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PROTOCOL

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STUDY DRUG:	Acalabrutinib (ACP-196)
IND NUMBER:	146525 (exempt)
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Principal Investigator	Stephanie Lee, MD, MPH 1100 Fairview Ave N, D5-290 Seattle, WA 98109 Email: sjlee@fredhutch.org
SPONSOR:	Stephanie Lee, MD, MPH Fred Hutchinson Cancer Research Center Principal Investigator: Stephanie Lee, MD, MPH
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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
BTK	Bruton tyrosine kinase
CBC	complete blood count
CFR	Code of Federal Regulations
CLL	chronic lymphocytic leukemia
cGMP	current Good Manufacturing Practice
CR	complete response
CTCAE	Common Terminology Criteria For Adverse Events
DOR	duration of response
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
FFS	failure-free survival (survival free from addition of another systemic chronic GVHD treatment, relapse or death)
GVHD	graft-versus-host disease
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	informed consent form
IRB	institutional review board
KPS	Karnofsky Performance Status
MCL	mantle cell lymphoma
MR	mixed response
NIH	National Institutes of Health
ORR	overall response rate (complete plus partial remission)
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PR	partial response
SAE	serious adverse event
SFU	safety follow up visit
TT	treatment termination visit
WOCBP	women of child-bearing potential

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STUDY SYNOPSIS

Study Title:	Acalabrutinib for chronic graft-versus-host disease
Protocol Number:	FH 8801
Sponsor:	Stephanie Lee, MD, MPH
Study Drug:	ACALABRUTINIB (ACP-196)
Phase:	2
Study Centers:	Subjects will be enrolled in up to 5 centers in the United States.
Study Objectives:	Primary Objective: • Determine the best overall response rate (complete plus partial response) to acalabrutinib in patients who require second or later line therapy for chronic GVHD. Secondary Objectives: • Determine duration of response, change in patient-reported outcomes, failure-free survival (FFS) (duration of relapse-free survival without adding another systemic treatment for chronic GVHD), and organ-specific response rates. • Store peripheral blood samples for future biologic studies.
Study Design:	This is a Phase 2, multicenter, single arm, open-label study of oral acalabrutinib in subjects with chronic GVHD. 50 subjects with moderate to severe cGVHD, as defined by the NIH Consensus Development Project Criteria, will receive acalabrutinib for second or later line therapy.
Dose Regimen/Route of Administration:	Acalabrutinib is provided as orange, oval, biconvex tablets for oral administration. Acalabrutinib 100 mg will be administered at 100 mg twice daily (approximately every 12 hours) in 28-day cycles. Subjects will remain on treatment for 6 cycles, with an option to continue for a total of 24 cycles.
Safety Parameters:	All grade 3 or higher adverse events and all serious adverse events will be collected.
Pharmacodynamic and Biomarker Parameters:	20 mL peripheral blood will be collected before treatment and after 1 and 3 cycles of acalabrutinib and stored as viable peripheral blood mononuclear cells and plasma for future biologic studies
Sample Size:	50

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Inclusion Criteria:	1. Men and women ≥ 18 years of age. 2. Moderate-severe chronic GVHD, diagnosed per the 2014 NIH criteria 3. Progression or recurrence of active chronic GVHD signs/symptoms after treatment with steroids 4. Karnofsky Performance Status ≥70% 5. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib. 6. Men must refrain from sperm donation during the study. 7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing tablets without difficulty. 8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.
Exclusion Criteria:	1. Hospitalization for evaluation or management of an infection within the last 8 weeks 2. Change in immunosuppressive regimen within the 2 weeks prior to enrollment 3. Noncompliance 4. Treatment of chronic GVHD with ibrutinib 5. Received any investigational drug within 30 days or 5 half-lives (whichever is shorter) before first dose of study drug. 6. Recurrent or prior malignancy (or any other malignancy that requires active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years. 7. 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. 8. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease that would limit absorption of oral medication. 9. Received a live virus vaccination within 28 days of first dose of study drug. 10. Known history of infection with HIV 11. Uncontrolled, active significant infection (eg, bacterial, viral, fungal or progressive multifocal leukoencephalopathy).

