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UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Clinical Study Protocol RG1006269

Acalabrutinib in combination with anti-CD19 Chimeric antigen receptor T-cells (CART) in B-cell lymphoma

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

ABBREVIATION	TERM
ACTH	adrenocorticotropic hormone
AE	adverse event
AIHA	autoimmune hemolytic anemia
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
aPTT	activated partial thromboplastin time
ART	antiretroviral therapy
ASH	American Society of Hematology
BTK	Bruton's tyrosine kinase
CART	chimeric antigen receptor T-cell
CLL	chronic lymphocytic leukemia
CNS	central nervous system
CR	complete response
CRP	C-reactive protein
CRS	cytokine release syndrome
CSF	cerebral spinal fluid
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CYP3A4	cytochrome P450 3A4
DLBCL	diffuse large B-cell lymphoma
DSMB	Data and Safety Monitoring Board
DSMC	Consortium Data and Safety Monitoring Committee
EBV	Epstein-Barr virus
EGFR	epidermal growth factor receptor
FL	follicular lymphoma
HbsAg	hepatitis B surface antigen
HGBCL	high grade B-cell lymphoma
HIV	human immunodeficiency virus
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
ITP	idiopathic thrombocytopenic purpura
MAS	macrophage activation syndrome

MCL	mantle cell lymphoma
NK	natural killer
NT	neurotoxicity
PBMC	peripheral blood mononuclear cells
PJP	pneumocystis jiroveci pneumonia
PD	progressive disease
PD-1	programmed cell death protein 1
Q12	every twelve hours
QD	daily
PCR	polymerase chain reaction
PI	principal investigator
PRBC	packed red blood cells
R/R	relapsed/refractory
SAE	serious adverse event
sCRS	severe cytokine release syndrome
SOC	standard of care
SOP	standard operating procedures
SRC	Scientific Review Committee
tFL	transformed follicular lymphoma
TLS	tumor lysis syndrome
TPP	therapeutics product program
WBC	white blood cell
WHO	World Health Organization
WOCBP	Women of child-bearing potential

Protocol Title	Acalabrutinib in combination with anti-CD19 Chimeric antigen receptor T-cells (CART) in B-cell lymphoma
Protocol Number	RG10056269
Protocol Sponsor	Ajay Gopal, MD, University of Washington
Trial Phase	Phase I/II
Trial Type	Interventional
Clinical Indication	B-cell non-Hodgkin lymphoma including diffuse large B-cell lymphoma (DLBCL), high-grade B-cell lymphoma (HGBCL), primary mediastinal large B-cell lymphoma (PMBCL) and transformed follicular lymphoma (tFL), follicular lymphoma (FL)
Study Objectives	**Primary Objectives** 1. To evaluate the safety and feasibility of combining acalabrutinib and anti-CD19 CART therapy in B-cell lymphomas. **Secondary Objectives** 1. To estimate the clinical efficacy as measured by complete response (CR) rate of acalabrutinib and anti-CD19 CART therapy. 2. To determine the clinical efficacy of combination therapy for specific molecular subtypes of B-cell lymphomas (primary mediastinal B-cell lymphoma, high grade B-cell lymphomas with ≥ 2 translocations, germinal center, non-germinal center, follicular lymphoma). 3. To estimate the response rate and disease control rate (CR+PR+SD) following bridging prior to CART. **Exploratory Objectives** 1. To describe the impact of acalabrutinib on T-cell subsets, IL-6 levels, cytokine levels
Study Design	Phase I/II single arm, unblinded trial.
Population	B-cell non-Hodgkin lymphoma. The following histologies will be included: 1. Diffuse large B-cell lymphoma (DLBCL) 2. High-grade B-cell lymphoma (HGBCL) 3. Primary mediastinal large B-cell lymphoma (PMBCL) and 4. Transformed follicular lymphoma (tFL) 5. Indolent (grade 1-3a) Follicular lymphoma (FL)

	Two arms: 1. Non-HIV infected patients 2. HIV infected patients
Endpoints	**Primary Endpoint** • Toxicity as defined by the following: grade ≥ 3 CRS, grade ≥ 3 NT within 30 days of infusion of axi-cel. **Secondary Endpoints** • Complete response rate following CART, per Lugano criteria overall survival, progression-free survival. • Response rate and disease control rate (CR+PR+SD) following bridging prior to CART **Exploratory Endpoints** • T-cell subsets, IL-6, cytokine levels.
Type of control	No treatment control
Investigation Drug	Acalabrutinib
Dose	100 mg every 12 hours starting up to 3 weeks and at least 24 hours before leukapheresis
Route of administration	Oral
Regimen	Acalabrutinib followed by Axicabtagene ciloleucel (Axi-Cel) treatment
Trial Blinding	Unblinded, open label
Treatment Groups	1 group
Efficacy Assessments	Safety assessment will occur through the study and consist of continuous surveillance and recording of adverse events (AEs) and serious adverse events (SAEs). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring. Subjects may have post- treatment follow-up for disease status up to 5 years at longest, or until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.
Number of trial subjects	50 (20 large B-cell lymphoma and 20 follicular lymphoma, 10 HIV associated lymphoma).
Estimated duration of trial	36 months (estimated time from first subject enrollment through final subject completion of study intervention)

Duration of Participation	15 months. Subjects will be followed for up to 5 years per standard of care.

1. BACKGROUND

Anti-CD19 chimeric antigen receptor T-cells (CART) demonstrate efficacy in B-cell malignancies, leading to FDA approval of axicabtagene ciloleucel (axi-cel) and tisagenlecleucel for large B-cell lymphomas (DLBCL) in 2017 and 2018, respectively and most recently axi-cel for indolent follicular lymphoma (FL) after two prior lines of therapy[1-2]. However, durable responses are only seen in a minority of study-treated patients, most typically in those who achieve an early complete response (CR)[1-3]. The remaining patients will suffer progressive disease (PD) and succumb to their lymphomas. A proportion of patients may also achieve an initial response following CART but ultimately suffer relapse. Some patients never even receive CART due to disease progression in the weeks between leukapheresis and CART infusion. Thus, strategies such as combination regimens to improve outcomes over all phases of CART are warranted. Bruton's tyrosine kinase (BTK) inhibitors demonstrate single agent anti-lymphoma activity, are well tolerated, and have been shown in preclinical models to increase persistence of activated T-cells, decrease regulatory T-cells, and augment effector functions of anti-CD19 CARTs[4]. As such, we postulate that combining the 2nd generation BTK inhibitor acalabrutinib with anti-CD19 CART will be safe, feasible, and show improved efficacy compared to anti-CD19 CART given alone. The simple intervention of adding a BTK inhibitor in this phase I/II study has the potential to improve outcomes for patients with relapsed/refractory (R/R) DLBCL and FL while enhancing our understanding of the biology of cellular therapeutics.

2. STUDY PURPOSE AND RATIONALE

2.1 Rationale for Investigation

It is clear that more effective strategies are needed to improve both initial CR rates and durable CR rates for patients receiving CART. Combining CART with novel agents targeting different pathways in the pathophysiology of B-cell lymphoma is one strategy. Multiple studies now indicate the benefits of BTK inhibitors in treating B-cell malignancies, with FDA approvals in chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL) and Waldenstrom macroglobulinemia. In preclinical models, BTK inhibitors such as ibrutinib and acalabrutinib have been found to augment CART expansion and efficacy. Particularly for CLL, ibrutinib has been demonstrated to increase the in vivo persistence of $CD4^+$ and $CD8^+$ activated T-cells while diminishing the immunosuppressive responses of malignant B-cells by down regulating CTLA-4 and PD-1 expression in T-cells.[5] Fraitta et. al (*Blood* 2016) reported three patients with CLL having received ibrutinib prior to anti-CD19 CART, two benefiting from a PR and one with CR[4]. While these numbers are small, they provide data showing the feasibility of combining BTK inhibitors with CART. Furthermore, Gauthier et al presented data at the American Society of Hematology (ASH) 2018 annual meeting on the combination of ibrutinib with the CD19-specific CART JCAR017, currently used in late clinical trials, showing that the concurrent administration of this BTK-inhibitor did not affect the frequency or severity of neurotoxicity while decreasing the rates of cytokine-release syndrome (Gauthier et al. *Blood* 2020). The immunomodulatory effects of BTK inhibitors provide rationale in combining BTK inhibition with CART, further supported by studies

indicating how ibrutinib improves *ex vivo* CART expansion and *in vivo* CART proliferation while enhancing CART function.[6] Acalabrutinib has also been shown to increase peripheral proliferation of CART, while enhancing *in vivo* efficacy in tumor models.[6] Acalabrutinib has less off-target inhibitory effects compared to ibrutinib, and these off target effects may lead to platelet dysfunction, severe bleeding and other untoward side effects including rash.[7] Therefore, acalabrutinib may be the preferred approved BTK inhibitor to combine with CART, given the well-reported and serious toxicities of cytokine-release syndrome (CRS) and neurotoxicity (NT) which may be seen in CART. These preliminary data support our hypothesis that combining acalabrutinib with anti-CD19 CART will be safe and feasible**.**

Published data on the two FDA-approved anti-CD19 CART agents (axicabtagene ciloleucel, tisagenlecleucel), in addition to lisocabtagene maraleucel (JCAR017) which is being used in late clinical trials for R/R large B-cell lymphomas, report a best complete response (CR) rate between 40-63% and CR rate at 6 months between 30-50%.[1-3] In addition, although the ZUMA-5 trial noted a continued remission rate of 75% at 18 months after axicabtagene ciloleucel in R/R FL patients, follow up time is short. These data show that despite advances in this field incorporating CART in the R/R setting, the majority of patients receiving CART still do not obtain durable responses or achieve cure. Aggregate outcomes from the University of Washington/Fred Hutchinson Cancer Center (UW/FHCC) found that roughly 30% of large B-cell lymphoma patients receiving CART achieved a CR, a rate comparable to the literature. Furthermore, data from the UW/FHCRC show statistically inferior survival for individuals who develop PD at initial disease response assessment following CART infusion compared to those who obtain an initial CR, partial response (PR) or stable disease (SD), then subsequently progress. We found a median overall survival (OS) of 5.3 months after patients exhibited evidence for PD. Those with initial PD after CART had a median OS of 3.75 months, while the median OS for those whose disease responded initially to CART then subsequently progressed was 13.42 months, emphasizing the much needed work in this setting to improve patient outcomes and survival (Chow et. al, ASH 2018).

