabrutinib. 3rd occurrence (despite supportive care): - Same as for 1st occurrence, but resume both umbralisib and acalabrutinib at next lower dose level (dose reduction for both). If toxicity appears to be attributable specifically to umbralisib or acalabrutinib, investigator discretion may be used to maintain the current dose of umbralisib or acalabrutinib while reducing the dose of the other agent by one dose level based on attribution. 4th occurrence (despite supportive care): - Discontinue both acalabrutinib and umbralisib. Delay ublituximab until ≤ grade 1; thereafter, resume ublituximab at full dose and schedule.

Umbralisib and acalabrutinib Dose Reduction Recommendations

Study Drug	Starting Dose	1st Dose Reduction	2nd Dose Reduction
Umbralisib (once daily, and according to schedule)	800 mg	600 mg	400 mg

Acalabrutinib	100 mg PO BID	100 mg PO once daily (QD)	N/A

- A maximum of two dose level reductions are allowed for umbralisib.
- If a subject requires a dose reduction of umbralisib (or acalabrutinib) due to study drug related toxicity, the dose may not be re-escalated. If further evaluation of the toxicity reveals the event was not related to umbralisib (or acalabrutinib), this should be recorded in the medical record and dose re-escalation to the previous dose may be considered in consultation with the Study PI.
- If a subject: 1/ is already at the lowest dose level of umbralisib (or acalabrutinib) following prior dose reduction(s) due to study drug related toxicity, and 2/ experiences a different toxicity that would require a dose reduction, then, in consultation with Study PI, umbralisib (or acalabrutinib) may be delayed and then resumed at the same dose level when the toxicity resolves as indicated in the table for that particular toxicity.
- In case of concurrent toxicities, follow the more stringent dose modification recommendations.

8.0 AGENT INFORMATION

8.1 Ublituximab

8.1.1 Other names

TG-1101

8.1.2 Description

Ublituximab is a novel third generation chimeric anti-CD20 monoclonal antibody bioengineered for potent activity, exhibiting a unique glycosylation profile with a low fucose content, designed to induce superior antibody-dependent cytotoxicity (ADCC). Ublituximab is produced by a stable expression in a clone of the rat myeloma cell line YB2/0.

Please refer to the investigator brochure for additional details.

8.1.3 Mechanism of action

Ublituximab exhibits competitive complement-dependent cytotoxicity (CDC), on par with rituximab, and has also been demonstrated to induce programmed cell death (PCD) upon binding to the CD20 antigen on B-lymphocytes. Ublituximab has a unique protein sequence, and targets epitopes on CD20 not targeted by rituximab or ofatumumab, both currently approved anti-CD20 antibodies.

8.1.4 Pharmacokinetics and Metabolism

Please refer to the investigator brochure.

Ublituximab is a 147 kDa glycoprotein.

8.1.5 Toxicology

8.1.5.1 Expected human toxicities

See Section 6.1 for detailed list of anticipated AEs.

8.1.5.2 Potential effects on pregnancy and lactation

The effects of ublituximab on pregnancy and lactation are unknown.

8.1.6 Formulation

Ublituximab is a sterile, clear to opalescent, preservative-free concentrate for solution for intravenous (IV) by infusion administration.

Ublituximab will be supplied at a concentration of 25 mg/mL in 6 mL (150 mg) or 36 mL (900 mg) single-use glass vials. Ublituximab is packaged in either a kit containing 6 vials or in a carton containing one single vial.

8.1.7 Storage

Ublituximab must be stored in a secured, limited-access, refrigerated area at a temperature ranging from +2°C / + 8°C (36-46°F). Temperature should be monitored, documenting minimum and maximum daily. Ublituximab must not be frozen.

Once a vial of ublituximab has been opened and/or diluted it must be used immediately. If not used immediately, diluted solutions must be stored refrigerated. The storage duration of ublituximab diluted in poly vinyl chloride (PVC) or non-PVC polyolefin (PO) material is up to 24 hours when refrigerated at 2-8°C (36-46°F). After allowing the diluted bag to come to room temperature, use immediately. Expiration memorandums will be provided noting lot expiration dates. For questions about expiry email productquality@tgtxinc.com.

8.1.8 Preparation and Handling

Ublituximab should only be diluted in 0.9% NaCl before use. No data are available for other solutions such as 5% dextrose and 5% mannitol.

Dilutions for ublituximab are as follows:

Dose of ublituximab for infusion	**Volume of ublituximab (25 mg/mL)**	**Volume of NaCl 0.9% to be removed**	**Final volume in perfusion bag**
900 mg	36 mL	36 mL	500 mL

The compatibility of ublituximab with medical devices was investigated using polyvinyl chloride (PVC) and polyolefin (PO) infusion bags containing 0.9% NaCl and PVC and PO infusion lines. Compatibility was assessed using physiochemical parameters (visual appearance, protein content, protein fragmentation and aggregation) and biological activity. Based on this study, ublituximab is compatible in both the PVC and PO infusion bags and the PVC and PO infusion lines over a dosing range of 150-900 mg of ublituximab.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the study agent in a self-contained and protective environment.

8.1.9 Administration

Ublituximab is administered as an intravenous infusion. Please refer to Section 5.4.2 for administration guidelines.

Diluted ublituximab should be checked before administration for cloudiness, color, or deposits. Ublituximab should not be administered if the product does not conform to specifications. Immediately inform TG Therapeutics, Inc. of any product quality concerns or questions via email to productquality@tgtxinc.com.

It is recommended that ublituximab be administered immediately after dilution. Ublituximab should NOT be mixed the day before and mixing should only occur once confirmed that patient is eligible for therapy on the day of treatment.

No other treatment may be co-administered with ublituximab (other than for immediate intervention for adverse event).

8.1.10 Supplier

Ublituximab will be supplied free of charge by TG Therapeutics.

8.1.11 Ordering

Ublituximab drug orders shall be placed using the IP Order Request form provided by TG Therapeutics and directed to ISTdrugorder@tgtxinc.com.

Allow 7 to 10 business days between drug ordering and drug arrival. Order Monday through Wednesday to ensure shipment arrives Monday through Friday. Ensure staff will be available to unpack shipment immediately upon arrival. Immediately inform TG Therapeutics, Inc. of any product quality concerns or questions via email to productquality@tgtxinc.com.

8.1.12 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent using a drug accountability log.

8.1.13 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from TG Therapeutics or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures.

Destruction will be documented in a drug accountability log.

8.2 Acalabrutinib

Acalabrutinib is an investigational product. 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).

Please refer to the investigator brochure and package insert for additional details.

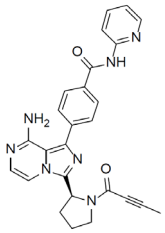
8.2.1 Other names

Calquence®; ACP-196

8.2.2 Description

Acalabrutinib is an inhibitor of Bruton tyrosine kinase (BTK).

Structural formula:



Empirical formula:	$C_{26}H_{23}N_7O_2$
Molecular weight:	465.5 g/mol
Chemical name:	(S)-4-(8-amino-3-(1-but-2-ynoylpyrrolidin-2-yl)-imidazo[1,5-α] pyrazin-1-yl)-N-(pyridin-2-yl)-benzamide

8.2.3 Mechanism of action

In B cells, BTK signaling results in activation of pathways necessary for B-cell proliferation, trafficking, chemotaxis, and adhesion. Acalabrutinib and its major metabolite ACP-5862 inactivate BTK by forming a covalent bond with a cysteine residue in the kinase active site. This leads to inhibition of signaling through the BCR. In nonclinical and clinical studies, acalabrutinib inhibited BTK-mediated activation of downstream signaling proteins CD86 and CD69 and inhibited malignant B-cell proliferation and survival.

8.2.4 Pharmacokinetics and Metabolism

Elimination half-life:	Acalabrutinib: 1 hour, ACP-5862, active metabolite: 3.5 hours.
Total body clearance:	71 L/h
Absorption:	Tmax, oral: 0.9 hours Bioavailability, oral: 25% Effect of food: Cmax decreased by 73%; Tmax delayed by 1 to 2 hours
Distribution:	Protein binding: 97.5%
Volume of distribution:	Vd: 101 L
Metabolism:	Liver: Primary site ACP-5862 (major): Active Substrate of CYP3A (primary), P-glycoprotein, and BCRP Inhibitor of BCRP; weak inhibitor of CYP3A4/5, CYP2C8, and CYP2C9 Weak inducer of CYP1A2, CYP2B6, and CYP3A4
Elimination:	Renal excretion: 12%; less than 2% as unchanged drug Fecal excretion: 84%; less than 2% as unchanged drug

8.2.5 Toxicology

8.2.5.1 Expected human toxicities

See Section 6.2 for detailed list of anticipated AEs.

8.2.5.2 Potential effects on pregnancy and lactation

Acalabrutinib may cause fetal harm and dystocia.

No data are available regarding the presence of acalabrutinib or its active metabolite in human milk.

8.2.6 Standard dose adjustments

Recommended guidelines if co-administration with a CYP3A inhibitor or inducer is unavoidable:

Dose Modifications for Acalabrutinib with concomitant CYP3A inhibitors or inducers		
CYP3A*	Co-administered Drug	Acalabrutinib Dose Modification
Inhibition	Strong CYP3A inhibitor	Avoid concomitant use. If these inhibitors will be used short-term (such as anti-infectives for up to 7 days), interrupt acalabrutinib.
	Moderate CYP3A inhibitor	100 mg once daily (QD)
Induction	Strong CYP3A inducer	Avoid concomitant use. If these inducers cannot be avoided, increase the acalabrutinib dose to 200 mg BID during concomitant administration with the strong inducer and return to the recommended dose of 100 mg BID after stopping the strong CYP3A inducer.
*Refer to Appendix E for examples of CYP3A inhibitors and inducers		

8.2.7 Formulation

The investigational product, acalabrutinib tablets for oral administration, is supplied as orange, oval, film-coated, biconvex, debossed with “ACA 100” on one side and plain on the other, containing 100 mg acalabrutinib as the active ingredient.

Inactive ingredients in the tablet core are low-substituted hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet coating consists of copovidone, ferric oxide yellow, ferric oxide red, hypromellose, medium-chain triglycerides, polyethylene glycol 3350, purified water and titanium dioxide.

8.2.8 Storage

Acalabrutinib tablets are packaged in bottles and should be stored according to the storage conditions as indicated on the label. The storage condition for acalabrutinib tablets is below 20°C-25°C.

Retain in original package until dispensing.

8.2.9 Administration

Acalabrutinib is administered orally. Please refer to Section 5.4.3 for administration guidelines.