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	12. Known history of drug-specific hypersensitivity or anaphylaxis to study drug (including active product or excipient components).

	13. Active bleeding, history of bleeding diathesis (eg, hemophilia or von Willebrand disease). 14. Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura). 15. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer. 16. Taking warfarin or equivalent vitamin K antagonist. 17. History of significant cerebrovascular disease or event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug. 18. Major surgical procedure within 30 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. 19. 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. 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.

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Concomitant Medications:	**<u>Permitted Concomitant Therapy</u>** • other systemic treatment for chronic GVHD **<u>Prohibited Concomitant Therapy</u>** • warfarin or equivalent vitamin K antagonists • strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer

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1.0 BACKGROUND INFORMATION

1.1 CHRONIC GRAFT-VERSUS-HOST DISEASE

Chronic graft vs. host disease (chronic GVHD) is a major late complication of allogeneic hematopoietic cell transplantation (HCT) that affects up to 10-50% of HCT survivors. The syndrome is associated with major transplant-related morbidity, mortality, infectious complications, prolonged duration of immune suppression, and impaired patient-reported quality of life.[1-8] Thus, it represents a major obstacle to recovery and survival following HCT, and its prevention and treatment are of significant importance. The syndrome is characterized by diverse clinical manifestations, but the most commonly affected organs are the skin, eyes, mouth, and liver.[9] However, most organs can be involved, with parallels to other systemic immune-mediated disorders.

1.2 CHRONIC GVHD DIAGNOSIS AND CLASSIFICATION

Diagnosis and classification of the syndrome has undergone major revision following the 2005 and 2014 NIH Consensus Conferences on Chronic GVHD. The diagnosis of chronic GVHD is based on the presence of diagnostic manifestations of the syndrome or distinctive manifestations supported by confirmatory biopsy or testing. Chronic GVHD severity is scored according to objective criteria for each organ involved, which is summarized for an overall global severity score of mild, moderate, or severe (Appendix 1).[10,11] Mild disease is generally well-tolerated and may sometimes be managed with topical or local therapies. Moderate-severe disease is associated with higher mortality and requires systemic treatments.[12] Patients with moderate-severe disease will be enrolled in this trial.

1.3 THERAPY OF ESTABLISHED CHRONIC GVHD

Accepted standard primary therapy for chronic GVHD includes 0.5-1 mg/kg of prednisone or equivalent with or without a calcineurin inhibitor.[1,13,14] The addition of other systemic immune-suppressive agents to initial therapy has not provided benefit, as evidenced by trials adding azathioprine, thalidomide, hydroxychloroquine, and mycophenolate mofetil to initial treatment with steroids.[15-18] Published primary chronic GVHD therapy trials demonstrate that on average 27% will achieve complete response, and 60% will achieve overall response (complete + partial response) by 6-9 months after starting initial therapy.[13,15-19] A study testing the addition of ibrutinib to standard primary therapy has finished accrual.

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Based on insufficient response to primary therapy or a flare of chronic GVHD after tapering of initial therapy, many will go on to require additional immune-suppressive agents for chronic GVHD control. “Steroid-refractory” chronic GVHD has most commonly been defined as either progressive manifestations despite one month of treatment, or incomplete response despite two months of 1-2 mg/kg of prednisone or equivalent.[1] In addition to steroid-refractoriness, other clinical indications for additional lines of systemic immune suppressive therapy include steroid dependence and steroid intolerance. Patients with steroid-dependent chronic GVHD can’t tolerate tapering prednisone due to recurrent chronic GVHD manifestations. Steroid intolerant patients have medical complications of steroid therapy (e.g. hyperglycemia, edema, psychosis, osteoporosis), and thus require additional immune-suppressive agents to control GVHD and facilitate taper of prednisone. Multiple immune-suppressive therapies, including pharmacologic agents, monoclonal antibodies, and strategies such as extracorporeal photopheresis have demonstrated moderate activity in this setting, both ameliorating objective chronic GVHD manifestations, as well as facilitating taper of systemic steroids.[20] Their effectiveness is suboptimal, however, and many patients will require multiple agents to achieve disease control. A retrospective study showed that patients with chronic GVHD received a median of three lines of treatment and were on systemic immunosuppression for a median of 5 years. When patients stopped systemic treatment, between 30-50% of patients needed to restart treatment a median of 3-6 months later for recurrent symptoms.[21]