The role of pre-CART bridging therapy, defined as treatment given between the crucial time between leukapheresis for T-cell collection and infusion of the CART product back to the patient, was also explored in a cohort of patients at the UW/FHCRC. Before CART infusion is accomplished, a series of critical steps are required; therefore, an average of at least 2-3 weeks elapse between leukapheresis and infusion of the final CART product to the patient.[10,11] A proportion of patients remain at very high risk for manifesting progressive lymphoma during this period of time, urging providers to employ bridging therapy as a means to control disease during CART manufacturing. Therapies differ widely, ranging from corticosteroids, chemotherapy, radiotherapy to molecularly-targeted and more novel agents. Data from the UW/FHCRC suggest patients who received any form of bridging therapy prior to CART had a numerically inferior 12-month event free survival (21.0% v. 42.8%) and OS (31.8% v. 57.4%) compared to those not receiving any bridging therapy (Lynch et. al, unpublished). While not statistically significant, these data suggest that patients requiring bridging therapy are likely sicker and in more need of urgent therapy prior to receiving CART.

In summary: CD19 directed CART reliably appears to cure about one-third of treated patients with DLBCL and is an effective therapy for approximately 75% of patients with R/R FL with short follow up. Opportunities to improve outcomes of standard CART therapy include 1) during the pre-CART bridging

period to cytoreduce or stabilize disease, 2) concurrently with CART therapy to increase the CR rate, and 3) following CART administration to maintain remissions. Preliminary data indicate that BTK inhibition may be able to safely accomplish some of these goals, but this has not been evaluated in a prospective controlled manner. This study will evaluate the combination of the oral BTK inhibitor acalabrutinib with the CD19 directed CART axicabtagene ciloleucel (axi-cel).

2.2 HIV Positive Cohort

Although the incidence of lymphoma has decreased in the post-antiretroviral therapy (ART) era compared to the pre-ART era, patients with HIV remain at significantly increased risk of developing lymphoma compared to their HIV-uninfected counterparts[15]. Current treatment outcomes are better than the past (in large part due to concurrent ART); however, health disparities remain - in large part due to differential access to cancer treatment[16]. Indeed, researchers found that HIV-positive patients with DLBCL and Hodgkin's lymphoma were less likely to receive cancer treatment than HIV-negative patients[16].

Notably, among an appropriately selected population, the outcomes of HIV-infected patients are nearly comparable to HIV-uninfected patients with regard to certain subtypes of lymphoma, including both DLBCL and classic Hodgkin's lymphoma[17, 18]. Treatment options in the relapsed/refractory setting; however, have been particularly disappointing[19-21]. In a retrospective analysis of 78 HIV-infected patients with relapsed or refractory NHL, the ORR was 31% with a 1-year OS survival of under 40%[22]. Improved access to lymphoma directed treatment, including access to novel agents including CAR-T cells, is necessary.

Unfortunately, patients with HIV are often excluded from participation in clinical trials. In a review of 46 new drug applications of agents which received FDA approval between 2011 and 2015, colleagues found that 39 of the clinical trials specifically excluded (N=30) or likely excluded (N=9; "active infection") patients with HIV. Furthermore, none of the studies had specific inclusion criteria for HIV-infected patients[23]. To date, all of the trials which have led to the FDA approval of these agents have excluded patients with HIV. Given this unmet need, both the National Compressive Care Network (NCCN) and the American Society of Clinical Oncology–Friends of Cancer Research HIV Working Group have recently advocated expanding clinical trial opportunities for HIV-infected patients[23, 24]. Indeed the NCCN, indicates that the inclusion of patients living with HIV/AIDS "in cancer clinical trials should be encouraged whenever feasible"[24].

Notably, the BTK protein is upregulated in T cells of patients with HIV, and data suggest that inhibiting the BTK protein via a BTK-inhibitor can lead to cell death of HIV infected T cells[25]. Therefore, the use of acalabrutinib and other BTK-inhibitors are a particularly attractive agent for patients with HIV. Indeed, the AIDS Malignancy Consortium, a National Cancer Institute clinical consortium, is conducting a phase 1 study of ibrutinib in combination with rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin in HIV-infected patients with stage II-IV DLBCL (ClinicalTrials.gov Identifier: NCT03220022).

While we recognize that data from the HIV-positive cohort will not contribute to the trial endpoints, the data obtained will provide pilot safety (and potentially efficacy) data that may be used to inform

clinical care or the subsequent development of a future protocol for this underserved population. Adding this arm will also provide access to clinical research to a group of patients that are typically excluded.

2.3 Dose Rationale

2.3.1 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 (Calquence™) is manufactured by AstraZeneca. It is an irreversible 2nd generation, small-molecule Bruton's tyrosine kinase (BTK) inhibitor, designed to be more selective and potent compared to its 1st generation counterpart, Ibrutinib[8]. BTK is an essential cytoplasmic signaling kinase downstream of the B-cell receptor pathway, important in the development, proliferation, maturation, differentiation, apoptosis and migration of B-cells; hence, its important role in multiple B-cell neoplasms has been an active area of research[9]. Acalabrutinib is FDA approved in the treatment for relapsed MCL based on Phase II single-arm data as described in the ACE-LY-004 trial at a dose of 100mg twice daily[10]. The most common (>20%) adverse events (AE) (all grades) with acalabrutinib were headache (38%), diarrhea (31%), fatigue (27%), and myalgia (21%). The most common grade ≥3 adverse reactions were anemia (8%), neutropenia (5%), and pneumonia (5%). Currently, the ACCEPT Trial (NCT03571308) is combining acalabrutinib with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (R-CHOP) in a Phase Ib/II trial as front-line treatment for DLBCL. Results from the American Association for Cancer Research (AACR) Annual Meeting in 2018 (Chicago, IL) reported 6 eligible patients recruited to the first cohort at a dose of 100mg acalabrutinib once daily, with a further 4 patients recruited to the second cohort at a dose of 100mg twice daily[11]. Acalabrutinib was used as monotherapy for R/R DLBCL, activated B-cell subtype, at a dose of 100mg twice daily (NCT02112526), results reported at the American Society of Clinical Oncology (ASCO) annual meeting in 2018 (Chicago, IL)[12]. Common AEs (any grade) were diarrhea (43%), fatigue (43%), anemia (29%), cough (29%) and dizziness (29%); common Grade 3/4 AEs were anemia (24%), fatigue (10%) and abdominal pain (10%). Three patients had Grade 5 AEs (respiratory failure, meningeal progression, and sepsis), none of which were drug related. The authors concluded that acalabrutinib as monotherapy for R/R DLBCL was well-tolerated and showed activity in the R/R setting, reporting an overall response rate (ORR) of 24%, 5 of 21 patients with ≥ partial response (PR) and 19% exhibiting a complete response (CR). As such, the rationale behind the 100mg twice daily is based off the FDA-approved dosing for relapsed MCL and safety data available for studies using acalabrutinib as monotherapy or in combination therapy for large B-cell lymphomas and FL.

2.3.2 Axicabtagene ciloleucel (Axi-Cel)

Axicabtagene ciloleucel (axi-cel) (Yescarta ®) is a CD19-directed genetically modified autologous T-cell immunotherapy manufactured by Kite Pharma/Gilead Sciences, FDA-approved as of October 2017 for the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more

lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma (PMBCL), high grade B-cell lymphoma (HGBCL) and DLBCL arising from follicular lymphoma (transformed follicular lymphoma, tFL). It was also approved in March 2021 for treatment of indolent (grade 1-3a) FL after two or more lines of systemic therapy. It is not indicated for the treatment of patients with primary central nervous system lymphoma. Per package insert, axi-cel is administered as a single infusion bag containing a suspension of CAR-positive T cells in approximately 68 mL. The target dose is $2x10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2x10^8$ CAR-positive viable T cells. Lymphodepleting chemotherapy will be administered prior to infusion of axi-cel, as specified in the FDA-approved package insert. Axi-cel will be administered in accordance with standard of care and obtained from commercial sources.

3 STUDY OBJECTIVES

3.1 Primary Objective

To evaluate the safety and feasibility of combining acalabrutinib and anti-CD19 CART therapy in B-cell lymphomas.

3.2 Secondary Objective(s)

4. To estimate the clinical efficacy as measured by complete response (CR) rate of acalabrutinib and anti-CD19 CART therapy.
5. To estimate the clinical efficacy of combination therapy for specific molecular subtypes of large B-cell lymphomas (primary mediastinal B-cell lymphoma, high grade B-cell lymphomas with ≥ 2 translocations, germinal center, non-germinal center) and grade 1-3a FL.
6. To estimate the response rate and disease control rate (CR+PR+SD) following bridging prior to CART.

3.3 Exploratory Objectives

To describe the impact of acalabrutinib on T-cell subsets, IL-6 levels, cytokine levels

3.4 Projected Target Accrual

Table 1: Targeted / Planned Enrollment

Ethnic Category	**Patient Numbers**		
	Females	**Males**	**Total**
Hispanic or Latino	2	3	5
Not Hispanic or Latino	22	23	45
Ethnic Category Total of All Subjects	24	26	50
Racial Category			
American Indian / Alaska Native	0	0	0
Asian	2	3	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	3	3
White	22	20	42

More than One Race	0	0	0
Racial Categories: Total of All Subjects	24	26	50

4 STUDY ENDPOINTS AND DESIGN

4.1 Endpoints

1) Primary Endpoint: Toxicity as defined by the following: grade ≥ 3 CRS, grade ≥ 3 NT within 30 days of infusion of axi-cel.
2) Secondary Endpoints: Complete response rate following CART, per Lugano criteria, overall survival, progression-free survival. Response rate and disease control rate (CR+PR+SD) following bridging prior to CART
3) Exploratory Endpoint: T-cell subsets, IL-6, cytokine levels.