8.2.10 Supplier

Acalabrutinib will be supplied free of charge by AstraZeneca.

8.2.11 Ordering

Sites will place orders for acalabrutinib by completing a Drug Request Form.

8.2.12 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent using a drug accountability log.

8.2.13 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from AstraZeneca or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures.

Destruction will be documented in a drug accountability log.

8.3 Umbralisib

8.3.1 Other names

TGR-1202, UKONIQ™

8.3.2 Description and mechanism of action

Umbralisib is a highly-specific and orally available dual inhibitor of phosphoinositide-3-kinase (PI3K) delta (δ) and casein kinase 1 epsilon (CK1ε) with nanomolar inhibitory potency, and high selectivity over the alpha, beta, and gamma Class I isoforms of PI3K.

Please refer to the investigator brochure for additional details.

8.3.3 Pharmacokinetics and Metabolism

Please refer to the investigator brochure.

8.3.4 Toxicology

8.3.4.1 Expected human toxicities

See Section 6.3 for detailed list of anticipated AEs.

8.3.4.2 Potential effects on pregnancy and lactation

Small molecule agents such as umbralisib are known to cross the placenta barrier, and as such, umbralisib should not be administered to pregnant women. No formal reproductive toxicology studies have been conducted. The effects of umbralisib on pregnancy and lactation are unknown.

8.3.5 Formulation

Umbralisib is supplied in 200 mg oval, light green tablets with “L474” debossed on one side, for oral administration. The primary packaging is HDPE bottles each containing 30 tablets.

Umbralisib is manufactured by Alembic Pharmaceuticals and supplied by TG Therapeutics, Inc.

8.3.6 Storage

Umbralisib must be stored in a secured limited-access area between 20°C and 25°C. Excursions permitted between 15°C and 30°C. Do not freeze.

8.3.7 Administration

Umbralisib is administered orally. Food increases the exposure of umbralisib. Please refer to Section 5.4.4 for administration guidelines.

8.3.8 Supplier

Umbralisib will be supplied free of charge by TG Therapeutics.

8.3.9 Ordering

Umbralisib drug orders shall be placed using the IP Order Request form provided by TG Therapeutics and directed to ISTdrugorder@tgtxinc.com.

Allow 7 to 10 business days between drug ordering and drug arrival. Order Monday through Wednesday to ensure shipment arrives Monday through Friday. Ensure staff will be available to unpack shipment immediately upon arrival. Immediately inform TG Therapeutics, Inc. of any product quality concerns or questions via email to productquality@tgtxinc.com.

8.3.10 Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent using a drug accountability log.

8.3.11 Destruction and Return

The investigator is responsible for keeping accurate records of the clinical supplies received from TG Therapeutics or designee, the amount dispensed to participants, and the amount remaining at the conclusion of the trial.

Any unused agent at the end of the study, expired agent, and damaged agent will be destroyed according to applicable federal, state, local and institutional guidelines and procedures.

Destruction will be documented in a drug accountability log.

9.0 CORRELATIVE/ SPECIAL STUDIES

9.1 Research Sample Collection and Dispensation

9.1.1 Correlative tumor tissue

9.1.1.1 Time points of Collection

Baseline tissue: When available, archival tissue from diagnostic tumor biopsies will be retrieved and submitted post-enrollment.

Progression/ Relapse: if safe and feasible, submission of left-over tissue from a standard of care tumor biopsy (fresh core or excisional biopsy) for participants who progress/relapse during study is encouraged.

9.1.1.2 Guidelines for archival specimens

Using the formalin-fixed paraffin embedded (FFPE) tissue block, the following samples will be processed for correlative studies:

- If tissue block is available submit:
  - 6 paraffin scrolls measuring 10 μm thick placed into a tube and frozen at -80° C
  - AND
  - 10 x 5 μm thick unstained slides
- If tissue block is unavailable submit:
  - 20 x 5 μm thick unstained slides

9.1.1.3 Labeling of samples

Samples will be labeled with the COH protocol #, subject ID (issued by DCC), institution, date, time point of collection, and if applicable patient initials.

9.1.1.4 Sample shipment and receiving lab

Samples will either be taken to (COH only) or batch-shipped (non-COH sites) to Dr. Danilov's laboratory (Kaplan Clinical Research Building 1st floor, 158-1022). For all sites, please include the **Correlative Tissue form (Appendix F)** with your shipment.

Please note that samples should be **batch-shipped from non-COH sites on Monday to Thursday** in time for receipt Tuesday to Friday. **Refer to Appendix G for tissue shipping details.**

9.1.2 Bone marrow samples

9.1.2.1 Overview and Time points

Bone marrow aspirates will be obtained at the time points indicated in Table 9.1.2.1.

Table 9.1.2.1 Overview of correlative bone marrow studies

Time points of collection	Total volume collected	Tube type	Type of analysis	Receiving laboratory and post-collection instructions
Each time a bone marrow biopsy is performed per the protocol or as part of standard of care (refer to Study Calendar, Footnote "p").	10 ml	Purple-top (K+EDTA)	Gene expression profiling, RNASeq, ATAC-Seq, immunoblotting, MRD	Dr. Danilov's lab Please follow the same post-collection instructions and shipping guidelines as for blood samples collected in purple-top tubes (Table 9.1.3.3, Appendix H (collection form), and Appendix I).

9.1.2.2 Labeling of bone marrow samples

Label tubes with COH protocol #, subject ID (issued by DCC), institution, date and actual time point of collection, and if applicable patient initials.

9.1.3 Correlative blood

9.1.3.1 Overview and Time points

Peripheral blood will be collected prior to study treatment/procedures at the time points indicated in Table 9.1.3.1

Table 9.1.3.1 Overview of correlative blood studies

Time points of collection	Total volume collected	Tube type	Type of analysis	Receiving laboratory
▪ C1D1	30 ml	Purple-top (K+EDTA)	FACS/Cytokine Clonoseq	Dr. Danilov's lab
	Up to 10 mL*	Cell-free DNA BCT® (Streck)*	ctDNA	
▪ C2D1	20 ml	Purple-top (K+EDTA)	FACS/Cytokine ClonoSeq	
▪ C8D1 ▪ C14D1 ▪ EOM** ▪ At relapse	20 ml	Purple-top (K+EDTA)	FACS/Cytokine ClonoSeq	
	Up to 10 mL*	Cell-free DNA BCT® (Streck)*	ctDNA	

***** At least 5 mL. Cell-Free DNA BCT® (glass, 10 mL volume) tubes from Streck. Cat. No, as of April 2020, for a box of 100 tubes is: 218962.

** EOM = End of maintenance.

9.1.3.2 Labeling of blood samples

Label tubes with COH protocol #, subject ID (issued by DCC), institution, date and actual time point of collection (e.g. C1D1 for Day 1 of Cycle 1), and if applicable patient initials.

9.1.3.3 Collection and post-collection guidelines

Refer to Table 9.1.3.3 for collection and post-collection instructions.

Refer to Appendix H and Appendix I for blood collection form and blood shipping guidelines, respectively.

Table 9.1.3.3 Blood sample collection and post-collection instructions.

Tube Type	Collection details	Post-collection instructions
Purple-top	1- Blood samples will be collected from an indwelling venous catheter or by venipuncture. 2- Invert tubes eight times after collection. 3- **Do not freeze** samples. Store samples at 15-25°C until shipment.	**COH only:** **Promptly** deliver the blood samples **at ambient temperature** (15-25°C) to Dr. Danilov's lab (Kaplan Clinical Research Building 1st floor, 158-1022). Samples should be processed in Dr. Danilov's lab **within** 24 hours of collection. **Non-COH sites only:** **Ship overnight at ambient temperature** (15-25°C) to Dr. Danilov's lab. See **Appendix I**. Include with shipment: · Blood sample collection form (**Appendix H**). · Copy of latest CBC results (with differential) and date of test.
Cell-free DNA BCT® (Streck)*	1- Blood samples will be collected from an indwelling venous catheter or by venipuncture. ***Prevention of backflow:*** *(Because cell-free DNA BCT® contain chemical additives)* *a. Keep patient's arm in the downward position during the collection procedure.* *b. Hold the tube with the stopper in the uppermost position so that the tube contents do not touch the stopper or the end of the needle during sample collection.* *c. Release tourniquet once blood starts to flow in the tube, or within 2 minutes of application.* 2- Fill tube with up to 10 mL (but at least 5 mL) of blood. 3- Remove tube from adapter and immediately mix by gentle inversion 8 to 10 times. 4- **Do not freeze** samples. Store samples at 15-25°C until shipment.	

* Tubes are stable when stored at 2-30^{0}C through expiration date.

9.2 Laboratory Studies Performed

The exploratory objectives of this study are to evaluate the mechanisms of resistance as well as T-cell repertoire in participants with MCL that receive the AU2 regimen. The effects of AU2 treatment on T-cell repertoire will be evaluated by flow cytometry.

Peripheral blood samples will be diluted 1:1 with phosphate buffered saline (PBS) before separation of peripheral blood mononuclear cells (PBMCs) by density gradient centrifugation. Cells will be washed in RPMI 1640 supplemented with 10% fetal calf serum and viably frozen for storage in liquid nitrogen. Flow cytometry will be used to evaluate leukocyte subpopulations (e.g., CD3, CD4, CD45, CD14, CD16, CD56). Additional surface markers will be used to discriminate Tregs (CD4+CD25+FoxP3+CD127low), Th17 cells (IL-17+) and other immune cell populations.

Additionally, where available, tumor (MCL) cells will be isolated during the density gradient centrifugation from the peripheral blood and bone marrow, viably frozen and stored in liquid nitrogen. DNA, RNA and protein where feasible will be isolated using standard techniques and gene expression profiling, RNASeq, ATAC-Seq, immunoblotting and other relevant assays will be performed at a later date to explore mechanisms of drug resistance in MCL.

MRD (Minimal residual disease)

A research version of the clonoSEQ® assay will be used to assess MRD at pre-specified time points (Adaptive Biotechnologies, Seattle, WA). This is a next generation sequencing (NGS) MRD assay that leverages multiplex PCR followed by NGS to identify and track rearrangements of IgH, V-J, D-J and IgK/L loci as well as translocations in Bcl1/2-IgH.