In August 2017, the FDA approved ibrutinib, also a Bruton’s tyrosine kinase (BTK) inhibitor, for the treatment of adult patients with chronic GVHD after failure of one or more lines of systemic immunosuppressive therapy.[22] However, despite the lack of any direct comparative studies, acalabrutinib shows improved selectivity for BTK compared with ibrutinib,[23-25] suggesting it may have a role in treating chronic GVHD, if ibrutinib efficacy in chronic GVHD is mediated through its effect on B cells. Acalabrutinib was approved for treatment of mantle cell lymphoma in 2018.[26]

The overall burden of chronic GVHD despite routine pharmacologic GVHD prophylaxis, limited response to primary and secondary therapy, and the attendant morbidity and mortality all support the need for novel approaches in chronic GVHD treatment.

1.4 ASSESSMENT OF THERAPEUTIC RESPONSE IN CHRONIC GVHD

Following the 2014 NIH Consensus Conference, most clinical trials use the recommended response criteria to calculate response based on change scores in nine

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organ-specific measures, assessed prior to study treatment and at defined points afterwards. The organ-specific change scores are used to classify responses into complete (CR, resolution of all chronic GVHD manifestations), partial (PR, partial resolution of chronic GVHD manifestations without significant worsening in any organ), stable (SD, no change in organ involvement), mixed response (MR, improvement and worsening in different organs) and progressive (PD, significant worsening in at least one organ). The overall response rate (ORR) is the CR plus PR rate.[27]

Interpretation of previously published trials for secondary chronic GVHD treatment is limited by a number of factors, most notably heterogeneity in response determination. In the Phase 2 ibrutinib study that led to regulatory approval (N=42), the best ORR was 67%. The most common adverse events were fatigue, diarrhea, muscle spasms, nausea and bruising[22] Additional experience shows that some patients develop painful stomatitis. The publication reported that at a median followup of 13.9 months, 30 (70%) had stopped treatment.

1.5 ACALABRUTINIB (ACP-196)

Acalabrutinib (Calquence™) is manufactured by AstraZeneca. It is an irreversible 2nd generation, small-molecule Bruton's tyrosine kinase (BTK) inhibitor, that is more selective and potent compared to its 1st generation counterpart, Ibrutinib. Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally bioavailable in humans and is suitable for formulating in capsules and tablets. Acalabrutinib is approved in the US for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL). The approved dose is 100 mg twice daily.

Acalabrutinib is also being evaluated for the treatment of patients with other B-cell malignancies, including chronic lymphocytic leukemia (CLL) and diffuse large B cell lymphoma. Treatment with acalabrutinib for CLL showed an overall response rate of 95% with manageable toxicity.[28] Acalabrutinib was used as monotherapy for relapsed/refractory diffuse large B cell lymphoma (R/R DLBCL), activated B-cell subtype, at a dose of 100mg twice daily (NCT02112526), with results reported at the American Society of Clinical Oncology (ASCO) annual meeting in 2018 (Chicago, IL).

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The 100mg twice daily will be used in this study based on 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.

1.5.1 Mechanism of Action

Acalabrutinib is a potent irreversible inhibitor of BTK in vitro and in vivo. Pharmacology models have been used to define kinase selectivity of acalabrutinib in comparison to other BTK inhibitors, and to investigate functional effects of on-target and off-target activities. Acalabrutinib shows improved selectivity for BTK compared with ibrutinib.[23]. Functional inhibition of non-target cells (eg, T cells, NK cells, platelets) was not observed for acalabrutinib at clinically relevant concentrations.

1.5.2 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile; for detailed information on the safety pharmacology of acalabrutinib, refer to the Investigator Brochure.

1.5.3 Drug-drug Interaction Potential

For more detailed information on drug-drug interaction potential for acalabrutinib, refer to the Investigator Brochure.

Please refer to Section 3.8 Concomitant Therapy for guidance on drugs that may cause drug-drug interactions.