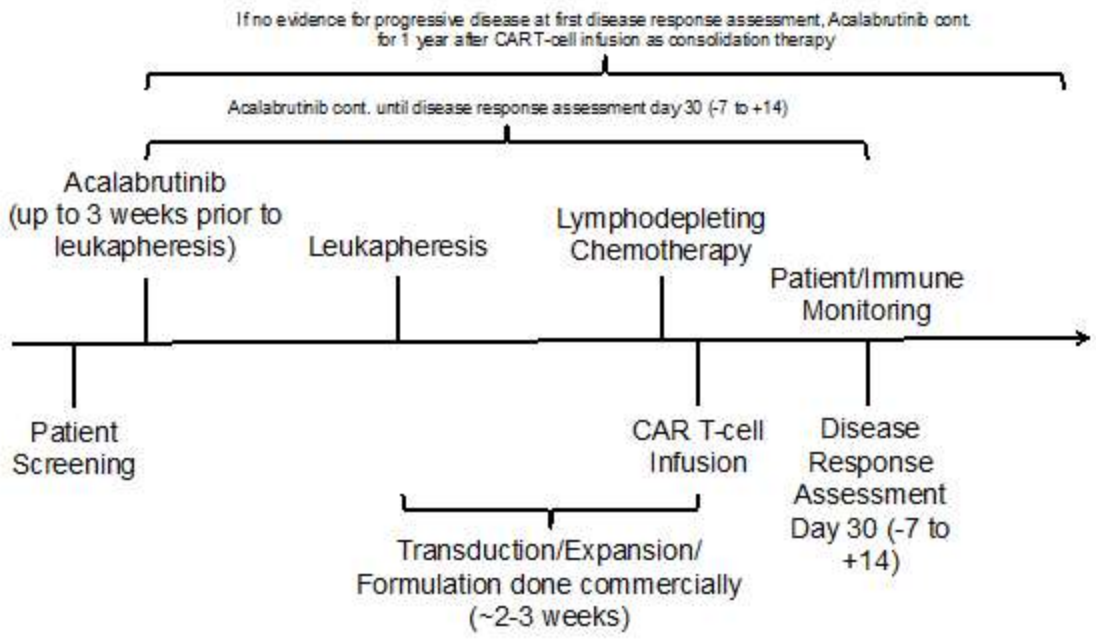
All study points from HIV positive and negative arm will be evaluated separately.

4.2 Experimental Design

This is an open-label, single-arm, Phase II study to assess the safety and potential efficacy of acalabrutinib combined with the anti-CD19 CART agent axi-cel. Axi-cel will be administered per FDA-approved dosing as a single infusion bag containing a suspension of CAR-positive T cells in approximately 68 mL. The target dose is $2x10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2x10^8$ CAR-positive viable T cells. Acalabrutinib will be administered at 100mg Q12h per FDA-approved dosing, starting up to 3 weeks prior to leukapheresis and continuing until (at least) the initial post CART restaging, with further continuation dependent upon response assessment.

4.3 Overall Study Design

Study Schema



4.4 Protocol Enrollment

We anticipate enrolling 50 patients over approximately 48 months. Before any study-specific procedures can be performed, all subjects must sign an informed consent form (ICF) in addition to a separate consent form outlining the apheresis procedure and potential risks of CART. It is anticipated that patients will receive an average of 10 weeks of therapy with acalabrutinib from the time of treatment initiation to the first disease assessment. Subjects may continue treatment with acalabrutinib in the absence of progressive disease and unacceptable toxicities. After discontinuing treatment with acalabrutinib, subjects will continue to be followed at standard of care intervals per institutional standards, up to a maximum of 5 years or death, whichever comes first.

5 STUDY POPULATION

The target study population consists of male or female patients 18 years or older who meet FDA-approved criteria for receiving axi-cel – R/R large B-cell lymphomas after two or more lines of systemic therapy including DLBCL not otherwise specified, high grade B-cell lymphoma (HGBCL), and DLBCL arising from follicular lymphoma (tFL) and R/R indolent FL after two or more lines of systemic therapy. Patients must meet all of the inclusion criteria and none of the exclusion criteria to be enrolled in this study.

Two arms will be enrolled: Non-HIV infected patients and HIV infected patients. All HIV infected patients will need to meet the general eligibility criteria in addition to the HIV Cohort eligibility criteria.

5.1 General Inclusion Criteria

1) Patients with histologically confirmed large B-cell lymphoma, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from follicular lymphoma, and indolent (grade 1-3a) FL.
2) Criteria must be met for receiving commercial axi-cel per FDA label.
3) ≥ 18 years of age.
4) Patients must be capable of understanding and providing a written informed consent.
5) Negative serum pregnancy test within 2 days of initiating acalabrutinib for women of childbearing potential (WOCBP), defined as those who have not been surgically sterilized or who have not been free of menses for at least 1 year.
6) Fertile male and WOCBP patients must be willing to use highly effective contraceptive methods before, during, and for at least 4 months after the CAR T-cell infusion or within 2 days of acalabrutinib, whichever is longer.
7) ECOG performance status of 0-1.
8) Patients must have acceptable organ function, as defined as:
   a) CrCl > 50 mL/min or serum creatinine ≤ 2.5
   b) Total bilirubin ≤ 1.5x the upper limit of normal
   c) AST and ALT ≤ 3x the upper limit of normal
   d) Adequate pulmonary function, defined as ≤ grade 1 dyspnea and SaO2 ≥ 92% on room air
   e) Adequate cardiac function, defined as left ventricular ejection fraction (LVEF) of ≥ 50% and without evidence for pericardial effusion
9) At least 1 measurable lesion ≥15 mm according to the International Working Group consensus response evaluation criteria in lymphoma (Younes 2017).

5.2 Exclusion Criteria

1) Active and uncontrolled systemic or clinically significant infection that would contraindicate myelosuppressive therapy or CART infusion.
2) Patients intolerant of acalabrutinib.
3) Patients with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases.
4) History of a seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with central nervous system (CNS) involvement.
5) Use of a strong CYP3A inhibitor OR inducer within 7 days of starting study drugs or requirement of use of strong CYP3A inhibitor OR inducer at the time of enrollment.
6) Disease that is known to be refractory to BTK inhibition.
7) Absolute neutrophil count (ANC) <1000/ul.
8) Platelets <50K/ul.
9) Another active malignancy requiring systemic treatment, unless approved by PI.
10) Clinically significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of

screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification. Subjects with controlled, asymptomatic atrial fibrillation during screening can enroll on study.

11) Inability to swallow whole pills, 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) Active bleeding, history of bleeding diathesis (eg, hemophilia or von Willebrand disease).
13) Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).
14) Receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days of first dose of study drug.
15) Prothrombin time/INR or aPTT (in the absence of Lupus anticoagulant) > 2x ULN.
16) History of significant cerebrovascular disease or event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.
17) Major surgical procedure within 7 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
18) Hepatitis B or C serologic status: subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR). Those who are hepatitis B surface antigen (HbsAg) positive or hepatitis B PCR positive will be excluded.
19) Subjects who are hepatitis C antibody positive will need to have a negative PCR result. Those who are hepatitis C PCR positive will be excluded.
20) Pregnant or breast feeding.
21) History of or ongoing confirmed central nervous system (CNS) lymphoma.
22) History of or ongoing confirmed progressive multifocal leukoencephalopathy (PML)

5.3 HIV Positive Cohort Eligibility Criteria

1) HIV-1 or HIV-2 infection, as documented by any federally approved, licensed HIV test
2) HIV plasma HIV-1 RNA below detected limit obtained by FDA-approved assays within 4 weeks prior to registration
3) CD4 cell count greater than 200 cells/mm3 obtained within 2 weeks prior to enrollment at any U.S. laboratory that has a clinical laboratory improvement amendments (CLIA) certification or its equivalent
4) Anti-retroviral treatment (ART) should be initiated > 4 weeks prior to study drug so that toxicity assessment of ART is separated from study drug. If patient is on an ART regimen that contains a strong CYP3A inhibitor (e.g ritonavir and cobicistat) or CYP3A inducer (e.g. efavirenz), changes in ART therapy should be considered in collaboration with HIV provider
5) No acute active HIV-associated opportunistic infection requiring antibiotic treatment

6) No uncontrolled systemic fungal, bacterial, viral, or other infection
7) Hemoglobin > 8.0 g/dl
8) Serum creatinine < 1.5 mg/dL OR creatinine clearance >60 mL/minAST and ALT < 2.5 x ULN

5.4 Reproductive Potential and Contraception Requirements

Any female patient who does not meet at least one of the following criteria will be considered to have reproductive potential:

- Post-menopausal for at least 12 consecutive months (i.e., no menses), or
- Undergone a sterilization procedure (hysterectomy, salpingectomy, or bilateral oophorectomy; tubal ligation is not considered a sterilization procedure)

Serum or urine pregnancy test for females of reproductive potential must be negative within 2 days before starting acalabrutinib.

WOCBP who are sexually active must use highly effective methods of contraception during treatment and for 4 months after CART or 2 days after acalabrutinib, whichever is later.

Definition for Highly Effective Methods of Contraception

Highly effective methods of contraception (to be used during heterosexual activity) are defined as methods that can achieve a failure rate of <1% per year when used consistently and correctly. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomy of a female subject's male partner (with medical assessment and confirmation of vasectomy surgical success)
- Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)

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

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

6 TREATMENT PLAN

6.1 Acalabrutinib Treatment

Acalabrutinib will be taken orally at 100mg by mouth approximately every 12 hours starting up to 3 weeks and at least 24 hours before leukapheresis. The tablets should be swallowed intact with water. Subjects should not chew, crush, dissolve, or cut the tablets. Acalabrutinib can be taken with or without food. Acalabrutinib may be continued for up to 1-year post CART infusion absent PD or unacceptable toxicity.

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

For the purposes of drug accountability and dosing subjects may record any missed doses of acalabrutinib on a drug diary. During hospitalization for CART infusion, drug accountability will be verified through medication administration records recorded in the EMR.

6.1.1 Acalabrutinib Investigational Product

Acalabrutinib (Calquence®) capsules

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

The capsule also contains compendial inactive ingredients: silicified microcrystalline cellulose, which is composed of microcrystalline cellulose and colloidal silicon dioxide, partially pregelatinized starch, sodium starch glycolate, and magnesium stearate.

The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, and indigotine (FD&C Blue2).

Acalabrutinib (Calquence®) tablets

The investigational product, acalabrutinib maleate tablet, is supplied as 100mg, orange, oval, biconvex tablet, with debossment 'ACA 100' on one side and plain on the reverse. Acalabrutinib tablets contain 100 mg of acalabrutinib (equivalent to 129 mg of acalabrutinib maleate). 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.

Storage - Acalabrutinib

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

6.1.2 Acalabrutinib Dosing Delays and Modifications

Patients should be followed closely for adverse events (AE) or laboratory abnormalities that might indicate acalabrutinib-related toxicity. If a patient experiences an acalabrutinib-related toxicity or other intolerable AE during the course of therapy, then acalabrutinib may be withheld, as necessary, until the AE resolves or stabilizes to an acceptable degree. It is important to note that multiple significant toxicities are expected following axi-cel including prolonged pancytopenia following lymphodepletion; thus, these dose modifications should be used only as guidelines to be considered in the appropriate clinical context by the treating team and are not mandatory per protocol. In addition, general guidelines for dose modification with strong/moderate CYP3A inhibitors/inducers are included in section 7.1.10.

Dose modifications guidelines for the following acalabrutinib-related treatment-emergent toxicities are provided in the table below. Note that these do not apply if toxicities are attributed to CART.