A portion of the samples collected in purple-top tubes at the following _five_ timepoints: whole blood (C1D1, C8D1, C14D1, C26D1 – 5 mL) and bone marrow (at the time of suspected CR only - 5 mL) will be stored at -80C in Dr. Danilov's laboratory until shipped to Adaptive Biotechnologies Inc. (Seattle, WA*) for DNA extraction and MRD assessment using the clonoSEQ assay. Briefly, the extracted genomic DNA will be PCR amplified using locus-specific multiplex primer sets for IgH (VDJ, DJ), IgK and IgL receptor genes, and translocations BCL1/IgH (J) and BCL2/IgH (J). The amplified DNA fragments will then be sequenced using the Illumina NextSeq 500 System to detect and quantify the previously identified dominant clonotype sequence(s) in the sample to determine the sample MRD level. The dominant clonotype sequences for each patient, consistent with the presence of malignancy, will be identified from paired high-disease-burden FFPE tissue samples.

cfDNA (cell free DNA)

cfDNA will be isolated in Dr. Danilov's laboratory and stored at -80C until analysis for tumor mutations (using NGS panels) and MRD.

9.3 Collection of data from standard of care tests at screening

Every effort should be made to collect the following data at screening on the tumor diagnostic material (lymph node, bone marrow, peripheral blood):

- HopeSeq (at City of Hope) or another panel at the external institution (existing results within 6 months are acceptable).
- FISH panel to include t(11;14), del(17p), del(11q), del(13q), MYC 8q24 Break Apart probe (existing results within 6 months are acceptable).
- Conventional cytogenetics (existing results within 6 months are acceptable).
- Ki-67, P53, SOX11 (by IHC – lymph node biopsy material only)

Failure to collect such data will not preclude enrollment on the trial and do not constitute a protocol deviation.

10.0 STUDY CALENDAR

All assessments may increase in frequency as clinically indicated.

Protocol Activity	Screening [a]	Protocol therapy [b]														Follow-up (~2 years)		
		Induction Phase (C1->C6)										Maintenance Phase (C7->C25) [c]			Optional Continuation with acalabrutinib only			
		C1				C2		C3		C4 to C6	Disease Staging [s]	C7 to C25	Disease Staging [s]	EOM*		Safety 30-days post [e]	Active Every 6 months [f]	Survival [g]
		D1 [d]	D2	D8 [d]	D15 [d]	D1 [d]	D15 [z]	D1 [d]	D15 [z]	D1 [d]	C4D1 C7D1	D1 [d]	C14D1 C20D1					
Informed Consent	X																	
Medical History	X																	
Eligibility	X																	
Registration	X																	
Physical Exam [h] & Vital signs [i]	X	X				X		X		X		Every other cycle [q]			X [u]	X		
ECOG Status (Appx. A)	X	X				X		X		X		Every other cycle [q]			X [u]	X		
Con-med review	X	X		X	X	X		X		X		Every other cycle [q]			X [u]	X		
AE Assessment	X	X		X	X	X		X		X		cycle [q]			X [u]	X		
INR, PT, aPTT	X																	
CBC w/diff, plt	X [k]	X		X	X	X	X	X	X	X		Every other cycle [q]			X [u]	X		
Serum chemistry [l]	X [k]	X	X [y]	X	X	X	X	X	X	X		Every other cycle [q]			X [u]	X		

Protocol Activity	Screening [a]	Protocol therapy [b]														Follow-up (~2 years)		
		Induction Phase (C1->C6)										Maintenance Phase (C7->C25) [c]			Optional Continuation with acalabrutinib only			
		C1				C2		C3		C4 to C6	Disease Staging [s]	C7 to C25	Disease Staging [s]	EOM*		Safety 30-days post [e]	Active Every 6 months [f]	Survival [g]
		D1 [d]	D2	D8 [d]	D15 [d]	D1 [d]	D15 [z]	D1 [d]	D15 [z]	D1 [d]	C4D1 C7D1	D1 [d]	C14D1 C20D1					
Serology: HCV, HBV, CMV [w]	X																	
CMV surveillance [x]										(X)		(X)			(X)			
12-lead EKG	X																	
ECHO or MUGA	X																	
Pregnancy [j]	X	X																
Correlative blood [m]		X				X						C8D1, C14D1		X		(X)	(X)	
Ublituximab		X		X	X	X		X		X		**On D1 of C8** and every other cycle thereafter [r]			-			
Umbralisib		On days 1-14				On Days 1-7 of each cycle						On Days 1-7 of each cycle						
Acalabrutinib		Every day of each Cycle										Every day of each Cycle			Every day of each Cycle			
PET-CT or CT [t]	X										X		X	X	X [u]	X	X	
Survival status																		X

Protocol Activity	Screening [a]	Protocol therapy [b]													Optional Continuation with acalabrutinib only	Follow-up (~2 years)		
		Induction Phase (C1->C6)										Maintenance Phase (C7->C25) [c]						
		C1				C2		C3		C4 to C6	Disease Staging [s]	C7 to C25	Disease Staging [s]	EOM*		Safety 30-days post [e]	Active Every 6 months [f]	Survival [g]
		D1 [d]	D2	D8 [d]	D15 [d]	D1 [d]	D15 [z]	D1 [d]	D15 [z]	D1 [d]	C4D1 C7D1	D1 [d]	C14D1 C20D1					
Correlative tumor tissue [v]	X [n]	---------- X [o] ----------																
Bone marrow biopsy/ aspirate p, v	X	----------X----------																

a. Screening activities to occur within 28 days prior to start of protocol therapy except for laboratory assessments.

b. In the absence of treatment delay, each treatment cycle lasts 28 ± 3 days during Induction, and 28 ± 7 days during Maintenance.

c. Maintenance phase for participants with stable disease or better response (PR or CR) at the end of Induction therapy.

d. Activities to be performed within 72 hours prior to study drug administration.

e. The Safety 30 days post-last dose assessments to occur 30 (±7) days post-last dose or, if > 30 days elapsed since last dose, within 7 days after decision to end treatment. Expedited reporting will occur during this period. Safety follow-up may be extended until resolution/ stabilization of reportable AEs.

f. For participants yet to progress, Active Follow-up will occur at 6, 12, 18 and 24 months (± 30 days for all) from last on-treatment scan until disease progression or the initiation of a new anti-lymphoma therapy.

g. Participants who end Active Follow-up will enter Survival Follow-up. Survival assessment to occur bi-annually or as requested by the Study PI via medical record review, review of social security registry, or telephone call.

h. *Standard physical exam* includes weight.

i. *Vital signs*: heart rate, blood pressure, respiration rate, and temperature.

j. *Women of childbearing potential*: Pregnancy serum test. For the screening time point, serum pregnancy test must be performed within 3 days prior to start of protocol therapy.

k. *Screening laboratory assessments* to be performed within 14 days prior to start of protocol therapy.

l. *Serum chemistry* panel to include: glucose, Blood Urea Nitrogen (BUN), creatinine, uric acid, total protein, albumin, magnesium, bicarbonate, calcium, inorganic phosphorous, sodium, potassium, chloride, total bilirubin, alkaline phosphatase, ALT, AST, and LDH.

m. Correlative blood will also be collected at time of relapse. Refer to Section 9.1.3 for additional information.

n. Archival tumor tissue to be submitted post-enrollment when available. Refer to Section 9.1.1.

o. If safe and feasible, submission of left-over tissue from a standard of care tumor biopsy (fresh core or excisional biopsy) for participants who progress/relapse during study is encouraged. Refer to Section 9.1.1.

p. Bone marrow biopsies will be performed at the following time points if feasible (please contact Study PI if bone marrow collection is not feasible at either time point to receive a waiver):

1- At baseline (during screening). If a patient had a recent bone marrow biopsy (within 90 days), this time point may be omitted after a discussion with the Study PI. In this case, a correlative sample will not be submitted.
2- At the time a CR is suspected based on imaging results (within 8 weeks after such result).
3- At the time of disease relapse.

At each time point, bone marrow samples will be collected for correlative studies (Section 9.1.2).

q. Every other cycle starting on C8D1 (i.e. on days of ublituximab infusion).

r. Ublituximab infusions are on Day 1 of C8, C10, C12, C14, C16, C18, C20, C22, C24, C26, C28, and C30.

s. Disease assessments (imaging) to occur on Days 1 (± 7 days).

t. PET-CT is strongly preferred. CT in lieu of PET-CT is allowed if patient is in CR and CR was already confirmed by PET-CT, and for patients for whom PET-CT is not feasible (with Study PI's approval).

u. Every 6 months (+/- 2 weeks) from last on treatment scan until end of protocol therapy.

v. NGS panel (HopeSeq at City of Hope), FISH analysis, conventional cytogenetics and IHC should be performed on tumor diagnostic material (lymph node, bone marrow, peripheral blood) based on disease characteristics, per institutional practice standards at screening. Every effort should be made to collect such data (Section 9.3).

w. Serum virology to include HBsAg, HBc antibody, HCV antibody and CMV IgG and IgM (or may do CMV by PCR at investigator discretion). If HBc antibody, HCV antibody or CMV IgG or IgM is positive, subject must be evaluated for the presence of active HBV, HCV or CMV by PCR.

x. CMV screening by PCR for all subjects receiving study treatment beginning in Cycle 4 and approximately every 3 to 4 cycles thereafter aligned with study visits.

y. This time point serves as TLS assessment. TLS assessment will be performed on Day 2 (+ 1 day).

z. Activities to be performed on D15 +/- 3 days.

* EOM = End of maintenance. Visit to occur at the end of Cycle 25 (with a +7 days window) and to include disease assessment (imaging).

11.0 ENDPOINT DEFINITIONS/MEASUREMENT OF EFFECT

11.1 Assessment of Response

Lymphoma response/progression will be evaluated using 2014 Lugano Classification (see Appendix C). [51]

Disease assessment will be performed by PET-CT. In patients in whom PET-CT is not feasible, CTs may be used in place of a PET-CT after discussion with the Study PI (Dr. Danilov). Patients must have a bone marrow biopsy performed at baseline and to confirm CR (if suspected based on imaging). After CR, additional bone marrow biopsy is only required if clinically indicated and at relapse. Additional necessary restaging studies including dedicated CT scans or MRI, are permitted at the investigator's discretion. PET-CT and CT results will be read by a radiologist at each study site and investigator response assessment will be performed.

For patients with progression of disease on imaging, it is strongly recommended that a confirmatory biopsy be obtained whenever possible.

11.2 Primary Endpoint(s)

Complete response (CR) rate: defined as the proportion of response-evaluable participants (see Section 12.2) that achieve a CR at the end of induction therapy. If a patient achieves CR earlier during induction therapy but is PD at the end of induction, the patient will be considered end of induction non-CR. If a patient achieves a CR earlier during induction but does not have a response evaluation at the end of induction for some reason (for example early termination of induction due to patient refusal), the prior CR will be carried over as the end of induction CR.

11.3 Secondary Endpoint(s)

Overall response rate (ORR): defined as the proportion of response-evaluable participants (see Section 12.2) that achieve a best response of either CR or PR during protocol therapy.