1.6 CLINICAL EXPERIENCE – ACALABRUTINIB

For more detailed information on the clinical experience for acalabrutinib, please refer to the Investigator Brochure.

1.6.1 Clinical Efficacy

There have been no reports of the use of acalabrutinib for chronic GVHD. Acalabrutinib has been studied as monotherapy and in combination therapy for the treatment of MCL, CLL, prolymphocytic leukemia, Richter's syndrome and other hematologic malignancies.

1.6.2 Adverse Events

An aggregate safety analysis of acalabrutinib monotherapy was conducted in order to assess safety for acalabrutinib-exposed subjects with hematologic malignancies without confounding toxicity from combination therapy drugs. The analysis was performed on a 7-study integrated monotherapy population 'INT-7', which consisted of treated subjects

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in 5 acalabrutinib monotherapy studies (15-H-0016, ACE-CL-001, ACE-LY-002, ACE-LY-004, ACE-WM-001) and treated subjects in the acalabrutinib monotherapy treatment arms of 2 additional combination studies (ACE-LY-003 and ACE-MY-001). As of the 30 December 2018 data extraction date, the pooled INT-7 population represented 634 acalabrutinib-exposed subjects with a median exposure of 35.9 months (range, 0.03 – 58.32 months). Overall, the safety of monotherapy acalabrutinib in subjects with hematologic malignancies has been acceptable in the integrated analysis. An overview of AEs for this population is presented in Table 1-1.

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

Adverse Event Category	**N=634 n (%)**
Any treatment-emergent adverse events	
Any grade	630 (99.4)
Grade ≥3	384 (60.6)
Any adverse event related to acalabrutinib	
Any grade	492 (77.6)
Grade ≥3	147 (23.2)
Any serious adverse events	300 (47.3)
Adverse events leading to study drug discontinuation	60 (9.5)
Grade 5 (fatal) adverse event	32 (5.0)
INT-7 studies include 15-H-0016, ACE-CL-001, ACE-LY-002, ACE-LY-003, ACE-LY-004, ACE-MY-001, and ACE-WM-001. Note: A subject with multiple severity grades for a given adverse event was counted once under the maximum severity. Data as of 30 Dec 2018.	

Almost all subjects (630 [99. 4%]) had at least 1 AE, and over half (384 [60.6%] had at least 1 Grade ≥3 AE. The most commonly reported AEs of any grade were diarrhea and headache (44.5% each), contusion (28.4%), fatigue and upper respiratory tract infection (26.8% each), nausea (26.2%), cough (24.4%), and arthalgia (22.9%). The most frequently reported Grade ≥3 AEs were neutropenia (11.0%), anemia (7.6%), pneumonia (6.5%), hypertension (3.9%), thrombocytopenia (3.6%), and diarrhea (3.2%).

Treatment-related AEs were reported for 492 (77.6%) subjects, and 147 23.2%) subjects had Grade ≥3 treatment-related AEs. The most frequently reported treatment-related AEs of any grade were headache (31.1%), diarrhea (19.7%), contusion (17.8%), nausea (10.1%), fatigue (8.0%), petechiae (8.0%), neutropenia (7.6%), arthralgia (6.8%), and dizziness and myalgia (4.9% each). The most frequently reported treatment-related Grade ≥3 AEs was neutropenia (7.3%).

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

1.7 RISK ASSESSMENT

Acalabrutinib monotherapy has demonstrated efficacy in subjects with relapsed/refractory mantle cell lymphoma (MCL) and in subjects with treatment naïve or relapsed/refractory chronic lymphocytic leukemia (CLL).

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

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

1.7.1 Contraindications

No contraindications are known for acalabrutinib.

1.7.2 Important Identified Risks

1.7.2.1 Hemorrhage

Serious hemorrhagic events, including fatal events, have occurred in clinical trials with acalabrutinib. Grade 3 or higher bleeding events, including gastrointestinal, intracranial, and epistaxis have been reported in 2% of patients. Overall, bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients with hematological malignancies.