- Related grade 4 neutropenia (< 500/µL) for > 7 days (neutrophil growth factors are permitted per American Society of Clinical Oncology (ASCO) guidelines [Smith 2006] and use must be recorded).
    - If grade 4 neutropenia is attributed to CAR T-cell therapy and/or lymphodepleting chemotherapy (grade ≥ 3 neutropenia seen in 78% of subjects in ZUMA-1 study), recommend continuing acalabrutinib and initiating standard institutional prophylactic antimicrobial therapy with low threshold to work up infectious etiologies and switch to empiric/broad spectrum antimicrobial therapy if clinically indicated
- Related grade 3 thrombocytopenia.
    - If grade 3 thrombocytopenia is attributed to CAR T-cell therapy (grade ≥ 3 thrombocytopenia seen in 38% of subjects in ZUMA-1 study, grade ≥3 thrombocytopenia was seen in 3-6% with acalabrutinib [acalabrutinib PI]), recommend continuing acalabrutinib with consideration for 1) transfusing platelets to maintain platelet count 20,000- 50,000/µL, and 2) reversing any coagulopathy by transfusing cryoprecipitate for fibrinogen > 150mg/dL and/or FFP for INR < 1.5
- Related grade 4 thrombocytopenia.
    - If grade 4 thrombocytopenia is attributed to CAR T-cell therapy and there is no evidence for bleeding, recommend continuing acalabrutinib and transfusing platelets to maintain platelet count 20,000- 50,000/µL, reversing any coagulopathy by transfusing cryoprecipitate for fibrinogen > 150mg/dL and/or FFP for INR < 1.5
    - If grade 4 thrombocytopenia is attributed to CAR T-cell therapy and there is evidence for active bleeding, recommend holding acalabrutinib and transfusing platelets to maintain platelet count 20,000- 50,000/µL, reversing any coagulopathy by transfusing cryoprecipitate for fibrinogen > 150mg/dL and/or FFP for INR < 1.5
- Related grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- Any other Grade 4 toxicity or clinically significant Grade 3 toxicity that can be resolved to baseline or grade 1 without dose reduction.

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

Subjects that are required to hold for > 3 weeks or discontinue acalabrutinib due to acalabrutinib-related toxicity will be removed from the therapeutic portion of the study but may continue to receive axi-cel as SOC and will be followed for secondary endpoints.

If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥ 4 weeks or it is clear that the toxicity was not secondary to acalabrutinib alone then dose may be increased to the next higher dose level, at the discretion of the investigator. Similarly, if it is clear after discontinuation that the toxicity was not due to acalabrutinib the drug may be restarted at the discretion of the investigator. The maximum dose of acalabrutinib is 100mg by mouth q12 except as per section 7.1.10.

6.2 Leukapheresis

In general, following enrollment on the study and after starting acalabrutinib, a leukapheresis collection will be performed on each subject to obtain peripheral blood mononuclear cells (PBMCs) for the production of chimeric antigen receptor-positive viable T cells. The leukapheresis will be performed using institutional standard operating procedures (SOPs) for obtaining PBMCs. If a technical issue arises during the procedure or in the processing of the product, or if insufficient cells are manufactured for the FDA-approved dose of axi-cel at a target dose of $2x10^6$ CAR-positive viable T cells per kg body weight, with a maximum of $2x10^8$ CAR-positive viable T cells, the subject may undergo a second collection procedure. Subjects ineligible for a vein-to-vein apheresis may elect to have a percutaneous central venous access catheter inserted to support this collection per SOC. A separate apheresis consent form must be signed by the subject prior to the procedure. In general, acalabrutinib may be continued through the time of leukapheresis.

6.3 Lymphodepleting Chemotherapy

In general, subjects will receive lymphodepleting chemotherapy 2 – 11 days prior to the infusion of CAR T cells to reduce the tumor burden prior to and to provide lymphodepletion to facilitate T-cell survival. The preferred regimen will be combination therapy with cyclophosphamide 500 mg/m^2 intravenously and fludarabine 30 mg/m^2 intravenously approximately on the fifth, fourth, and third day before infusion of axi-cel, per clinical SOC. Post lymphodepleting monitoring will be per institutional SOC, but in general will include daily lab and clinical assessments until the period of significant cytopenia and toxicity is resolving.

6.4 Axicabtagene ciloleucel (Axi-Cel) Treatment

Axi-cel will be administered by IV infusion per clinical SOC. All subjects must sign a separate consent form outlining the risks of production, infusion, and possible toxicities of CART prior to axi-cel administration.

6.4.1 Preparation of Cell Product

The leukapheresis product will be cryopreserved, shipped, manufactured, tested, and released per standard procedures for commercial axi-cel. Patients that are unable to receive commercial axi-cel due to an out of specification product or any other quality control issue that may require additional regulatory requirements such as a single patient IND or enrollment in a clinical trial to receive the product will be removed from this study, will be considered inevaluable for the primary endpoint, and may be replaced. If this occurs, acalabrutinib will be permanently discontinued.

6.4.2 Axi-Cel Infusions

Axi-cel will be administered by IV infusion per clinical SOC or institutional standards. Infusion in general should be scheduled to occur between 36 and 96 hours after completion of lymphodepleting chemotherapy. However, the infusion may be delayed to allow for resolution of adverse events (AEs) related to the acalabrutinib, disease, lymphodepleting chemotherapy, or other factors.

6.5 Recommended Supportive Care, Additional Treatment, and Monitoring

Prophylactic treatment/measures are recommended for patients at risk for tumor lysis syndrome (TLS) according to institutional or clinical standards. Guidelines to provide supportive care for the management of CRS is detailed in Appendix G and H.

The use of red blood cells (PRBC) and platelet transfusions, and/or colony-stimulating factors is permitted according to institutional or clinical standards.

The use of prophylactic or empiric anti-infective agents (eg, trimethoprim/sulfmethoxazole for pneumocystis jeroveci pneumonia [PJP] prophylaxis, broad spectrum antibiotics, antifungals (see excluded concomitant medications in Appendix I), or antiviral agents for febrile neutropenia) is permitted according to institutional standards. Warfarin or other vitamin K antagonists are not permitted.

Prophylactic anti-seizure medication is generally recommended for all patients per standard of care for axi-cel (Appendix H). Hospitalization may be required to manage treatment-associated toxicities.

7 POTENTIAL RISKS

Management of all toxicity will be at the discretion of the primary treating teamper axi-cel standard of care.. Input and guidance from the PI or sub-investigators are recommended. Guidelines are noted below.

7.1 Acalabrutinib

7.1.1 Risk Assessment

7.1.1.1 Contraindications

No contraindications are known for acalabrutinib.

7.1.2 Important Identified Risks

The following summarizes the important identified risks observed with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator's Brochure.

7.1.3 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.

7.1.4 Infection

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.

7.1.5 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia, 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.

7.1.6 Second Primary Malignancies

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

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

7.1.7 Atrial Fibrillation

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

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

During CRS it is strongly advised for subjects to be placed on telemetry for cardiac monitoring during hospitalization as is done with the clinical use of BTK inhibitors, and electrolytes should be monitored and repleted as clinically appropriate.

7.1.8 Important Potential Risks

There is one important potential risk for acalabrutinib monotherapy. Information related to this important potential risk is presented below. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib Investigator's Brochure.

7.1.9 Hepatotoxicity

The mechanism underlying hepatotoxicity events of non-infectious etiology is currently unknown. Following a comprehensive review of hepatotoxicity events in the acalabrutinib clinical program, there was insufficient evidence to establish an association between hepatotoxicity events and acalabrutinib due to the contribution of confounding factors, absence of clinical symptoms, and quick recovery without treatment for patients with transaminase elevations. There is limited evidence regarding hepatotoxicity of noninfectious etiology from literature for other BTK inhibitors.

7.1.10 Drug-Drug Interactions

Because acalabrutinib is metabolized by CYP3A, concomitant administration of acalabrutinib with a strong CYP3A may increase exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer may decrease acalabrutinib exposure and could reduce efficacy. The concomitant use of strong inhibitors/inducers of CYP3A (see Appendix I) should be avoided when possible.

If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong or moderate CYP3A4 while on study, the subject should be monitored closely for any potential toxicities. In general the following guidelines should be used

whenever possible: Strong CYP3A Inhibitors: Avoid co-administration with a strong CYP3A inhibitor. If a strong CYP3A inhibitor will be used short-term, interrupt acalabrutinib. Moderate CYP3A Inhibitors: When acalabrutinib is co-administered with a moderate CYP3A inhibitor, reduce acalabrutinib dose to 100 mg once daily. Strong CYP3A Inducers: Avoid co-administration with a strong CYP3A inducer. If a strong CYP3A inducer cannot be avoided, increase the acalabrutinib dose to 200 mg twice daily. See Appendix I for a list of known strong in vivo inhibitors or inducers of CYP3A.

7.2 Axi-cel

Management of all toxicity will be at the discretion of the primary treating team with or without guidance from the PI or sub-investigators. Acute infusional toxicity may occur during or shortly after axi-cel infusion. In addition, CRS and NT have been reported specifically after axi-cel T-cells and will be emphasized**;** however, **Guidelines for grading and management of these complications, in addition to other potential toxicities, are listed in Appendix G and H**.

7.2.1 Cytokine Release Syndrome Management Guidelines

Administration of CAR T cells such as axi-cel may be associated with CRS. CRS may be characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, coagulation abnormalities, organ dysfunction, and neurologic abnormalities. Management of CRS will be entirely at the discretion of the attending of record and treatment team. However, guidelines for management of CRS are also noted in Appendix G.

If a patient becomes febrile or develops symptoms of CRS, cytokine levels, serum ferritin, C-reactive protein (CRP), coagulation studies, and/or markers of tumor lysis syndrome (eg, chemistry, uric acid, lactate dehydrogenase [LDH]) may be measured, and persistence and/or phenotype of the transgene-expressing cells may be evaluated, as clinically indicated.

Any patient who develops clinical evidence of symptoms related to CRS should have a work-up to exclude infection or other causes, as clinically appropriate. Initial treatment should consist of supportive measures as dictated by the clinical and laboratory findings, and may include fluid replacement, medications to support blood pressure, antipyretics, oxygen supplementation, anti-seizure medications, and broad-spectrum antibiotics if infection cannot be excluded as a potential etiology for the signs and symptoms.

A modification of the CTCAE CRS grading scale has been established to better reflect CAR T cells associated CRS (Lee 2014). Patients with Grade ≥ 3 CRS (severe CRS; sCRS) and/or Grade 2 CRS with progressive symptoms and signs should typically be treated with tocilizumab 8 mg/kg IV (max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hrs and usually no more than 4 doses total) and corticosteroids (dexamethasone 10 mg IV every q6-12 hrs). If not on Levetiracetam, initiate at 500mg PO BID as appropriate. Non responders to tocilizumab may require additional anti-cytokine therapy, at which point, the treating attending and team should be in communication with the IMTX attending. If vasopressors are required, ICU transfer should take place.