Progression-Free Survival (PFS): defined as the duration of time from start of protocol treatment to time of disease relapse/progression, start of non-protocol anti-lymphoma therapy, or death due to any cause, whichever occurs earlier. For patients who are alive and have not had disease relapse/progression at the last follow-up, it is censored at the time of last follow-up. .

Overall Survival (OS): defined as the duration of time from start of protocol treatment to time of death due to any cause. For patients who are alive at last follow-up, it will be censored at the time of last follow-up.

Duration of Response (DOR): Defined as the time from the first achievement of PR or CR to time of PD, start of non-protocol anti-lymphoma therapy, or death, whichever earlier. Patients who never achieve PR or CR during protocol therapy are excluded. Patient who has not had any of the failure events above at last follow-up is censored at the time of last follow-up.

Toxicity: Toxicity and adverse events will be recorded using the NCI CTCAE 5.0 scale. Observed toxicities will be summarized by type (organ affected or laboratory determination such as absolute neutrophil count), severity (by NCI CTCAE v5.0 and nadir or maximum values for lab measures), date of onset, duration, reversibility, and attribution.

11.4 Exploratory Endpoint(s)

Exploratory endpoints include T-cell population and function measures, gene expression/mutation profiles, and MRD assessed by ClonoSeq assay.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design

This is a multicenter, single-arm Phase 2 study evaluating AU2 therapy for patients with previously untreated MCL. Patients will first receive 6 cycles of AU2 (acalabrutinib + umbralisib + ublituximab) induction; those who achieve SD or better response after induction will then receive 19 cycles of maintenance with the 3 agents, during which ublituximab will only be given every 2 cycles. Each cycle will be 28 days. Participants may continue therapy with acalabrutinib beyond 25 cycles of Induction + Maintenance therapy at the treating physician's discretion. Response will be evaluated just prior to C4, C7 (End of Induction), C14, C20 , EOM (end of maintenance), every 6 months thereafter until end of protocol therapy (if patient continues with oral agents only beyond 25 cycles), and at Safety visit.

The primary endpoint is complete response (CR) rate after AU2 induction therapy. Secondary endpoints include toxicities of AU2 induction and maintenance therapy, overall response rate to protocol therapy, duration of response, progression free survival, and overall survival.

The study sample size is based on the desire to discriminate a promising CR rate of 50% (alternative hypothesis) from a disappointing CR rate of 25% (null hypothesis) after AU2 induction. These response rates were chosen because 1) BR, a current standard, has been associated with an ORR of 80-90% and a CR rate of 40% [5, 7]; 2) In the phase 2 ACE-LY-004 trial in R/R MCL, treatment with acalabrutinib was associated with an ORR of 81% and a CR rate of 40% [39]. However, it is anticipated that this study will enroll a higher proportion of patients with high-risk MCL (*TP53* aberrations, CK) where BR is ineffective.

Simon's optimal two-stage design will be used. In the first stage, 9 evaluable patients will be accrued. If there are 2 or fewer CRs in these 9 patients, the study will be stopped. Otherwise, 15 additional evaluable patients will be accrued for a total of 24. The null hypothesis will be rejected and AU2 induction therapy will be considered promising if 10 or more CRs are observed in 24 evaluable patients. This design yields a 1-sided type I error rate of 0.05 and power of 0.8. When the CR rate is disappointing (25%), there is an 60% chance that the study will be terminated after the first stage.

12.2 Evaluable Participants and Participant Replacement

- ***Evaluable for toxicity***: Patients who receive at least one dose of protocol therapy are evaluable for toxicity.
- ***Evaluable for response endpoints:***

Evaluable patients are defined as eligible participants who have received at least one cycle of Induction therapy and have at least one disease evaluation post-baseline.

Patients will be evaluable and be considered non-CR in the primary 2-stage response evaluation, if the reason why they did not finish at least 1 cycle of induction therapy or discontinued induction therapy prior to having a response assessment was progressive disease or toxicity. All other patients without 1+ cycle or 1+ response assessment post-baseline, such as those who terminated due to patient refusal or investigator decision, will be inevaluable and replaced.

12.3 Sample Size and Accrual Rate

The 2-stage Simon optimal design, as described above, will require up to 24 response evaluable patients. Accounting for up to 10% inevaluable patients that need to be replaced, the maximum accrual for the study will be 27 patients. Combining all participating sites, we project that the study accrual can be completed within 2 years, with an estimated accrual rate of approximately 1 patient per month.

12.4 Interim Analyses/Stopping Rules

12.4.1 Interim Efficacy Monitoring

The study will perform an interim analysis of CR rate per the Simon's 2-stage rule as described above in Section 12.1.

12.4.2 Toxicity Monitoring

We will monitor the rate of the following adverse events that are **at least possibly** related to protocol treatment at any time during study treatment:

- Grade ≥3 diarrhea which does not resolve within 3 days with best supportive care
- Febrile neutropenia
- Grade ≥2 pneumonitis
- Grade ≥4 elevations of AST, ALT or Grade ≥3 elevation of bilirubin
- Grade ≥4 infection
- New onset grade 4 atrial fibrillation in patients without a history of atrial fibrillation
- Major hemorrhage defined as serious or Grade 3 or higher bleeding or any central nervous system bleeding.
- Severe (grade 4) cutaneous reaction

This monitoring will include all patients who received at least 1 dose of the protocol treatment. The expected rate of patients having any of these toxicities should be <33%. The first monitoring will occur when the 6^{th} patient completes the first induction cycle, and it will include all available cycles from the first 6 patients. If more than 1 patient experience any of the toxicities above at the first monitoring, accrual will be halted; study data will be reviewed by the study committee and the City of Hope Data and Safety Monitoring Committee (DSMC). Study amendment may be proposed if necessary. Accrual will not be resumed until approved by DSMC. If 0 or 1 patient has these toxicities at the first monitoring, accrual will continue as planned and the result of this first monitoring will be submitted to DSMC at the next PMT report. Subsequent monitoring will be performed every 6 months as part of each PMT report. If at such review 33% or more of the patients experience these toxicities, the study accrual will be temporarily halted; a full review of these events and other toxicities will be performed by the study team and DSMC. Patient accrual will not resume until approved by the DSMC to do so. In addition, COH DSMC will review all toxicities every 6 months and may make their independent assessment and recommendations.

12.5 Statistical Analysis Plan

Patient demographics and baseline disease characteristics will be summarized using descriptive statistics. For continuous variables, descriptive statistics such as number, mean, standard deviation, standard error,

median (range) etc. will be provided. For categorical variables, patient counts and percentages will be provided.

CR rate after Induction therapy will be estimated by the proportion of response-evaluable patients achieving CR after Induction therapy, along with the 95% exact binomial confidence interval. ORR during protocol therapy will be similarly estimated. PFS and OS will be estimated using the product-limit method of Kaplan and Meier along with the Greenwood estimator of standard error; 95% confidence interval will be constructed based on log-log transformation. Median PFS/OS will be estimated when available. Observed toxicities of Induction therapy and Maintenance therapy will be summarized by type, severity, and attribution.

For the exploratory objectives, summary statistics and graphics will be used to describe the T cell population and function measures, MRD status, and other correlative analyses. Exploratory correlative analysis will be used to explore the association between the MRD status or gene expression/mutation profiles and clinical outcomes.

13.0 DATA HANDLING, DATA MANAGEMENT, RECORD KEEPING

13.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

13.2 Data Capture Methods and Management

Data for this trial will be collected using City of Hope's electronic capture system (EDC) that is compliant with 21 CFR Part 11.

Study personnel will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF).

13.3 Case Report Forms/Data Submission Schedule

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Investigator or designee in a timely fashion.

All data will be collected using electronic data collection, stored as indicated in Section 13.2, and will be submitted according to the timelines indicated in Table 13.3.

Table 13.3 Data Submission Schedule

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Forms	Within 14 calendar days of registration
Baseline Assessment Forms	Within 14 calendar days of registration
Treatment Forms	Within 10 calendar days of treatment administration
Adverse Event Report Forms	Within 10 calendar days of AE assessment/notification

Form	Submission Timeline
Response Assessment Forms	Within 10 calendar days of the response assessment
Other Assessment Forms (concomitant medications)	Within 10 calendar days of the assessment
Off Treatment/Off Study Forms	Within 10 calendar days of end of treatment/study
Follow up/Survival Forms	Within 14 calendar days of the follow up activity

13.4 Regulatory Records

The Investigator will maintain regulatory records, including updating records in accordance with Good Clinical Practice guidelines and FDA regulations.

14.0 REPORTING OF ADVERSE EVENTS, UNANTICIPATED PROBLEMS & OTHER EVENTS OF INTEREST

The research team is responsible for classifying adverse events (AEs) and unanticipated problems (UPs) as defined in the relevant regulations and reporting to all applicable parties, including but not limited to the COH IRB, DSMC, Food and Drug Administration (FDA), National Institutes of Health (NIH) and other collaborators, e.g., pharmaceutical companies. The research team is responsible for the continued monitoring and tracking of all AEs in order to ensure non-reportable events are reviewed and monitored and do not rise to a reporting level.

14.1 Assessment of Adverse Events

The site Investigator will be responsible for determining the event name, and assessing the severity (i.e., grade), expectedness, and attribution of all adverse events as applicable per the City of Hope Clinical Research Adverse Event and Unanticipated Problem policy (available from the DCC). Adverse events will be characterized using the descriptions and grading scales found in NCI CTCAE v5.0. A copy of the scale can be found at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm.

The following definitions will be used to determine the causality (attribution) of the event to the study agent or study procedure.

- **Unrelated –** The event is clearly NOT related to study treatment, and is clearly related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant medications administered to the participant.
- **Unlikely –** The event is unlikely related to the study treatment, and is most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible –** The event may be related to study treatment, as it follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Probable –** The event is most likely related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is unlikely related to the participant's clinical state, other therapeutic interventions, or concomitant drugs.

- **Definite –** The event is clearly related to the study treatment, as it follows a reasonable temporal sequence from the time of drug administration and a known response pattern to the study drug, and is not reasonably explained by other factors such as the participant's condition, therapeutic interventions, or concomitant drugs.

14.2 Adverse Events of Special Interest (AESI)

Adverse Events of Special Interest (AESI) are events that may not typically be considered to meet the regulatory criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the timely review of safety data and narrative. It can be e. g. a non-serious non-specific start of an event, which may be an early manifestation of a serious potential risk.

14.2.1 Ventricular arrhythmias

Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation, etc.) are adverse events of special interest (AESIs) for participants exposed to acalabrutinib, and must be reported to AstraZeneca expeditiously, irrespective of regulatory seriousness criteria or causality (Sections 14.5 and 14.7).