The mechanism for hemorrhage is not well understood. Acalabrutinib may further increase the risk of hemorrhage in patients receiving antithrombic agents and these patients should be monitored for signs of bleeding. Consider the benefit-risk of withholding acalabrutinib for 3-7 days pre- and post-surgery depending on the surgery and the risk of bleeding.

Because of these risks, patients receiving therapeutic warfarin or equivalent vitamin K antagonists will be excluded.

1.7.2.2 Infection

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Serious infections (bacterial, viral or fungal), including fatal events and opportunistic infections, have occurred in clinical studies with acalabrutinib. The most frequently 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 patients who are at increased risk for opportunistic infections. Monitor patients for signs and symptoms of infection and treat as medically appropriate. Because of these risks, patients with uncontrolled infection or potential prior hepatitis virus infections will be excluded.

1.7.2.3 Cytopenia

Treatment-emergent Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Subjects should be closely monitored as appropriate. Patients with significant baseline neutropenia or thrombocytopenia are excluded.

1.7.2.4 Second Primary Malignancies

Events of second primary malignancies, including non-skin carcinomas, have occurred in clinical studies with acalabrutinib. The most frequently reported second primary malignancy was skin cancer. Monitor subjects for the appearance of skin cancers. If a subject develops a second primary malignancy (other than non-melanoma skin cancer), discontinue acalabrutinib. Advise protection from sun exposure.

1.7.2.5 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, and 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 appropriate.

1.7.3 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.

1.7.3.1 Hepatotoxicity

The mechanism underlying hepatotoxicity events of non-infectious etiology is currently

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

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE:

Determine the best overall response rate to acalabrutinib in patients who require second or later line therapy for chronic GVHD.

2.2 SECONDARY OBJECTIVES:

2.2.1. Describe the safety and tolerability of acalabrutinib in the chronic GVHD population

2.2.2. Determine the duration of response among patients achieving a complete or partial response

2.2.3. Determine the change in patient-reported outcomes, specifically the Lee cGVHD Symptom Scale score and the PROMIS-29, between enrollment and follow-up

2.2.4. Determine the failure-free survival (FFS) (duration of relapse-free survival without adding another systemic treatment for chronic GVHD)

2.2.5. Determine organ-specific response rates

2.2.6. Store peripheral blood mononuclear cells and plasma for future biologic studies

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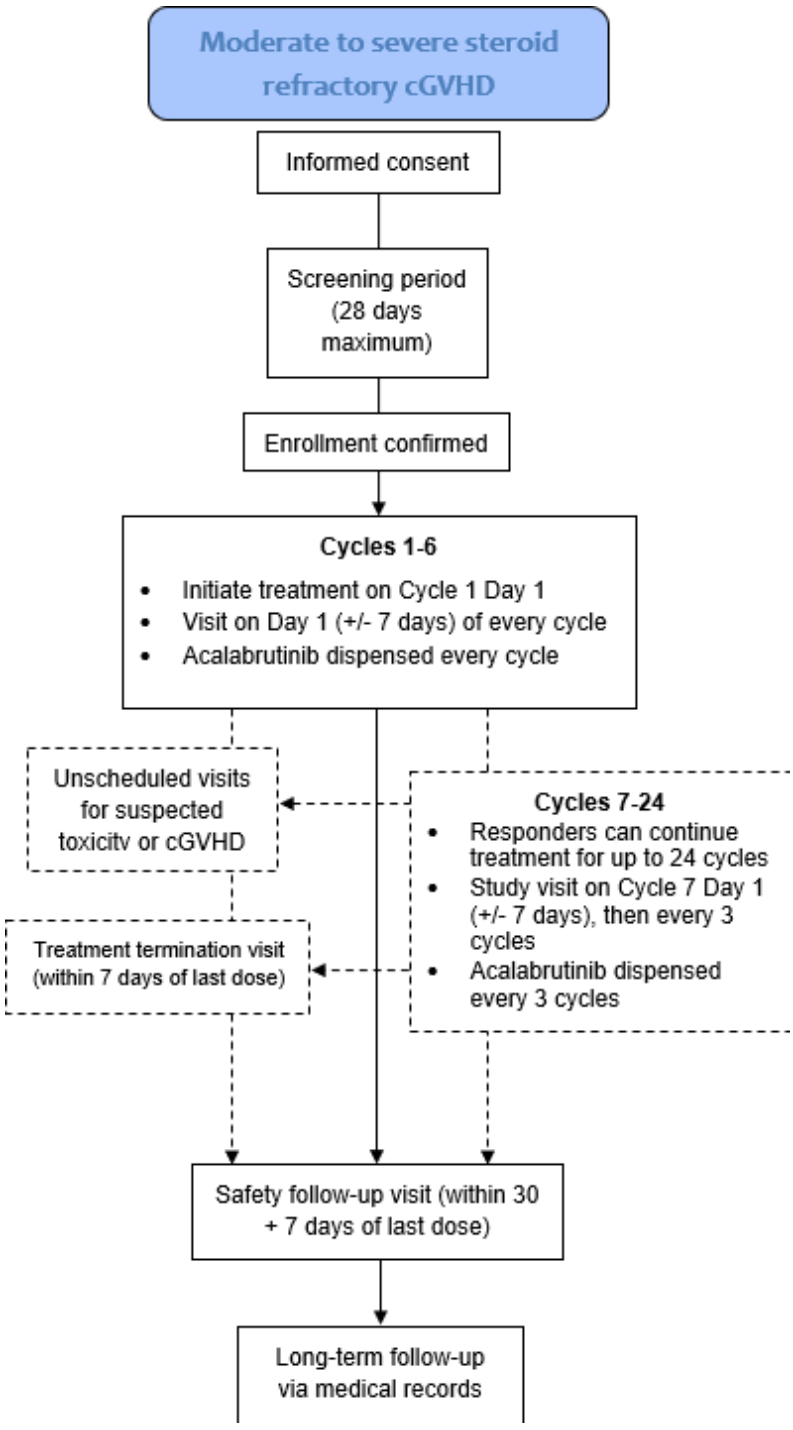
3.0 STUDY DESIGN