7.2.2 Neurologic Toxicity Management Guidelines

Neurotoxicity may manifest as delirium, seizures, focal neurologic deficits, and/or coma and has been reported after CAR T cell therapy. Neurotoxicity is usually reversible but can be irreversible or fatal. Levetiracetam (500 mg bid PO starting dose) or other anti-seizure medication should be considered prophylactically prior to treatment with axi-cel.

For patients who develop mild neurologic manifestations (Grade 1), symptomatic care in addition to neurologic workup such as neurology consultation, fundoscopic exam, MRI and/or CT imaging (brain, spine), diagnostic lumbar puncture with opening pressure, EEG evaluation and levetiracetam are recommended. Discussion between the treating attending and team with the IMTX attending is recommended. If neurologic toxicity is associated with concurrent CRS symptoms, tocilizumab 8mg/kg IV (max 800 mg in a single dose) should be considered. For patients who develop moderate impairment (Grade 2), supportive care and neurologic workup as for Grade 1 should continue with heavy consideration for ICU transfer. If neurologic toxicity is *not* associated with CRS, corticosteroids should be administered (e.g. dexamethasone 10 mg IV q6h or methylprednisolone 1mg/kg IV q12h or if refractory to anti-IL-6 therapy). Further supportive measures, anti-IL-6 therapies, high dose corticosteroids, anti-convulsive therapies for severely impaired (Grade 3) or critically impaired/obtunded (Grade 4) patients should be managed at the discretion of the treating attending and team with recommended input from the IMTX attending, ICU team and PI/sub-PI.

8 INFORMED CONSENT OF SUBJECT AND DONOR

Subjects will be seen at the Fred Hutchinson Cancer Center (FHCC) and/or University of Washington Medical Center (UWMC) for consideration of treatment options for their disease. The protocol will be discussed thoroughly with the subject and other family members if appropriate, and all known and potential risks to the subject will be described. The procedure and alternative forms of therapy will be presented as objectively as possible, and the risks and hazards of the procedure explained to the patient. Consent from the subject will be obtained by the PI or qualified designee using forms approved by the Cancer Consortium IRB. A summary of the informed consent form discussion detailing what was covered will be dictated in the patient's medical record.

The Investigator or qualified designee must obtain documented consent from each potential subject prior to participating in a clinical trial. Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial. The original signed Consent Form will be maintained with the subject's study records and a copy will be maintained as part of the subject's medical records.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

The informed consent will adhere to IRB/ requirements, applicable laws and regulations and Sponsor-Investigator requirements.

9 RESPONSE ASSESSMENT

Objective responses to the therapeutic regimen will be assessed using physical examination, imaging, and if necessary, bone marrow biopsies according to standard response criteria as previously published. A PET scan should be obtained at 3 time points: 1. prior to the start of acalabrutinib, 2. prior to lymphodepletion, and 3. day 30 (-7 to +14 days) after axi-cel infusion. This imaging modality is preferred to a CT scan which, at minimum, should be done of the neck (if neck disease was present prior to start of study), chest, abdomen, and pelvis. The day 30 scan will be used for initial disease response assessment to ascertain if a patient has achieved a complete response, partial response, stable disease or progressive disease (see below). Additional imaging may be obtained, if clinically indicated, at any point during the study period. If a PET-CT is not performed then the CT scan must be of diagnostic quality. If a subject discontinues acalabrutinib due to drug-related toxicities as noted in Section 6.1.2 – 6.1.3, they will still undergo follow up for secondary endpoints.

Complete Response: Subjects with a complete response per Lugano Criteria to treatment at the day 30 disease response assessment may have CT imaging performed at 3 month intervals after T cell infusion, or as clinically indicated, while continuing acalabrutinib for up to 1-year post CAR T infusion if there is no evidence for relapsed disease and if tolerated.

Partial Response: Subjects with a partial response per Lugano Criteria to treatment at the day 30 disease response assessment will have CT or PET-CT imaging performed at approximately 3 month intervals after T cell infusion, or as clinically indicated, while continuing acalabrutinib for up to 1-year post CAR T infusion if there is no evidence for relapsed disease and if tolerated.

Stable Disease: Subjects with stable disease per Lugano Criteria at the day 30 disease response assessment may 1) obtain CT or PET-CT imaging at 3 months after T cell infusion while continuing acalabrutinib with subsequent imaging at discretion of the Attending Physician, 2) undergo excisional or core-needle biopsy of a site deemed to be involved by lymphoma to assess for disease persistence while continuing acalabrutinib, or 3) come off study while preparing for next-line therapy. Subjects who come off study may continue acalabrutinib until day 1 of their next-line therapy.

Progressive Disease: Subjects with progressive disease per Lugano Criteria at the day 30 disease response assessment will come off study, but may continue acalabrutinib until day 1 of their next-line therapy up to 30 days after their initial response assessment.

FDG-PET:

1. Prior to (within 4 weeks of) starting acalabrutinib and after any prior therapy.
2. Prior to (within 14 days) lymphodepleting chemotherapy
3. Day 30 after CART (-7 to +14 days). Diagnostic CT may be substituted for FDG-PET at the discretion of the PI if sufficient information to evaluate response can be obtained from this modality.

Bone marrow aspirate and biopsy (morphology and flow cytometry):

1. Prior to (within 4 weeks) of starting acalabrutinib and after any prior therapy (may be waived by the PI).
2. For subjects who had detectable lymphoma (by morphology, flow cytometry, or molecular testing) in the baseline bone marrow biopsy or did not have a baseline marrow, a repeat bone marrow biopsy and aspirate should be performed at day 30 (± 14 days, with pathology and flow cytometry) to confirm a radiographic CR.

10 CLINICAL AND LABORATORY EVALUATIONS

A tabular schedule of mandatory and standard of care guidelines for clinical and laboratory events is provided in Appendix A & B. The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical or other factors.

10.1 Research Samples

In addition, research blood draws for exploratory endpoints (T-cell subsets, cytokine levels, IL-6 levels; see section 4.1) may be obtained as follows and as listed in Appendix C

1. Prior to start of acalabrutinib
2. After start of acalabrutinib and prior to leukapheresis OR on day of leukapheresis
3. 3 days +/- 2 prior to axi-cel infusion
4. 3 days +/- 2 after axi-cel infusion

11 LONG TERM FOLLOW UP

Subjects will be followed per institutional standard of care. In general, subjects should be evaluated a minimum of approximately every 3 months if on acalabrutinib consolidation, with additional details noted in Appendix D. Subjects may be monitored as per standard of care for disease status up to 5 years at longest, or until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. New primary malignancies within 3 years after the last dose of the investigational product will be reported as an AE if known by the research team.

12 ADVERSE EVENT REPORTING

The investigator is responsible for ensuring that AEs and SAEs that are observed or reported during the study are recorded and reported as required by the study protocol.

12.1 Adverse Event Definitions

- **Adverse Event**
  An Adverse Event (AE) is any untoward medical occurrence in a clinical investigation subject administered a medicinal product; the event does not necessarily have a causal relationship with study drug administration or usage. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally

associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- **Serious Adverse Event**
  A serious adverse event (SAE) is defined as an untoward medical occurrence that results in any of the following outcomes:
  1. Death.
  2. Life-threatening situation (i.e., with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).
  3. In-patient hospitalization or prolongation of existing hospitalization. Inpatient hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions for administration of the study drug, procedures required by the study protocol, or tumor-related diagnostic procedures are not considered serious. A scheduled admission for logistical reasons such a scheduled administration of a therapy will not be scored as a SAE.
  4. Persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions.
  5. Congenital anomaly/birth defect.
  6. An important medical event that requires intervention to prevent one of the above outcomes.

- **Unexpected Adverse Event**
  An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the investigator brochure, protocol, consent form, or FDA-approved product labeling.

- **Adverse Events of Special Interest (AESI)**
  The following events are adverse events of special interest (AESIs) for subjects exposed to acalabrutinib, and must be reported to the sponsors expeditiously (see Section 12.1 for reporting instructions), irrespective of seriousness or causality:

    - Ventricular arrhythmias requiring intervention

12.2 Monitoring and Recording Adverse Events

Adverse Events may be spontaneously identified by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For serious AEs, the investigator or authorized sub-investigator must determine the severity of the event (graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5), the relationship of the event to each study drug (acalabrutinib and axi-cel), and whether the event is expected or unexpected. Serious Adverse Events must be reported from the date the participant signs Informed

Consent through 30 days after administration of the last dose of acalabrutinib. Any SAE that occurs up to 30 days after completion of acalabrutinib treatment should be reported to AstraZeneca if known by the research team. New primary malignancies within 3 years after the last dose of the investigational product will be reported to AstraZeneca if known by the research team.

All SAEs required to be reported to AstraZeneca are to be submitted to the AstraZeneca Product Safety mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com

It is important to note that multiple AEs are expected to occur as part of standard axi-cel therapy including lymphodepleting chemotherapy and most are not relevant to evaluating the safety of adding acalabrutinib to this regimen. In order to focus on the relevant AEs, only those of grade 3 or higher will be collected with the exception of CRS and neurotoxicity for which at all grades will be recorded. SAEs of any grade will be captured.

Planned hospital admissions or surgical procedures for an illness or disease that existed before the subject was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es).

12.3 Grading of the Severity of an Adverse Event

AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For cytokine release syndrome, the CRS Grading Scale provided in Appendix F will be used to grade severity.

12.4 Attribution of Adverse Event

Association or relatedness to the study agent will be assessed by the investigator as follows:

Definite (must have all 4)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the subject's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure
Probable (must have 3)	• Has a reasonable temporal relationship to the intervention • Could not have readily been produced by the subject's clinical state or have been due to environmental or other interventions • Follows a known pattern of response to intervention • Disappears or decreases with reduction in dose or cessation of intervention
Possible (must have 2)	• Has a reasonable temporal relationship to the intervention

	• Could not have readily been produced by the subject's clinical state • Could not readily have been due to environmental or other interventions • Follows a known pattern of response to intervention
Unlikely (must have 2)	• Does not have a temporal relationship to the intervention • Could readily have been produced by the subject's clinical state • Could have been due to environmental or other interventions • Does not follow a known pattern of response to intervention • Does not reappear or worsen with reintroduction of intervention

12.5 Adverse Event Reporting Period

Adverse events of grade 3 or higher will be monitored and recorded at the start of acalabrutinib and until 30 days after the last dose of acalabrutinib, with the exception of CRS and neurotoxicity for which at all grades will be recorded. AEs with an onset date prior to the start of study drug will not be recorded. A subject withdrawn from the study because of an adverse event must be followed until the clinical outcome from the adverse event is determined.