14.2.2 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.

Refer to Section 14.7 for guidelines on reporting secondary malignancies to the industry partners.

14.2.3 Abnormal Liver Function Tests

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN should be reported to AstraZeneca expeditiously (Sections 14.5 and 14.7).

14.3 Overdose and Pregnancies

14.3.1 Overdose

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

Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF even if not associated with an AE. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF.

Any accidental or intentional overdose with ublituximab or umbralisib that is symptomatic, even if not fulfilling a seriousness criterion, is to be reported to TG Therapeutics as indicated in Sections 14.5 and 14.7 on an SAE form, and following the same process described for SAEs.

If a study drug overdose occurs, the subject should stop study drug dosing and be clinically monitored as appropriate, managing symptoms/side effects that may occur.

For any participant experiencing an acalabrutinib overdose, observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological 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 is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Refer to Sections 14.5 and 14.7 for guidelines on reporting overdose of acalabrutinib to AstraZeneca.

14.3.2 Pregnancies

14.3.2.1 Female participants:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring after the participant receives the first dose of protocol therapy up to 2 days post-last dose of acalabrutinib and 30 days post-last dose of ublituximab or umbralisib are considered immediately reportable events. **Protocol therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Study PI and the DCC immediately within 24 hours of awareness (Sections 14.5.1.1 and 14.5.1.2)**. The female subject may be referred to an obstetrician-gynecologist (preferably one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator should make every effort to follow the female participant until completion of the pregnancy per institutional policies, and should notify the Study PI.

Abnormal pregnancy outcomes and neonatal deaths that occur within 28 days of birth should be reported as an SAE per expedited reporting guidelines. Any infant death after 28 days that the Investigator suspects is related to the in utero exposure to protocol therapy should also be reported as an SAE per expedited reporting guidelines. The Study PI or designee will subsequently inform AstraZeneca and TG therapeutics (Section 14.7).

14.3.2.2 Male participants:

If a female partner of a male participant becomes pregnant, the male participant should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. In the event a participant's partner becomes pregnant, the pregnancy should be reported to AstraZeneca and TG Therapeutics (Section 14.7).

The Investigator should make every effort to follow the outcome of the pregnancy per institutional policies, and should notify the Study PI.

14.4 Routine AE Collection and Reporting Guidelines

AEs will be collected from the signing of informed consent until ending study participation. Routine AE reporting will occur via data entry into the study eCRF. AEs will be monitored by the Protocol Management Team (PMT). AEs reported through expedited processes (e.g., reported to the IRB, DSMC, FDA, etc.) must also be reported in routine study data submissions.

AEs recorded in the eCRF include:

- For each cycle and safety follow-up period, all grade 3 and higher AE for each type **AND** the highest grade of AE for each type (if grade 1 or 2)
- All SAEs

14.5 Expedited Reporting

Table 14.5 indicates what events must be reported expeditiously.

Table 14.5 Criteria for Expedited Reporting

Time point	What to report
From signing of the consent to study completion	• All UPs
From signing of the consent to treatment initiation	• All SAEs
For the time period beginning at treatment through 30 days following cessation of treatment	• All SAEs* regardless of relationship to protocol therapy • All UPs and AEs that meet the definition of a UP • Ventricular arrhythmias (Section 14.2.1) • Abnormal liver function tests (Section 14.2.3) • Overdose of acalabrutinib, ublituximab or umbralisib (Section 14.3.1) • Pregnancies and lactation
From Day 1 of protocol therapy up to 2 days post last dose of acalabrutinib and 30 days post last dose of ublituximab or umbralisib	• Pregnancies and lactation
Post Safety Follow-Up to removal from study	• All SAEs* that are considered probably or definitely related to acalabrutinib, umbralisib or ublituximab
NOTE: All events reported expeditiously require follow-up reporting until the event is resolved, stabilized, or determined to be irreversible by the investigator. **The DCC should be consulted prior to ending the follow-up of events that have stabilized.** *** Refer to Section 14.7 for guidelines on reporting secondary malignancies to the industry partners.**	

14.5.1 Expedited reporting guidelines **(COH only)**

14.5.1.1 To the COH DSMC/IRB

Serious Adverse Events that require expedited reporting and unanticipated problems will be reported according to the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy. This includes all SAEs and UPs that meet COH DSMC/IRB expedited reporting criteria that occurred at COH and non-COH sites.

14.5.1.2 To Participating Investigators

- Report all expedited reportable AEs to participating investigators as an IND Safety Report occurring within 30 calendar days of receipt of sponsor (lead site) notification, and indicate whether or not a protocol and/or consent form change is required. A cover letter will indicate the protocol title, the IND#, whether the FDA was informed (if applicable), and, for non-COH sites, a statement that the report should be submitted to their local IRB for review if applicable per local IRB policy.

- Forward to participating sites all IND safety reports received from AstraZeneca and TG Therapeutics, indicating whether a consent form or protocol change is required within 30 days of notification to Study PI.

14.5.2 Expedited reporting guidelines **(non-COH sites only)**

14.5.2.1 To the DCC/Study PI

All events that meet the criteria specified in Table 14.5 will be reported to the DCC and Study PI within 24 hours of notification that the event met the expedited reporting criteria.

1. Sites are to report to their local IRB per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB submission and corresponding IRB response.
2. Document/describe the AE/UP on each of the following:
    a. MedWatch 3500A or local IRB submission document*
    MedWatch 3500A is downloadable form at http://www.fda.gov/medwatch/getforms.htm
    *The local IRB submission document may be used if the document template is approved by the DCC
    b. Expedited Reporting Coversheet. A modifiable Microsoft Word document is available from the DCC. An electronic signature on the document will be accepted.
3. Scan and email above documents to the Study PI (adanilov@coh.org) and DCC@coh.org with the subject title as "[AU2 for previously untreated MCL] SAE COH IRB #20459".
    a. If available, sites may include the local IRB submission for this event in the submission.
4. If an email receipt from DCC personnel is not received within one working day, please email DCC@coh.org.

14.6 Reporting to the FDA

The study PI (or designee) will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI with the preparation of the report and submit the report to the FDA in accordance with the approved City of Hope Clinical Research Adverse Event and Unanticipated Problem policy.

Serious Adverse Events meeting the requirements for expedited reporting to the Food and Drug Administration (FDA), as defined in 21 CFR 312.32, regardless of the site of occurrence, will be reported as an IND safety report using the MedWatch Form FDA 3500A for Mandatory Reporting.

The criteria that require reporting using the MedWatch 3500A are:

- Any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA **no later than 7 calendar days** after initial receipt of the information [21 CFR 312.32(c)(2)]
- Any adverse experience associated with use of the drug that is both serious and unexpected must be submitted **no later than 15 calendar days** after initial receipt of the information [21 CFR 312.32(c)(1)]
- Any follow-up information to a study report shall be reported **as soon as** the relevant information becomes available. [21 CFR 312.32(d)(3)]

The final IND report will be distributed to the Study PI and DCC. If it is determined that the IND safety report requires a change to the protocol or the consent form, the DCC will include instructions to participating sites for local IRB reporting.

In addition, on behalf of the study PI, OIDRA will submit annually within 60 days of the anniversary of the date the IND went into effect, an annual report to the FDA which is to include a narrative summary and analysis of the information of all FDA reports within the reporting interval, a summary report of adverse drug experiences, and history of actions taken since the last report because of adverse drug experiences.

14.7 Reporting to Industry Partners

The Study PI (or designee) will:

- Report the following to AstraZeneca and TG Therapeutics per the guidelines provided in Table 14.7 below.
  - AstraZeneca: email: AEMailboxClinicalTrialTCS@astrazeneca.com
  - TG Therapeutics: email: safety@tgtxinc.com, (copy gabriel.green-lemons@tgtxinc.com and donna.gesumaria@tgtxinc.com)
- Assist AstraZeneca/ TG Therapeutics in investigating any SAE and will provide any follow-up information reasonably requested by AstraZeneca/ TG Therapeutics.

Table 14.7 Timeframes for Reporting to AstraZeneca/ TG Therapeutics

Type of Report	Reporting Timeframes to AstraZeneca	Reporting Timeframes to TG Therapeutics
Pregnancy and suspected pregnancy	Pregnancy and suspected pregnancy: **Within 24 hours** of being aware of the event using a Pregnancy Report Form	Pregnancy (including of male participant partner), pregnancy outcome with 6-month follow up from end of pregnancy (birth, abortion [spontaneous, accidental or therapeutic], voluntary termination, etc.): **Within 24 hours** of being aware of the event using a Pregnancy Report Form
All expedited SAE reports (includes AESIs [specified in Section 14.2]) Note: See below for guidelines on reporting secondary malignancies.	**Within 24 hours** of being aware of the event via a MedWatch 3500A form. Note: Overdose of acalabrutinib should be reported as an "overdose" report. If there is an associated AE/SAE, this should be reported too.	**Within 24 hours** of being aware of the event via a MedWatch 3500A form including SAEs experienced during pregnancy and congenital anomalies/birth defects.
Aggregate safety reports	Forward to AstraZeneca at time of COH PMT report): AEMailboxClinicalTrialTCS@astrazeneca.com	Forward to TG Therapeutics at time of COH PMT report): safety@tgtxinc.com gabriel.green-lemons@tgtxinc.com donna.gesumaria@tgtxinc.com dmarsico@tgtxinc.com

- Reporting of secondary malignancies
  - AstraZeneca:

Adverse Events (AEs) for malignant tumours reported during the 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 tumour event should be assessed and reported as a Non-Serious AE. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, 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 tumours, 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 tumour event in question is a new malignant tumour (i.e., it is not the tumour 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 tumour under study). Malignant tumours 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 tumour.

- TG Therapeutics: Secondary malignancies do not need to be reported as SAEs to TG Therapeutics.

- Forward to AstraZenaca and TG Therapeutics copies of initial/annual/final FDA IND submissions. Email: AEMailboxClinicalTrialTCS@astrazeneca.com and dmarsico@tgtxinc.com.

15.0 ADHERENCE TO THE PROTOCOL & REPORTING OF PROTOCOL DEVIATIONS

Deviations from the protocol should be avoided, except when necessary to eliminate immediate hazard(s) for the protection, safety, and well-being of a research participant. As a result of deviations, corrective actions are to be developed by the study staff and implemented promptly. All protocol deviations and planned protocol deviations will be reported in accordance with the City of Hope Clinical Research Protocol Deviation policy.