This is a single arm, phase II study of 50 evaluable subjects treated with acalabrutinib for moderate-severe chronic GVHD that has progressed or recurred despite treatment with prednisone. Subjects will take acalabrutinib 100 mg by mouth twice per day for 28 day cycles. Subjects will remain on treatment for 6 cycles, with an option to continue for up to two years total if responding and tolerating the drug. Study visits will be on Day 1 of each cycle through 6 cycles, then every 3 cycles while on study drug. A safety follow-up visit will occur 30 days after last dose.

Refer to Appendix 2 for a comprehensive list of study assessments and their timing. The study schema is provided below (Figure 3-1). Patients may be on study for a maximum of 28 days for the screening period, 24 cycles of study treatment and 30 +7 days of the last dose for the safety follow up (SFU) visit. Unless subjects withdraw consent, they will continue to be followed after the SFU through medical record review for new systemic chronic GVHD treatment, disease relapse, and survival (in order to calculate FFS).

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Figure 3-1. Study Schema



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3.1 STUDY PARAMETERS

3.1.1 Efficacy Parameters

See Section 5.5.1 for definitions.

3.1.2 Safety Parameters

The safety of acalabrutinib will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent grade 3 or higher AEs, any serious adverse events or AEs leading to discontinuation of study treatment or death.

For consistency of interpretation, AEs and laboratory results will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5. Standard definitions for seriousness will be applied (see Section 6.1).

3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

A single arm, open-label trial is justified by the rarity of chronic GVHD and no prior experience for this indication. Acalabrutinib 100 mg will be administered twice daily for 28-day cycles, according to the FDA-approved dose for mantle cell lymphoma.[4]

3.3 SELECTION OF STUDY POPULATION

3.3.1 Inclusion Criteria

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

1. Men and women ≥ 18 years of age.
2. Moderate-severe chronic GVHD, diagnosed per the 2014 NIH criteria
3. Progression or recurrence of active chronic GVHD signs/symptoms after treatment with steroids
4. Karnofsky Performance Status ≥70%
5. Woman of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib.
6. Men must refrain from sperm donation during the study.
7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing tablets without difficulty.
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