The following events are *not* identified as AEs in this study:

- Disease progression or relapse including AEs that are a result of disease progression or relapse or treatment of such.
- Hospitalization for the purpose of facilitating lymphodepleting chemotherapy and/or T cell infusion is not considered an AE. Any AE requiring prolongation of this hospitalization beyond what is expected with commercial axi-cel will be recorded and subject to applicable SAE reporting.
- Medical or surgical procedures in and of themselves, including those that require hospitalization (e.g., surgery, endoscopy, biopsy procedures) are not considered AEs. However, an event or condition requiring such procedures may be an AE.

12.6 Pregnancy

The Sponsor-Investigator should report any occurrences to AstraZeneca/Acerta-Pharma per contractual guidelines.

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days [2-day guidance applicable to acalabrutinib monotherapy only] after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drug

[guidance applicable to acalabrutinib monotherapy only]. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

12.7 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 study specific CRF.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF. If the associated AE fulfills serious criteria, the event should be reported to AstraZeneca/Acerta-Pharma per contractual guidelines.

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

12.8 Adverse Event Reporting Requirements

12.8.1 Reporting to IRB

The investigator or designee must report events to the FHCC IRB in accordance with the policies of the IRB.

13 STATISTICAL CONSIDERATIONS

The planned sample size of 40 evaluable subjects is designed around estimating the safety of acalabrutinib in combination with the anti-CD19 CART axi-cel in patients with relapsed/refractory large B-cell lymphomas and indolent FL. The primary endpoint is the rate of CRS and NT and the secondary endpoint is overall response rate (ORR) which will be evaluated separately for large B-cell lymphoma and FL.

To protect the safety of patients, the study incorporates a stopping rule to be applied to the first 40 patients: if the lower bound of a 1-sided 90% exact binomial confidence interval of the discontinuation rate due to unacceptable toxicities (defined as: Grade 5 AE, medically significant Grade ≥ 4 AE, and medically significant Grade ≥ 3 AE lasting > 2 weeks) that are possibly, probably, or definitely attributable to treatment is > 10%,Operationally, any of the following would trigger such a rule: 2 out of the first ≤ 5 or 3 out of the first ≤ 11 or 4 out of the first ≤ 18 or 5 out of the first ≤ 25, or 6 out of the first ≤ 32, or 7 out of the first ≤ 40 subjects have unacceptable toxicity that are possible, probably, or definitely attributable to treatment. If the true probability of unacceptable toxicity is 2.5%, the probability of study suspension under the above rule is approximately 0.06; if the true probability is 30%, the probability of suspension is approximately 0.97 (probabilities estimated from 5,000 simulations).This rule will apply to medically significant $\geq$ Grade 4 toxicities that are possibly, probably or definitely attributable to

treatment, with the exception of Grade 4 CRS for < 72 hours, and Grade 4 Fever. We will be monitoring DLT rate (defined in section 13.1.1) and the study chair may stop to review the safety profile at any time due to toxicities observed, e.g., DLT rate > 33%. If this stopping rule is met, further treatment for all subjects enrolled will be immediately halted. A safety evaluation will be performed and reviewed with DMC.

To protect the safety of patients, the study incorporates a stopping rule: if the lower bound of a 1-sided 90% exact binomial confidence interval of the discontinuation rate due to severe toxicities (defined as: DLT in section 13.1.1) that are possibly, probably, or definitely attributable to treatment is > 20%, the study will be suspended pending review by an ad hoc committee (DSMB). Furthermore, we will add a stopping rule to some rare but severe AEs (any ≥ Grade 3 hemorrhage that does not resolve to < Grade 3 within 7 days or any ≥ Grade 3 arrhythmia that does not resolve to < Grade 3 within 7 days). Using a similar 1-sided 90% exact binomial confidence interval on those severe AEs, if the lower bound is > 5%, the study will be suspended. The committee will make a recommendation to continue the study at the dose of 100mg Q12h, deescalate the study dose to 100mg QD, or terminate, or otherwise modify the study. These recommendations will consider the totality of the toxicity data, the patient mix, and efficacy data including frequency of response.

Operationally, any of the following would trigger such as rule for DLTs: 2 out of the first 2 or 3 out of the first $\leq$ 6 or 4 out of the first $\leq$ 9 or 5 out of the first $\leq$ 13 or 6 out of the first $\leq$ 16 or 7 out of the first $\leq$ 20 or 8 out of the first $\leq$ 24 or 9 out of the first $\leq$ 28 or 10 out of the first $\leq$ 32 or 11 out of the first $\leq$ 40 subjects have DLTs. If the true probability of DLT rate is 5%, the probability of study suspension under the above rule is approximately 0.005; if the true probability is 40%, the probability of suspension is approximately 0.93 (probabilities estimated from 5,000 simulations).

For the severe AEs of hemorrhage or arrhythmia, if there are 2 out of the first $\leq$ 10 or 3 out of the first $\leq$ 22 or 4 out of the first $\leq$ 35 or 5 out of the first $\leq$ 40 subjects with one of these events, the study will be suspended. If the stopping rule is met, further treatment with acalabrutinib for all subjects who have not yet recovered from the acute toxicity of axi-cel will be immediately halted. Patients in the maintenance phase will not be required to stop study drug. A safety evaluation will be performed and reviewed with the DSMB. The study chair may stop to review the safety profile at any time due to toxicities observed.
Patients in the HIV positive arm will be evaluated separately for safety, but will follow the same DLT and stopping rule parameters as the HIV negative arm. Specifically, if 2 out of the first 2 or 3 out of the $\leq$10 subjects have severe toxicities (defined as: DLT in section 13.1.1) that are possibly, probably, or definitely attributable to treatment is > 20%, the HIV positive arm will be suspended pending review by an ad hoc committee (DSMB). DLTs which occur in the HIV positive arm will not impact the non-HIV cohort.

13.1 Safety Assessment

13.1.1 Dose Limiting Toxicity (DLT)

For the purpose of this study, the initial observed DLT will be considered the event which counts toward safety suspension rules. DLTs will be assessed for 30 days following the infusion of the

CART cell product. The following events will be considered DLTs for purposes of suspension rules if they are attributed as at least possibly related to the combination of acalabrutinib and axi-cel administration. Grading will be done in accordance with the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 for neurotoxicity and the Lee Criteria (Appendix F) for cytokine release syndrome, unless otherwise specified.

- Grade ≥ 4 neurotoxicity of greater than 7 days duration
- Grade ≥ 4 CRS (Lee Criteria) of greater than 7 days duration
- Any treatment-emergent Grade ≥ 4 non-hematologic AE of greater than 7 days duration
- Grade that does not resolve to < Grade 3 within 7 days
- Grade ≥ 3 hemorrhage
- Grade ≥ 3 arrhythmia that does not resolve to < Grade 3 with standard intervention within 3 days
- Grade ≥ 4 arrhythmia
- Death due to any cause other than following disease progression within 30 days of receiving axi-cel will be considered a DLT

13.1.2 Stopping and Suspension Rules

If sufficient evidence exists to suggest that the DLT rate exceeds rates that have been reported with axi-cel alone, the study will be suspended pending review by an ad hoc committee (DSMB). The ad hoc committee will make a recommendation to continue the study at the dose of 100mg Q12, deescalate the study dose to 100mg QD, or terminate the study.

14 DATA AND SAFETY MONITORING PLAN

14.1 Overall Scope of Monitoring Activities

Institutional support of trial monitoring will be in accordance with the FHCRC/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan (DSMP). Under the provisions of this plan, FHCRC Clinical Research Support coordinates data and compliance monitoring conducted by consultants, contract research organizations, or FHCRC employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), FHCRC Scientific Review Committee (SRC) and the FHCRC/University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

14.2 Monitoring the Progress of Trial and Safety of Participants

The first level of trial oversight for this protocol will be provided by the Principal Investigator, Research Manager, and Research Coordinator(s), who will provide continuous oversight of the trial. These individuals will meet to review recently acquired data, stopping rules, and adverse events. Serious adverse events will be reviewed upon occurrence to ensure prompt and accurate reporting. The data recorded in the research charts, protocol database and study specific CRFs will be compared with the actual data available from the medical record and/or clinical histories. Data detailed in the research charts will include the nature and severity of all study-specified toxicities. The Principal Investigator and all other investigators on the protocol have received formal training in the ethical conduct of human research. In addition, the DSMB will meet if any of the stopping rules are triggered. The DSMB will include individuals not directly involved with the study with expertise in lymphoma, immunotherapy/cellular therapy and statistics.

15 DATA MANAGEMENT/CONFIDENTIALITY

The medical record containing information regarding treatment of the subject will be maintained as a confidential document, within the guidelines of the Fred Hutchinson Cancer Center and the University of Washington Medical Center.

The investigator will ensure that data collected conform to all established guidelines for coding collection, key entry and verification. Each subject is assigned a unique subject number to assure subject confidentiality. Information forwarded to the FDA, NIH, NCI or other agencies about patients on this protocol refers to subjects by a coded identifier and not by name. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents. Additional clinical data may be made available from the Fred Hutch Clinical Oncology Research Entrance database, which is managed and verified independently of the research group.

16 TERMINATION OF STUDY

The PI may terminate the study at any time. The IRB and FDA also have the authority to terminate the study should it be deemed necessary or after the last treated subject has completed up to 5 years follow up.

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APPENDIX A: EVALUATIONS AND PROCEDURES

Evaluations	Screening (-28 days)	Treatment Start	Lymphodepleting Chemotherapy	T cell Infusion (Day 0)	Day 1 (+/- 1 Day)	Day 3 (+/- 1 Day)	Day 7 (+/- 1 Day)	Day 10 (+/- 1 Day)	Day 14 (+/- 1 Day)	Day 21 (+/- 1 Day)	Day 30 (+/- 1 Day)	
I/E criteria	X											
Informed consent/HIPAA	X											
Medical history[a]	X											
Physical exam	X											
Vitals[b]	X											
ECOG performance status	X											
Pregnancy test[c]	X											
ECHO/MUGA	X											
PET/CT[d]	X		X								X	
BMA/BMB[e]	X										X	
Acalabrutinib[f]		X										
Leukapheresis		X										
Lymphodepleting chemotherapy[g]			X									
T cell infusion				X								
CBC, differential, platelet count	X											

Evaluations	Screening (-28 days)	Treatment Start	Lymphodepleting Chemotherapy	T cell Infusion (Day 0)	Day 1 (+/- 1 Day)	Day 3 (+/- 1 Day)	Day 7 (+/- 1 Day)	Day 10 (+/- 1 Day)	Day 14 (+/- 1 Day)	Day 21 (+/- 1 Day)	Day 30 (+/- 1 Day)	
Hepatic function with LDH; renal function with Mg	X											
Coagulation (PT/INR, aPTT)	X											
Hepatitis B & C Serology	X											
Safety Evaluations												
AEs	AEs will be continuously monitored based on clinical data.											