Non-COH Sites:

Deviations meeting the criteria specified in the City of Hope Clinical Research Protocol Deviation policy (available from the DCC) will be reported to the DCC and Study PI within **24 hours** of notification that the event occurred.

Procedure for reporting deviations to the COH DCC:

1. Document the deviation on the Deviation Reporting Coversheet or submit your site-specific protocol deviation log if the log format has been approved for use by the DCC. This modifiable Microsoft Word document is available from the DCC. An electronic signature on this document will be accepted.
2. Scan and email the Deviation Reporting Coversheet or protocol deviation log to the Study PI (adanilov@coh.org) and DCC@coh.org **within 24 hours** of notification of the deviation with the email subject title of "[AU2 for previously untreated MCL] Deviation COH IRB #20459". If

an email receipt from the DCC is not received within one working day, please email DCC@coh.org.

3. Sites are to report to their local IRB and DSMC per their site's specific institutional and IRB guidelines. As soon as possible, non-COH sites will provide to the COH DCC copies of the IRB and/or DSMC submission and corresponding response(s).

16.0 STUDY OVERSIGHT, QUALITY ASSURANCE, & DATA AND SAFETY MONITORING

16.1 All Investigator Responsibilities

An investigator is responsible for ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the investigator's care; and for the control of drugs under investigation.

16.2 Study Principal Investigator Responsibilities

The Study Principal Investigator is responsible for the conduct of the clinical trial, including overseeing that sponsor responsibilities are executed in accordance with federal regulations.

16.3 Protocol Management Team (PMT)

The Protocol Management Team (PMT), minimally consisting of the study PI, collaborating investigators, site investigators, research nurse, clinical research associate/coordinator, and the study biostatistician, is responsible for ongoing monitoring of the data and safety of this study, including implementation of the stopping rules for safety/toxicity.

The PMT is recommended to meet (in person or via teleconference) to review study status. The meeting is a forum to discuss study related issues including accrual, SAE/AE/UPs experienced, study response, deviations/violations, and study management issues. The appropriateness of further subject enrollment and the specific intervention for subsequent subject enrollment are addressed.

16.4 Quality Assurance

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and regulatory requirements, and that the quality and integrity of study data and data collection methods are maintained. Monitoring for this study will be performed by the City of Hope Office of Clinical Trials Monitoring (OCTM), within City of Hope's Office for Safety and Data Quality.

Details of clinical site monitoring are documented in the OCTM SOP and the Risk Based Monitoring (RBM) plan. These documents specify the frequency of monitoring, monitoring procedures, the amount of subject data to be reviewed, and the distribution of monitoring reports to the study team and the COH DSMC.

16.5 Risk Determination

This is a high risk study, as defined in the City of Hope Institutional DSMP. This determination was made because this study involves a COH IND.

16.6 City of Hope Data and Safety Monitoring Committee

The COH Data and Safety Monitoring Committee (DSMC) will review and monitor study progress, compliance, toxicity, safety, and accrual data from this trial via the PMT Progress Report (submitted by the Study Principal Investigator according to the frequency outlined in the City of Hope Institutional DSMP). The DSMC is composed of clinical specialists who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Protocol Management Team.

16.7 Protocol Amendments

Proposed amendments to the protocol require review and approval by TG Therapeutics, Inc. and AstraZeneca prior to implementation. After approval by TG Therapeutics, Inc. and AstraZeneca, the amendment will be submitted formally to the FDA by the Principal Investigator. If an amendment to the protocol substantially alters the study design or the potential risks to patients, patients' consent to continue participation in the study should be obtained per institutional policies.

17.0 ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979) and the Declaration of Helsinki.

17.2 Regulatory Compliance

This study is to be conducted in compliance with the IRB approved protocol and according to the following considerations:

- US Code of Federal Regulations (CFR) governing clinical study conduct
  - Title 21 Part 11 – Electronic Records; Electronic Signatures
  - Title 21 Part 50 – Protection of Human Subjects
  - Title 21 Part 54 – Financial Disclosure by Clinical Investigators
  - Title 21 Part 56 – Institutional Review Boards
  - Title 21 Part 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
  - Title 21 Part 312 – Investigational New Drug Application
  - Title 45 Part 46 – Protection of Human Subjects
- US Federal legislation, including but not limited to
  - Health Insurance Portability and Accountability Act of 1996
  - Section 801 of the Food and Drug Administration Amendments Act
- Applicable state and local laws. For research occurring in California, this includes but is not limited to State of California Health and Safety Code, Title 17
- Applicable institutional research policies and procedures

17.3 Institutional Review Board

An Institutional Review Board (IRB) that complies with the federal regulations at 45 CFR 46 and 21 CFR 50, 56 and State of California Health and Safety code, Title 17, must review and approve this protocol, informed consent form and any additional documents that the IRB may need to fulfill its responsibilities

(Investigator's Brochure, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) prior to initiation of the study. Revisions to approved documents will require review and approval by the IRB before the changes are implemented in the study. All institutional, NCI, Federal, and State of California regulations must be fulfilled.

Each participating non-COH institution must provide for the review and approval of this protocol and the associated informed consent documents by an appropriate IRB holding a current US Federal wide Assurance issued by and registered with the Office for Human Research Protections (OHRP). The protocol and consent will be reviewed and approved by the COH IRB before submission to a participating site IRB.

The IRB's written unconditional approval of the study protocol and the informed consent document must be in the possession of the investigator, and, for external sites, the possession of the DCC, before the study is initiated.

The IRB will be informed of serious unexpected, unanticipated adverse experiences, and unanticipated problems occurring during the study, and any additional adverse experiences in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

All participating sites must follow the lead institution's IRB-approved protocol.

17.4 Informed Consent

Each participating non-COH institution will be provided with a model informed consent form. Each institution may revise or add information to comply with local and/or institutional requirements, but may not remove procedural or risk content from the model consent form. Furthermore, prior to submission to the site's IRB (initial submission and amendments), the consent and accompanying HIPAA form, if separate to the consent, must be reviewed and approved by the DCC.

The Principal Investigator or IRB approved named designee will explain the nature, duration, purpose of the study, potential risks, alternatives and potential benefits, and all other information contained in the informed consent document. In addition, they will review the experimental subject's bill of rights if applicable, and the HIPAA research authorization form. Prospective participants will be informed that they may withdraw from the study at any time and for any reason without prejudice, including as applicable, their current or future care or employment at City of Hope or participating institution or any relationship they have with City of Hope or participating institution. Prospective participants will be afforded sufficient time to consider whether or not to participate in the research.

After the study has been fully explained, written informed consent will be obtained from either the prospective participant or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

A copy of the signed informed consent will be given to the participant or his/her legally authorized representative. The original signed consent must be maintained by the site investigator and available for inspection by sponsor designated representatives, or regulatory authority at any time.

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation.

17.5 Participant Withdrawal

Participants may withdraw from the study at any time and for any reason without prejudice. The withdrawal must be documented per institutional policies. The COH DCC should be promptly notified of the change in participant status.

Participant withdrawal may consist of any of the following with regard to study procedures and data collection:

- Withdrawal from study treatment, but agreement to continue with active study procedures and chart review and survival follow-up.
- Withdrawal from study treatment and all active procedures, but agreement for chart review and survival follow-up.
- Withdrawal from study treatment, all active procedures, and any future data collection.

Participants who agreed to the collection of research blood samples may withdraw consent to use their specimens, if they are not yet processed as detailed in the consent form. Once the PI and site PI is notified of this withdrawal of informed consent, the research specimens will not be used in any research. At that time, any of the existing specimens will be destroyed.

17.6 Special and Vulnerable Populations

17.6.1 Women and Minorities

The study is open to anyone regardless of gender, race or ethnicity. Efforts will be made to extend the accrual to a representative population. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

Pregnant women are excluded because the effects of study drugs on embryogenesis and reproduction are unknown. Acalabrutinib may cause fetal harm.

17.6.2 Pediatric Population

The incidence of mantle cell lymphoma is rare in the pediatric population.

17.6.3 HIV Positive Individuals

Participants with HIV are excluded due to concerns about inadvertent augmentation of infectious and/or inflammatory activity.

17.6.4 Vulnerable Populations

Per 45 CFR §46.111 (a)(3) and 45 CFR §46, Subparts B-D identifies children, prisoners, pregnant women, mentally incapacitated persons, and economically or educationally disadvantaged persons as vulnerable populations.

Adults lacking capacity to consent are not excluded from participation. This study does not pose additional risks for adults lacking capacity than for the general population. In such instances, informed consent will be sought and documented from the prospective participant's legally authorized representative in agreement with institutional policies and local IRB approval.

Economically/educationally disadvantaged persons are not actively targeted for participation, nor are they excluded from participation. This study does not pose additional risks for economically/educationally disadvantaged persons than for the general population.

17.7 Participant Confidentiality

Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples in addition to any study information relating to participants.

This research will be conducted in compliance with federal and state requirements relating to protected health information (PHI), including the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). HIPAA regulations require a signed subject authorization informing the subject of the nature of the PHI to be collected, who will have access to that information and why, who will use or disclose that information, and the rights of a research participant to revoke their authorization for use of their PHI. In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508. When results of this study are reported in medical journals or at meetings, identification of those taking part will not be disclosed and no identifiers will be used.

Medical records of subjects will be securely maintained in the strictest confidence, according to current legal requirements. Data will be entered, analyzed and stored in encrypted, password protected, secure computers that meet all HIPAA requirements. All data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number.

Source documents provided to the DCC for the purpose of auditing or monitoring will be de-identified and labeled with the study number, subject ID, and if applicable patient initials.

The Investigator/Institution will permit direct access to source data and documents by sponsor representatives, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

Participant specimens will be de-identified (coded) prior to submission to research laboratories. The specimens will be labeled with the study number, subject (accession) ID, date and time point of collection. The key to the code will be maintained in the COH clinical trials management system which is a secure environment.

17.8 Use of Unused (Leftover) Specimens Collected for this Trial

Unused samples in existence at study completion (i.e. completion of all research activities under this study) will either be: (a) placed in a COH IRB approved biorepository with some clinical information and potentially PHI attached or (b) discarded.

With regard to which option will apply, each site IRB may choose to either: (a) leave the determination to the participant via a question in the informed consent document, which would be communicated to the study registrar (DCC) at the time of participant registration, OR b) may choose to make a single determination on behalf of their respective participants, and communicate that determination to their respective participants via the informed consent.

Samples may only be used for correlative analyses described in the protocol approved by TG Therapeutics, Inc. Unused samples may not be used for other purposes without prior approval by TG Therapeutics. Investigators and institution may not provide samples taken from study subjects to anyone outside of their institution for any purpose without written pre-approval by TG Therapeutics, Inc.