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3.3.2 Exclusion Criteria

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

1. Hospitalization for evaluation or management of an infection within the last 8 weeks
2. Change in immunosuppressive regimen within the 2 weeks prior to enrollment
3. Noncompliance
4. Treatment of chronic GVHD with ibrutinib
5. Received any investigational drug within 30 days or 5 half-lives (whichever is shorter) before first dose of study drug.
6. Recurrent or prior malignancy (or any other malignancy that requires active treatment), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years.
7. 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.
8. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease that would limit absorption of oral medication.
9. Received a live virus vaccination within 28 days of first dose of study drug.
10. Known history of infection with HIV
11. Uncontrolled, active significant infection (eg, bacterial, viral, fungal or progressive multifocal leukoencephalopathy).
12. Known history of drug-specific hypersensitivity or anaphylaxis to study drug (including active product or excipient components).
13. Active bleeding, history of bleeding diathesis (eg, hemophilia or von Willebrand disease).
14. Uncontrolled AIHA (autoimmune hemolytic anemia) or ITP (idiopathic thrombocytopenic purpura).
15. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
16. Requires warfarin or equivalent vitamin K antagonist.
17. History of significant cerebrovascular disease or event, including stroke or intracranial hemorrhage, within 6 months before the first dose of study drug.
18. Major surgical procedure within 30 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.
19. 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. 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. Child-Pugh score of C for hepatic impairment.

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21. Abnormal liver function tests with total bilirubin >2 mg/dL or ALT > 2 x upper limit of normal, unless abnormalities are due to liver GVHD, in which case total bilirubin >3 mg/dL or ALT 5 x upper limit of normal are exclusions.
22. Absolute neutrophil count <1.0 x 10^9/L or use of myeloid growth factors within the past 2 weeks
23. Platelet count < 50 x 10^9/L or platelet transfusion or thrombomimetic agent within the past 2 weeks
24. Glomerular filtration rate < 50 mL/min/1.73 m^2
25. Breastfeeding or pregnant.
26. Concurrent participation in another clinical trial and receiving a non-FDA approved medication.

3.3.3 Enrollment Procedures

Potentially eligible patients will be approached at participating study centers. The treating clinician will review the informed consent document with them. After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be enrolled into the study. The screening period lasts from the date the subject signs consent until they complete the enrollment visit and start study drug and may be up to 28 days.

3.4 STUDY DRUG

3.4.1 Premedications

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

3.4.2 Formulation, Packaging, and Storage

Acalabrutinib

The investigational product, acalabrutinib maleate tablet for oral administration, is supplied as 100 mg, 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.

Acalabrutinib will be provided in white, high-density polyethylene bottles.

Refer to the acalabrutinib Investigator Brochure for additional information regarding the

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drug product to be used in this trial.

3.4.3 Administration of Study Drug

The tablets should be swallowed intact with water. Subjects should not attempt to chew, crush, dissolve, or cut the tablets. Acalabrutinib can be taken with or without food.

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

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 3.9.2.

3.4.4 Assuring Subject Compliance

During cycles 1 through 6, sufficient study drug will be dispensed at each study visit to cover one 28-day treatment cycle. For cycle 7 and beyond, study drug will be dispensed every three cycles. Study patients will document their compliance through medication logs. The subject study drug diary is provided in Appendix 3.

3.5 STUDY TREATMENT SCHEDULE

Acalabrutinib 100 mg will be administered orally twice daily for 28-day cycles.

3.6 DURATION OF THERAPY

Subjects will be treated with acalabrutinib for 6 cycles, with an option to continue for up to 24 cycles if responding and tolerating the drug.

3.7 DOSING DELAYS AND MODIFICATIONS

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

Dose modifications for the following treatment-emergent toxicities are provided in Table 3-1:

- Grade 4 neutropenia (< 500/μL) for > 7 days
- Grade 3 thrombocytopenia in presence of significant bleeding.

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- Grade 4 thrombocytopenia.
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- Any other treatment-related Grade 4 toxicity or unmanageable Grade 3 toxicity.

Table 3-1: Drug Modification Actions for Acalabrutinib

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

As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade ≤ 1. If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥ 4 weeks then the dose may be increased to the 100 mg bid dose, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. The maximum dose of acalabrutinib is 100 mg twice daily.