NOTE: The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical, or other factors.

[a] Medical history to include available hematologic, cytogenetic, flow cytometric, and histologic findings at diagnosis and time of enrollment as well as prior therapies and response to therapy

[b] Vital signs, including O_2 sat per SOC

[c] Urine or serum hCG test for females of reproductive potential must be negative within 2 days before starting acalabrutinib

[d] PET/CT to be obtained 1. prior to (within 4 weeks of) starting acalabrutinib, 2. prior to (within 14 days of) lymphodepleting therapy, and 3. 30 days after T cell infusion (-7 to +14 days)

[e] If clinically indicated, a bone marrow aspirate/biopsy should be performed and sent for pathologic analysis prior to (within 4 weeks of) starting acalabrutinib. This may be waived by the PI if deemed not clinically necessary. For subjects who had detectable lymphoma (by morphology, flow cytometry, or molecular testing) in the baseline bone marrow biopsy or did not have a baseline marrow, a repeat bone marrow biopsy and aspirate should be performed at day 30 (± 14 days, with pathology and flow cytometry) to confirm a radiographic CR

[f] Acalabrutinib to start up to 3 weeks and at least 24 hours prior to leukapheresis

[g] In general, lymphodepleting chemotherapy will be given 2 – 11 days prior to T cell administration

APPENDIX B: GUIDELINES FOR MINIMAL STANDARD OF CARE EVALUATIONS BY CLINICAL STAFF

Assessment	Screening (-28 Days)	Treatment Start	Lymphodepleting Chemotherapy	T cell Infusion (Day 0)	Follow-Up Evaluations							
					Day 1 (+/- 1 Day)	Day 3 (+/- 1 Day)	Day 7 (+/- 1 Day)	Day 10 (+/- 1 Day)	Day 14 (+/- 2 Day)	Day 21 (+/- 2 Day)	Day 30 (+/- 2 Day)	
Physical exam		X	X	X	X		X		X	X	X	
Vitals		X	X	X	X		X		X		X	
ECOG performance status		X	X	X	X		X		X	X	X	
Lumbar puncture/ CSF evaluation		X[a]										
Safety Evaluations												
AEs	AEs will be continuously monitored based on clinical data.											
Safety Laboratory evaluations (NOTE: Samples should be collected pre-dose as applicable on day of T cell infusion)												
CBC, differential, platelet count		X	X	X	X	X	X	X	X	X	X	
Hepatic function with LDH; renal function		X	X	X	X	X	X	X	X	X	X	
Uric acid		X	X	X	X	X	X	X	X	X	X	
Serum ferritin		X		X	X	X	X	X	X	X	X	
CRP		X		X	X	X	X	X	X	X	X	
IL-6		X		X	X	X	X	X	X	X	X	
RCL testing by VSVG qPCR												Per standard

Assessment	Screening (-28 Days)	Treatment Start	Lymphodepleting Chemotherapy	T cell Infusion (Day 0)	Follow-Up Evaluations							
					Day 1 (+/- 1 Day)	Day 3 (+/- 1 Day)	Day 7 (+/- 1 Day)	Day 10 (+/- 1 Day)	Day 14 (+/- 2 Day)	Day 21 (+/- 2 Day)	Day 30 (+/- 2 Day)	
												of care for axi-cel

NOTE: The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical, or other factors. Subjects may also be hospitalized in which case evaluations may be performed while the subject is hospitalized

[a] Typically done as SOC for any subject with a history of CNS disease or signs and symptoms of CNS or epidural disease, unless a negative lumbar puncture was performed within 30 days prior to start of acalabrutinib

APPENDIX C: SCHEDULE OF RESEARCH SPECIMENS

Assessment	Screening (-28 Days)	Treatment Start	Lymphodepleting Chemotherapy	T cell Infusion (Day 0)	Follow-Up Evaluations							
					Day 1 (+/- 1 Day)	Day 3 (+/- 1 Day)	Day 7 (+/- 1 Day)	Day 10 (+/- 1 Day)	Day 14 (+/- 2 Day)	Day 21 (+/- 2 Day)	Day 30 (+/- 2 Day)	
Research Laboratory evaluations												
Research Blood Draw[a]	X[b]	X[c]	X[d]		X[e]							

NOTE: The proposed days of all treatments and assessments are approximate and may vary due to scheduling, clinical, or other factors.

[a] Research specimens may include T-cell subsets, cytokine levels, and IL-6 levels

[b] Prior to start of acalabrutinib
[c] After start of acalabrutinib and prior to leukapheresis OR on day of leukapheresis
[d] 3 days +/- 2 prior to axi-cel infusion (may be done if patient is hospitalized)
[e] 3 days +/- 2 after axi-cel infusion (may be done if patient is hospitalized)

APPENDIX D: FOLLOW-UP FOR SUBJECTS MAINTAINED ON ACALABRUTINIB

	Follow-Up Evaluations			
Assessment	**3 mon.[e] (+/- 1 mon.)**	**6 mon.[e] (+/- 1 mon.)**	**9 mon.[e] (+/- 1 mon.)**	**12 mon. (End of Study Visit)[d] (+/- 1 mon.)**
Physical exam	X	X	X	X
Vitals	X	X	X	X
ECOG performance status	X	X	X	X
Lumbar puncture/ CSF evaluation[a]				
CT scan of Neck (as clinically indicated), Chest, Abdomen, and Pelvis[b]	X	X	X	X
BMA/BMB[a]				

Assessment	Follow-Up Evaluations			
	3 mon. [e] **(+/- 1 mon.)**	**6 mon.** [e] **(+/- 1 mon.)**	**9 mon.** [e] **(+/- 1 mon.)**	**12 mon. (End of Study Visit)**[d] **(+/- 1 mon.)**
CBC, differential, platelet count	X	X	X	X
Hepatic function with LDH; renal function	X	X	X	X
Other labs[c]				
Safety Evaluations				
AEs will be continuously monitored based on clinical data until 30 days after last dose of acalabrutinib or as otherwise stated.				

NOTE: The proposed days of all assessments are approximate and may vary due to scheduling, clinical, or other factors. Timing of Follow-Up Evaluations is based upon T Cell Infusion (Day 0).

[a] CSF analysis via FLOW cytometry and/or bone marrow aspiration/biopsy should be obtained If clinically indicated for concern of relapsed disease in the CNS or in the bone marrow

[b] PET/CT is recommended rather than diagnostic CT if there is clinical suspicion for relapsed disease or for patients that were not previously in CR.

[c] May be obtained as clinically indicated: uric acid, serum ferritin, CRP, IL-6, PT, PTT, fibrinogen, thrombin time, D-dimer, quantitative IgG

[d] After 12 months patients may be followed clinically for up to 5 years. Data will be gathered from the treating team.

[e] Follow-Up Evaluations may be performed via telehealth at the 3 mon., 6 mon., and 9 mon. visits. Laboratory assessments and CT scans may be performed at locations local to the patient. If approved by the Sponsor-Investigator, Acalabrutinib can be shipped directly to patients.

2. FOLLOW-UP FOR SUBJECTS NOT MAINTAINED ON ACALABRUTINIB

Patients not maintained on acalabrutinib will be followed clinically. In general, imaging, labs, and clinical assessment should be performed approximately every 3 months for the first year, but the final determination is at the discretion of the treating team. After 12 months patients may be followed clinically for up to 5 years.

APPENDIX E: ECOG Performance Status Scale

GRADE	SCALE
0	Fully active, able to carry out all pre-disease performance without restriction
1	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	Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX F: CRS Grading Criteria

Grade	Description of Symptoms
1: Mild	Not life-threatening, requires only symptomatic treatment such as antipyretics and anti-emetics (eg, fever, nausea, fatigue, headache, myalgia, malaise)
2: Moderate	Require and respond to moderate intervention: • Oxygen requirement < 40%, or • Hypotension responsive to fluids or low dose of a single vasopressor, or • Grade 2 organ toxicity (by CTCAE v4.03)[a]
3: Severe	Require and respond to aggressive intervention: • Oxygen requirement ≥ 40%, or • Hypotension requiring high dose of a single vasopressor (eg, norepinephrine ≥ 20 µg/min, dopamine ≥ 10 µg/kg/min, phenylephrine ≥ 200 µg/min, or epinephrine ≥ 10 µg/min), or • Hypotension requiring multiple vasopressors (eg, vasopressin + one of the above agents, or combination vasopressors equivalent to ≥ 20 µg/min norepinephrine), or • Grade 3 organ toxicity[a] or Grade 4 transaminitis (by CTCAE v4.03)
4: Life-threatening	Life-threatening: • Requirement for ventilator support, or • Grade 4 organ toxicity (excluding transaminitis)[a]
5: Fatal	Death

[b] Organ toxicity excludes neurotoxicity, which will be evaluated separately

Adapted from Lee et al., 2014 (Lee 2014)

Appendix G: Recommended Management of CRS

Grade	Symptoms	Suggested Treatment
Grade 1	Symptoms require symptomatic treatment only (e.g. fever, nausea, fatigue, headache, myalgia, malaise)	• Manage symptomatically with acetaminophen and antiemetics prn • If not on Keppra, initiate Keppra 500mg PO BID
Grade 2	Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% FiO2 or hypotension responsive to fluids or low-dose (definition) of one vasopressor or Grade 2 CTCAE v4.03 organ toxicity.	• Manage symptomatically with fluid bolus and oxygen. If not responsive to oxygen and fluid bolus: o Tocilizumab 8mg/kg IV, max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hours and no more than 4 doses total* o Non responders to tocilizumab may require additional anti-cytokine therapy. Contact IMTX Attending. • Transfer to ICU if vasopressors are required • Dexamethasone may be clinically indicated, check with IMTX Attending • If not on Keppra, initiate Keppra 500mg PO BID
Grade 3	Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% FiO2 or hypotension requiring high-dose or multiple vasopressors or Grade 3 CTCAE v4.03 organ toxicity or Grade 4 CTCAE v4.03 transaminitis.	• Transfer to ICU if vasopressors are required. In other clinical settings may also require ICU transfer. • Tocilizumab 8mg/kg IV, max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hours and no more than 4 doses total* • Non responders to tocilizumab may require additional anti-cytokine therapy. Contact IMTX Attending. • Dexamethasone 10 mg IV q 6-12h • If not on Keppra, initiate Keppra 500mg PO BID
Grade 4	Life-threatening symptoms. Requirements for ventilator support, continuous veno-venous hemodialysis or Grade 4 CTCAE v4.03 organ toxicity (excluding transaminitis).	• Transfer to ICU • Tocilizumab 8mg/kg IV, max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hours and no more than 4 total doses* • Non responders to tocilizumab may require additional anti-cytokine therapy. Contact IMTX Attending. • Methylprednisolone 1,000mg IV qd x 3d • If not on Keppra, initiate Keppra 500mg PO BID

Lee et al. 2014

APPENDIX H: Recommended Guidelines for Management of Toxicities Associated with Axi-cel

Acute Toxicity Associated with T-Cell Infusion

Examples of potential symptoms and signs associated with T-cell infusion reactions and guidelines for their initial management are listed below:

- Fever, chills, and temperature elevations > 38.3°C may be managed with acetaminophen 650 mg PO every 4 to 6 hrs. All patients who develop fever > 38.3°C or chills should have a blood culture drawn and the PI or designee should be notified.
- Headache may be managed with acetaminophen.
- Nausea and/or vomiting may be managed antiemetics (excluding corticosteroids).
- Hypotension should be managed initially by fluid administration.
- Hypoxemia should be managed initially with supplemental oxygen.