17.9 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study Sponsor (City of Hope) prior to participation in this study. All City of Hope investigators will follow the City of Hope conflict of interest policy.

17.10 Financial Obligations, Compensation, and Reimbursement of Participants

Acalabrutinib, ublituximab, and umbralisib will be provided free of charge to participants.

Neither the research participant nor the insurance carrier will be responsible for the research procedures related to this study.

Standard of care drugs or procedures provided during the course of study participation will be the responsibility of the research participant and/or the insurance carrier. The participant will be responsible for all copayments, deductibles, and other costs of treatment and diagnostic procedures as set forth by the insurance carrier. The participant and/or the insurance carrier will be billed for the costs of treatment and diagnostic procedures in the same way as if the participant were not in a research study.

In the event of physical injury to a participant resulting from research procedures, appropriate medical treatment will be available at City of Hope or at the non-COH site to the injured participant. There are no plans for City of Hope to provide financial compensation in the event of physical injury to a participant.

The research participant will not receive reimbursement or payment for taking part in this study.

17.11 Publication/ Data Sharing

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by City of Hope for the purposes of performing the study, will be published or passed on to any third party without the written approval of the Study PI. Any investigator involved with this study is obligated to provide City of Hope with complete test results and all data derived from the study.

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement between City of Hope, AstraZeneca, TG therapeutics, and participating non-COH institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

In accordance with the U.S. Public Law 110-85 (Food and Drug Administration Amendments Act of 2007 or FDAAA), Title VIII, Section 801, this trial will be registered onto ClinicalTrials.gov. Results will be reported on ClinicalTrials.gov generally within 12 months after the completion date unless criteria to delay submission are met per the final rule.

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APPENDIX A: ECOG PERFORMANCE STATUS SCALE

ECOG Performance Scale [52]	
Grade	**Descriptions**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX B: NYHA CARDIAC GRADING CRITERIA

Modified from Dolgin et al., 1994 [53]

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX C: LYMPHOMA RESPONSE CRITERIA [54]

Response	Site	CT-Based Response	PET-CT Based Response
Complete Response		Complete radiologic response (all of the following)	Complete metabolic response (even with a persistent mass)
	Lymph nodes and extralymphatic sites	Target nodes/nodal masses must regress to ≤1.5 cm in longest diameter (LDi). No extralymphatic sites of disease.	Score ≤ 3* with or without a residual mass on 5-point scale†. It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., 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.
	Nonmeasured lesion	Absent	Not applicable
	Organ enlargement	Regress to normal	Not applicable
	New lesions	None	None
	Bone marrow	Normal by morphology; if indeterminate, IHC negative	No evidence of FDG-avid disease in marrow
Partial Response		Partial remission (all of the following)	Partial metabolic response
	Lymph nodes and extralymphatic sites	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease
	Nonmeasured lesion	Absent/normal, regressed, but no increase	Not applicable
	Organ enlargement	Spleen must have regressed by > 50% in length beyond normal	Not applicable
	New lesions	None	None

Response	Site	CT-Based Response	PET-CT Based Response
	Bone marrow	Not applicable	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan
No response or stable disease		Stable disease	No metabolic response
	Target nodes/nodal masses, extranodal lesions	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met	Score 4 or 5† with no significant change in FDG uptake from baseline at interim or end of treatment
	Nonmeasured lesion	No increase consistent with progression	Not applicable
	Organ enlargement	No increase consistent with progression	Not applicable
	New lesions	None	None
	Bone marrow	Not applicable	No change from baseline
Progressive disease		Progressive disease requires at least 1 of the following	Progressive metabolic disease
	Individual target nodes/nodal masses	PPD progression:	Score 4 or 5† with an increase in intensity of uptake from baseline and/or
	Extranodal lesions	An individual node/lesion must be abnormal with: • Longest diameter (LDi) > 1.5 cm and • Increase by ≥ 50% from PPD nadir and • An increase in LDi or shortest diameter (SDi) from nadir 0.5 cm for lesions ≤ 2 cm 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 (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must	• New FDG-avid foci consistent with lymphoma at interim OR end-of-treatment assessment

Response	Site	CT-Based Response	PET-CT Based Response
		increase by at least 2 cm from baseline New or recurrent splenomegaly	
	Nonmeasured lesion	New or clear progression of preexisting nonmeasured lesions	None
	New lesions	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.
	Bone marrow	New or recurrent involvement	New or recurrent FDG-avid foci

Measured dominant lesions:

Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas.

Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation.

Nonmeasured lesions:

Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment).

†*PET 5-point scale*:

1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

Abbreviations:

CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross

product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

APPENDIX D: REGISTRATION COVERSHEET

COH IRB# 20459: A Phase 2 Study of Acalabrutinib and PI3Kδ inhibitor Umbralisib in Combination with Ublituximab (AU2) in Patients with Previously Untreated Mantle Cell Lymphoma

Data Coordinating Center:
City of Hope
1500 Duarte Road
Duarte, CA 91010
Tel: (626)-218-7904
Email: DCC@coh.org (use #secure# in subject line)

Site Principal Investigator
Name:

CRA/Study Coordinator:	Contact Number:
Patient's Initials: (F M L):	Institution:
	PI/ Sub-Investigator:
Patient's DOB:	IRB approval valid until (date):
Sex: _____Male _____Female	Date Informed Consent Signed:
	Projected start date of treatment:

Race		Ethnicity	
☐	Black	☐	Hispanic
☐	Caucasian	☐	Non-Hispanic
☐	Asian	☐	Other_____
☐	American Indian		
☐	Native Hawaiian/Pacific Islander		
☐	Other_____ _____		

Method of Payment:_____

Codes:

01 Private	**06** Military or Veterans Adm. sponsored
02 Medicare	**07** Self-pay (no insurance)
03 Medicare & private ins.	**08** No means of payment (no insurance)
04 Medicaid	**09** Unknown
05 Medicaid & Medicare	

Reason for Screen Failure:

Reason for Failing to Initiate Protocol Therapy:

APPENDIX E: PROTON PUMP INHIBITORS AND CYP3A INHIBITORS AND INDUCERS

Examples of proton pump inhibitors, and CYP3A inhibitors and inducers
Proton-pump inhibitors[1]
Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole, Dexlansoprazole
Strong CYP3A Inhibitors[1,2]
Ketoconazole, Clarithromycin, Itraconazole, Nefazodone, Saquinavir, Ritonavir, Indinavir, Nelfinavir, Voriconazole, Lopinavir, Telithromycin, Conivaptan, Posaconazole, Boceprevir, Telaprevir, Cobicistat, Idelalisib, Grapefruit, Starfruit, Seville Oranges
Moderate CYP3A Inhibitors[1,2]
Erythromycin, Verapamil, Diltiazem, Cyclosporine, Ciprofloxacin, Fluvoxamine, Fluconazole, Aprepitant, Imatinib, Nilotinib, Dronedarone, Crizotinib, Atazanavir, Letermovir, Duvelisib
Strong CYP3A Inducers[1,2]
Phenytoin, Carbamazepine, Rifampin, Mitotane, Fosphenytoin, St John's Wort, Enzalutamide Lumacaftor
[1]This is not an exhaustive list. Investigators should consult additional resources (e.g., website, drug label) for a full list or for more info on individual drugs. [2]Refer to Flockhart Table™ for a more detailed list of CYP3A inducers and inhibitors (https://drug-interactions.medicine.iu.edu/Main-Table.aspx).

APPENDIX F: CORRELATIVE TISSUE FORM (FOR ALL SITES)

A copy of this form should <u>accompany the sample shipments</u> to Dr. Danilov's laboratory.

Non-COH sites: refer to **Appendix G** for shipping instructions.

COH IRB number: 20459	Shipping date (MM-DD-YYYY): _____/_____/_____
Subject ID (issued by DCC):	Participant Initials (F, M, L) (if applicable):
Institution:	
Date of collection/ biopsy (MM-DD-YYYY): _____/_____/_____	
Time point: ☐ Baseline ☐ Progression	
Diagnosis:	
Tissue type (FFPE scrolls, slides, biopsies):	
Number of scrolls:	Number of slides:

CRA/Study Coordinator/Nurse Printed Name:
CRA/Study Coordinator/Nurse Signature:
Contact Number:

APPENDIX G: TISSUE SHIPPING GUIDELINES TO DR. DANILOV'S LABORATORY

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Thursday**. If this is not feasible, advance arrangements should be made with Dr. Danilov or his representative (DL-danilovlab@coh.org).

2. Notify Dr. Danilov or his representative (DL-danilovlab@coh.org) of impending shipment. Sites must create their own FedEx shipping labels.

3. **Slides/ Blocks:** Batch ship at room temperature via FedEx. During extreme heat, include refrigerated (not frozen) gel packs or gel insulators.

   It is recommended to ship samples via FedEx overnight (for a delivery by 3 pm or earlier the next day) or FedEx 2-day (with a morning delivery). During extreme heat, ship via FedEx overnight (for a delivery ideally by 10.30 am, or 3 pm the next day).

4. **Frozen samples** should be batch shipped on dry ice via FedEx overnight (for a delivery by 10.30 am the next day). The shipment should contain enough dry ice to last at least 72 hours.

5. On the day of shipment, email the sample shipment information to Dr. Danilov or his representative (DL-danilovlab@coh.org).

6. Ship samples with a **copy of the correlative tissue form (Appendix F)** and a **copy of the pathology report** to:

Dr. Alexey Danilov MD, PhD
Kaplan Clinical Research Building 1st floor, 158-1022
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
Telephone: 626-218-1959

APPENDIX H: CORRELATIVE BLOOD/ BONE MARROW COLLECTION FORM FOR NON-COH SITES ONLY

COH IRB number: 20459	Participant Initials (F, M, L) (if applicable):
Subject ID (issued by DCC):	Institution:

To be used by **non-COH sites** for the following blood/bone marrow samples being sent to **Dr. Danilov's lab**:

Blood Samples							
Blood Sample #	**Time point of Collection**	**Expected Volume**	**Tube Type Used**	**Collected Volume**	**Time of Collection**	**Date of Collection**	**Indicate which sample was collected**
1.	Cycle 1, Day 1	30 mL	Purple-top	_____ mL	____:____ AM/ PM	____/____/____	☐
		Up to 10 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
2.	Cycle 2, Day 1	20 mL	Purple-top	_____mL	____:____ AM/ PM	____/____/____	☐
3.	Cycle 8, Day 1	20 mL	Purple -top	_____ mL	____:____ AM/ PM	____/____/____	☐
		Up to 10 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
4.	Cycle 14, Day 1	20 mL	Purple -top	_____ mL	____:____ AM/ PM	____/____/____	☐
		Up to 10 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
5.	EOM (End of maintenance)	20 mL	Purple -top	_____ mL	____:____ AM/ PM	____/____/____	☐
		Up to 10 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐
6.	At relapse	20 mL	Purple -top	_____ mL	____:____ AM/ PM	____/____/____	☐
		Up to 10 mL	Cell-free DNA BCT	_____ mL	____:____ AM/ PM	____/____/____	☐

Bone Marrow Samples						
Indicate which sample was collected	**Time point of Collection**	**Expected Volume**	**Tube Type Used**	**Collected Volume**	**Time of Collection**	**Date of Collection**
☐	Baseline	10 mL	Purple -top	_____ mL	____:____ AM/ PM	____/____/____
☐	Suspected CR	10 mL	Purple -top	_____ mL	____:____ AM/ PM	____/____/____
☐	Relapse	10 mL	Purple -top	_____ mL	____:____ AM/ PM	____/____/____

A copy of this form should accompany the sample shipments to Dr. Danilov's lab.

Refer to the blood/bone marrow shipping guidelines for shipping instructions (Appendix I).

CRA/Study Coordinator/ Nurse:	Contact Number:
CRA/Study Coordinator/ Nurse Signature:	Date:

APPENDIX I: BLOOD & BONE MARROW SHIPPING GUIDELINES TO DR. DANILOV'S LABORATORY

*These guidelines apply to **non-COH sites** only.*

All biological material must be shipped according to applicable government and International Air Transport Association (IATA) regulations.

Shipping guidelines can also be found on the FedEx website.

1. Aim to ship samples on a **Monday through Thursday**. If this is not feasible, advance arrangements should be made with Dr. Danilov or his representative (DL-danilovlab@coh.org). Sites must create their own FedEx shipping labels.

1. Blood/bone marrow samples in **purple-top tubes** will be sent **overnight at ambient temperature (15-25°C)** in an appropriate container via FedEx. Cell-free BCT tubes **should be shipped as soon as possible but no more than 3 days after being drawn** via overnight courier at ambient temperature. All tubes must be stored at room temperature while awaiting shipment as cold temperatures can affect future analyses.

2. **On the day of shipment**, email Dr. Danilov or his representative (DL-danilovlab@coh.org) the FedEx shipment #.

3. Ship samples with a **copy of the correlative blood/bone marrow collection form** (Appendix H) and a **copy of the latest CBC results (with differential)** and the **date of the test** to:

Dr. Alexey Danilov MD, PhD
Kaplan Clinical Research Building 1st floor, 158-1022
City of Hope National Medical Center
1500 E. Duarte Road
Duarte, CA 91010
Telephone: 626-218-1959

APPENDIX J: HEPATITIS B SEROLOGIC TEST RESULTS

Interpretation of Hepatitis B Serologic Test Results

Hepatitis B serologic testing involves measurement of several hepatitis B virus (HBV)-specific antigens and antibodies. Different serologic "markers" or combinations of markers are used to identify different phases of HBV infection and to determine whether a patient has acute or chronic HBV infection, is immune to HBV as a result of prior infection or vaccination, or is susceptible to infection.

HBsAg **anti-HBc** **anti-HBs**	negative negative negative	Susceptible
HBsAg **anti-HBc** **anti-HBs**	negative positive positive	Immune due to natural infection
HBsAg **anti-HBc** **anti-HBs**	negative negative positive	Immune due to hepatitis B vaccination
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive positive negative	Acutely infected
HBsAg **anti-HBc** **IgM anti-HBc** **anti-HBs**	positive positive negative negative	Chronically infected
HBsAg **anti-HBc** **anti-HBs**	negative positive negative	Interpretation unclear; four possibilities: 1. Resolved infection (most common) 2. False-positive anti-HBc, thus susceptible 3. "Low level" chronic infection 4. Resolving acute infection

Adapted from: A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. Part I: Immunization of Infants, Children, and Adolescents. MMWR 2005;54(No. RR-16).

- **Hepatitis B surface antigen (HBsAg):** A protein on the surface of hepatitis B virus; it can be detected in high levels in serum during acute or chronic hepatitis B virus infection. The presence of HBsAg indicates that the person is infectious. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- **Hepatitis B surface antibody (anti-HBs):** The presence of anti-HBs is generally interpreted as indicating recovery and immunity from hepatitis B virus infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.
- **Total hepatitis B core antibody (anti-HBc):** Appears at the onset of symptoms in acute hepatitis B and persists for life. The presence of anti-HBc indicates previous or ongoing infection with hepatitis B virus in an undefined time frame.
- **IgM antibody to hepatitis B core antigen (IgM anti-HBc):** Positivity indicates recent infection with hepatitis B virus (≤6 mos). Its presence indicates acute infection.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention
Division of Viral Hepatitis

CDC

www.cdc.gov/hepatitis

APPENDIX K: HIGHLY EFFECTIVE CONTRACEPTION METHODS

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.

APPENDIX L-1: PATIENT DRUG DIARY INSTRUCTIONS

COH IRB number: 20459	Participant Initials (F, M, L) (if applicable):
Subject ID (issued by DCC):	Institution:

General Instructions:

1. Record the date and number of tablets that you took.
2. Record any comments, side effects, missed, vomited or skipped doses in the Comments column.
3. Bring this diary, all study drug bottles, and any unused tablets to each clinic visit. Do not throw away empty study drug bottles or unused tablets.
4. Do not share your drug supply or transfer it to any other container.

Umbralisib Specific Instructions:

- Take umbralisib **once a day within 30 minutes of starting a meal**, at approximately the same time each day.
- Tablets should be swallowed whole. The tablets should not be broken or chewed.
- If you miss a dose by **less than 12 hours**, take the missed dose right away. If you missed a dose by **more than 12 hours**, skip the missed dose and take the next dose at the usual time.
- If you vomit a dose, wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Acalabrutinib Specific Instructions:

- Take acalabrutinib **twice a day (about 12 hours apart) with or without food**, at approximately the same time each day.
- Tablets should be swallowed whole. The tablets should not be opened, broken or chewed.
- If you miss a dose by **less than 3 hours**, take the missed dose right away. If you missed a dose by **more than 3 hours**, skip the missed dose and take the next dose at the usual time.
- If you vomit a dose, wait until the next scheduled dose; do not take extra medicine to make up the vomited dose.

Study Contact Information	
Study Doctor **Phone:** **Name:**	**Study Nurse** **Phone:** **Name:**

APPENDIX L-2: PATIENT DRUG DIARY *** FOR CYCLE 1 ONLY ***

COH IRB number: 20459	Participant Initials (F, M, L) (if applicable):
Subject ID (issued by DCC):	Institution:
Cycle #: 1	*Cycle start date: _____*

*****For clinic staff use only*****

Umbralisib daily dose: _____ *mg (* _____ *tablets)*

Acalabrutinib dose: _____ *mg (* _____ *tablets)* _____ *a day*

CYCLE 1						
Cycle Day	**Week Day**	**Date**	**Umbralisib # of tablets taken**	**Acalabrutinib # of tablets taken**		**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
1				AM:	PM:	
2				AM:	PM:	
3				AM:	PM:	
4				AM:	PM:	
5				AM:	PM:	
6				AM:	PM:	
7				AM:	PM:	
8				AM:	PM:	
9				AM:	PM:	
10				AM:	PM:	
11				AM:	PM:	
12				AM:	PM:	
13				AM:	PM:	
14				AM:	PM:	
15				AM:	PM:	
16				AM:	PM:	

COH IRB number: 20459	Participant Initials (F, M, L) (if applicable):
Subject ID (issued by DCC):	Institution:

CYCLE 1 (continued)						
Cycle Day	**Week Day**	**Date**	**Umbralisib # of tablets taken**	**Acalabrutinib # of tablets taken**		**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
17				AM:	PM:	
18				AM:	PM:	
19				AM:	PM:	
20				AM:	PM:	
21				AM:	PM:	
22				AM:	PM:	
23				AM:	PM:	
24				AM:	PM:	
25				AM:	PM:	
26				AM:	PM:	
27				AM:	PM:	
28				AM:	PM:	

*****For clinic staff use only*****

# of Umbralisib tablets dispensed: _____ # of Umbralisib tablets returned: _____

# of Acalabrutinib tablets dispensed: _____ # of Acalabrutinib tablets returned: _____

Compare with drug diary entries made by participant/guardian.
If there is a discrepancy, please reconcile.

STUDY STAFF SIGNATURE/ INITIALS: **DATE:**

APPENDIX L-3: PATIENT DRUG DIARY *** FOR ALL OTHER CYCLES ***

COH IRB number: 20459	Participant Initials (F, M, L) (if applicable):
Subject ID (issued by DCC):	Institution:
Cycle #: ____	*Cycle start date:* _____

*****For clinic staff use only*****

Umbralisib daily dose: _____ *mg (* _____ *tablets)*

Acalabrutinib dose: _____ *mg (* _____ *tablets)* _____ *a day*

ALL OTHER CYCLES						
Cycle Day	**Week Day**	**Date**	**Umbralisib # of tablets taken**	**Acalabrutinib # of tablets taken**		**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
1				AM:	PM:	
2				AM:	PM:	
3				AM:	PM:	
4				AM:	PM:	
5				AM:	PM:	
6				AM:	PM:	
7				AM:	PM:	
8				AM:	PM:	
9				AM:	PM:	
10				AM:	PM:	
11				AM:	PM:	
12				AM:	PM:	
13				AM:	PM:	
14				AM:	PM:	
15				AM:	PM:	
16				AM:	PM:	

COH IRB number: 20459	Participant Initials (F, M, L) (if applicable):
Subject ID (issued by DCC):	Institution:

ALL OTHER CYCLES (continued)						
Cycle Day	**Week Day**	**Date**	**Umbralisib # of tablets taken**	**Acalabrutinib # of tablets taken**		**Comments** *Write down missed/ vomited doses, side-effects (e.g. nausea, vomiting etc.)*
17				AM:	PM:	
18				AM:	PM:	
19				AM:	PM:	
20				AM:	PM:	
21				AM:	PM:	
22				AM:	PM:	
23				AM:	PM:	
24				AM:	PM:	
25				AM:	PM:	

*****For clinic staff use only*****

# of Umbralisib tablets dispensed: _____ # of Umbralisib tablets returned: _____

# of Acalabrutinib tablets dispensed: _____ # of Acalabrutinib tablets returned: _____

Compare with drug diary entries made by participant/guardian.
If there is a discrepancy, please reconcile.

STUDY STAFF SIGNATURE/ INITIALS: **DATE:**