Patients requiring discontinuation of the infusion may be eligible for re-treatment if the cause is deemed not related to the infusion.

Cytokine Release Syndrome (CRS) Management Guidelines

Administration of CAR T cells such as axi-cel may be associated with CRS. CRS may be characterized by high fever, fatigue, nausea, headache, dyspnea, tachycardia, rigors, hypotension, hypoxia, myalgia/arthralgia, anorexia, coagulation abnormalities, organ dysfunction, and neurologic abnormalities. Management of CRS will be entirely at the discretion of the attending of record and treatment team. However, guidelines for management of CRS are also noted in Appendix G.

If a patient becomes febrile or develops symptoms of CRS, cytokine levels, serum ferritin, C-reactive protein (CRP), coagulation studies, and/or markers of tumor lysis syndrome (eg, chemistry, uric acid, lactate dehydrogenase [LDH]) may be measured, and persistence and/or phenotype of the transgene-expressing cells may be evaluated, as clinically indicated.

Any patient who develops clinical evidence of symptoms related to CRS should have a work-up to exclude infection or other causes, as clinically appropriate. Initial treatment should consist of supportive measures as dictated by the clinical and laboratory findings, and may include fluid replacement, medications to support blood pressure, antipyretics, oxygen supplementation, anti-seizure medications, and broad-spectrum antibiotics if infection cannot be excluded as a potential etiology for the signs and symptoms.

A modification of the CTCAE CRS grading scale has been established to better reflect CAR T cells associated CRS (Lee 2014). Patients with Grade ≥ 3 CRS (severe CRS; sCRS) and/or Grade 2 CRS with progressive symptoms and signs should typically be treated with tocilizumab 8 mg/kg IV

(max 800 mg in a single dose, may repeat q8h if needed, to max of 3 doses in 24 hrs and usually no more than 4 doses total) and corticosteroids (dexamethasone 10 mg IV every q6-12 hrs). If not on Levetiracetam, initiate at 500mg PO BID as appropriate. Non responders to tocilizumab may require additional anti-cytokine therapy, at which point, the treating attending and team should be in communication with the IMTX attending. If vasopressors are required, ICU transfer should take place.

Neurologic Toxicity Management Guidelines

Management of neurologic toxicity will be entirely at the discretion of the attending of record and treatment team. However, guidelines for management of neurologic toxicity are noted below.

Neurotoxicity may manifest as delirium, seizures, focal neurologic deficits, and/or coma and has been reported after CAR T cell therapy. Neurotoxicity is usually reversible but can be irreversible or fatal. Levetiracetam (500 mg bid PO starting dose) or other anti-seizure medication should be considered prophylactically prior to treatment with axi-cel.

For patients who develop mild neurologic manifestations (Grade 1), symptomatic care in addition to neurologic workup such as neurology consultation, fundoscopic exam, MRI and/or CT imaging (brain, spine), diagnostic lumbar puncture with opening pressure, EEG evaluation and levetiracetam are recommended. Discussion between the treating attending and team with the IMTX attending is recommended. If neurologic toxicity is associated with concurrent CRS symptoms, tocilizumab 8mg/kg IV (max 800 mg in a single dose) should be considered. For patients who develop moderate impairment (Grade 2), supportive care and neurologic workup as for Grade 1 should continue with heavy consideration for ICU transfer. If neurologic toxicity is *not* associated with CRS, corticosteroids should be administered (e.g. dexamethasone 10 mg IV q6h or methylprednisolone 1mg/kg IV q12h or if refractory to anti-IL-6 therapy). Further supportive measures, anti-IL-6 therapies, high dose corticosteroids, anti-convulsive therapies for severely impaired (Grade 3) or critically impaired/obtunded (Grade 4) patients should be managed at the discretion of the treating attending and team with recommended input from the IMTX attending, ICU team and PI/sub-PI.

Tumor Lysis Syndrome

Both lymphodepleting conditioning chemotherapy and axi-cel may cause TLS in patients with high disease burden. Management and prevention of TLS will be at the discretion of the primary treating team. It is suggested that patients with macroscopic evidence of disease be considered at risk for TLS and receive allopurinol prophylaxis before chemotherapy begins, unless contraindicated. Allopurinol should be continued for as long as the medical team determines appropriate after the infusion. Patients may receive additional hydration and urine alkalinization for the first 2 weeks after infusion. Management of TLS may include conservative therapy such as allopurinol, urinary alkalinization, and IV fluid hydration. Hyperkalemia may be treated with potassium-binding resins, diuresis, or insulin/dextrose therapy. Hyperphosphatemia may be treated with phosphate-binding resins. In severe cases,

rasburicase (in non-G6PD-deficient individuals) or renal dialysis may be necessary. Hospitalization will be at the discretion of the primary treating team.

Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a serious disorder potentially associated with uncontrolled activation and proliferation of CAR T cells and subsequent activation of macrophages. Management of MAS will be at the discretion of the primary treating team. MAS is typically characterized by high-grade, non-remitting fever, cytopenias, and hepatosplenomegaly, and may be difficult to distinguish from CRS. Laboratory abnormalities found in MAS include elevated inflammatory cytokine levels, serum ferritin, soluble IL-2 receptor (sCD25), triglycerides, and decreased circulating NK cells. Other findings include variable levels of transaminases, signs of acute liver failure, coagulopathy, and disseminated intravascular coagulopathy. While there are no definitive diagnostic criteria for MAS, it is typically diagnosed using published criteria for hemaphagocytic lymphohistiocytosis (Schulert 2015).

Patients treated with axi-cel should be monitored per SOC for MAS, and cytokine-directed therapy or corticosteroids should be considered as clinically indicated.

Adrenal Toxicity

Immune-mediated damage to the adrenal gland is a potential toxicity, and could be manifest as primary mineralocorticoid or glucocorticoid deficiency. Management of adrenal toxicity will be at the discretion of the primary treating team. Guidelines are noted below.

If mineralocorticoid and/or glucocorticoid insufficiency should occur, diagnosis may be difficult in the acute setting of CRS, and attention should be given to ensuring there is sufficient replacement therapy. For patients with hypotension in the absence of fever that is unresponsive to fluid boluses, fludrocortisone or other mineralocorticoid administration should be considered. If CRS requiring intervention with tocilizumab and dexamethasone should occur, the glucocorticoid and mineralocorticoid activity of dexamethasone 10 mg/bid will be sufficient; however, if hypotension recurs following cessation of dexamethasone, stress-dose hydrocortisone is recommended. Samples will be assayed for renin, aldosterone and cortisol levels.

B-Cell Aplasia

Management of B-cell aplasia will be at the discretion of the primary treating team. B-cell aplasia is an expected potential off-tumor, on-target toxicity associated with administration of targeted CAR T cells. Serum immunoglobulin levels may be obtained prior to and after treatment. Hypogammaglobulinemic patients (serum IgG < 400 mg/dL) should be considered for intravenous immunoglobulin replacement therapy according to institutional guidelines.

The following should be considered for infection prophylaxis, as clinically indicated:

1) Antibiotic: while neutropenic
2) Antifungal: start fluconazole on the day of infusion and continue for approximately 21 days after infusion
3) Antiviral: start before chemotherapy and continue for at least 3 months after infusion
4) Pneumocystis jiroveci pneumonia (PJP) prophylaxis: start approximately Day 21 after infusion and continue for at least 3 months after infusion

Persistent Uncontrolled T-cell Proliferation

Management of uncontrolled T-cell proliferation will be at the discretion of the primary treating team. Uncontrolled proliferation of CAR T cells has not been observed in clinical trials to date. However, in the unlikely event that clinically significant uncontrolled and persistent proliferation of T cells occurs in a study patient, initial therapy may involve treatment with corticosteroids (e.g., methylprednisolone 1 g IV). Anti-lymphocyte globulin, cytotoxic drugs, or administration of anti-EGFR monoclonal antibody (cetuximab), which has been shown to eliminate $EGFRt^{+}$ CAR T cells in murine models, may be considered in serious cases. If there is a progressive increase in CAR T cells to greater than 10% of T cells at more than 3 months after the last infusion is observed, an analysis for clonal expansion by deep sequencing of the T-cell receptor (TCR) beta gene (Adaptive Biotechnology) may be conducted.

False Positive HIV Nucleic Acid Tests

HIV and the lentivirus used to make axi-cel have limited, short spans of identical genetic material (RNA). Therefore, some commercial HIV nucleic acid test (NATs) tests may yield false-positive results in patients who have received axi-cel.

Management of Other Toxicities

Management of all toxicities will be at the discretion of the primary treating team. Guidelines are noted below. If a new onset CTCAE v.5 Grade ≥ 3 toxicity is observed following infusion, the patient will receive medical treatment appropriate for the physiological abnormalities. Grade ≥ 3 toxicity that is attributed to the infusion may be treated with corticosteroids (e.g., dexamethasone 10 mg IV every 4 to 12 hours), tocilizumab, or other cytokine-directed therapy after discussion with the PI or designee.

APPENDIX I: Known Strong in Vivo Inhibitors or Inducers of CYP3A

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

a. A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. Withdrawn from the United States market because of safety reasons.
d. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.
e. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive.

Source:

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