Avoid co-administration of strong CYP3A inhibitors with acalabrutinib. Alternatively, if the inhibitor will be used short-term, interrupt acalabrutinib. When acalabrutinib is administered with moderate CYP3A inhibitors, reduce the acalabrutinib dose to 100 mg once daily.

Treatment with acalabrutinib should be withheld for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Consider the benefit-risk of withholding acalabrutinib for at least 3-7 days pre- and post-surgery depending on the surgery and the risk of bleeding. Any other clinically important events where dose delays may be considered appropriate must be discussed with the Principal Investigator. If acalabrutinib needs to be held for more than 28 days for a treatment-related toxicity, it should not be restarted.

3.8 CONCOMITANT THERAPY

3.8.1 Permitted Concomitant Therapy

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Standard supportive care medications are permitted as per institutional standards. These include infectious prophylaxis and symptomatic management.

3.8.2 Prohibited or Restricted Concomitant Therapy

Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited. If therapeutic warfarin is started, acalabrutinib should be held. Restarting acalabrutinib requires discontinuation of warfarin and discussion with the overall study PI.

The concomitant use of strong inhibitors/inducers of CYP3A4 (see Appendix 4) is not allowed (see Section 3.9.2). See Section 3.7 for dose reduction or interruption when CYP3A inhibitors cannot be avoided. For additional information on drugs with potential drug-drug interactions, refer to Section 3.9.2.

3.9 PRECAUTIONS

3.9.1 Dietary Restrictions

Acalabrutinib can be taken with or without food. As acalabrutinib is metabolized by CYP3A, subjects should be strongly cautioned against using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

Otherwise, subjects should maintain their regular diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

3.9.2 Drug-drug Interactions

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

However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin decreased acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 4) is not allowed.

If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted at least 7 days before first dose of study drug. If a subject requires a moderate CYP3A4 inhibitor while on study, the acalabrutinib dose should be lowered to 100 mg daily and the subject should be monitored closely for any potential toxicities.

Subjects should avoid the use of calcium carbonate-containing drugs or supplements

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for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib.

3.9.3 Reproductive Toxicity

The potential for acalabrutinib to be excreted in breast milk of nursing mothers is unknown.

For results of acalabrutinib nonclinical reproductive toxicity studies, including definitive embryofetal development studies, please refer to the Investigator Brochure.

Women of childbearing potential (WOCBP) who are sexually active must use highly effective methods of contraception during treatment and for 2 days after the last dose of acalabrutinib. For male subjects with a pregnant or non-pregnant WOCBP partner, no contraception measures are required. However, male subjects should refrain from sperm donations while taking acalabrutinib until 28 days after their final dose. Please refer to Appendix 5 for detailed definitions for WOCBP and highly effective methods of contraception.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this study, or within 2 days after the last dose of acalabrutinib. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib immediately. Pregnancy in a female subject or a male subject's partner must be reported as outlined in Section 6.2.3.

3.9.4 Overdose Instructions

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

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

Any study drug overdose or incorrect administration of study drug should be noted on the appropriate CRF and reported to AstraZeneca. Overdoses with or without AEs are to be reported to AstraZeneca within 30 calendar days unless the report meets serious criteria.

All AEs associated with an overdose or incorrect administration of study drug should be recorded on the CRF. If the associated AE fulfills serious criteria, Investigators should report the event to the Sponsor within 24 hours using the SAE Reporting Form. The Sponsor should report any SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta-Pharma per contractual guidelines.

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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.

3.9.5 Medication Error, Drug Abuse, and Drug Misuse

3.9.5.1 Medication Error

A medication error is an unintended failure or mistake in the treatment process for Acalabrutinib that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- **Was identified and** participant received the drug
- Did not occur, but circumstances were recognised that could have led to an error.

3.9.5.2 Drug Abuse

Drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of Acalabrutinib for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the Data Entry Site (DES) using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse involves a person not enrolled in the study (such as a relative of the study participant).

3.9.5.3 Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of Acalabrutinib for medicinal purposes outside of the authorized product information, or for unauthorized Acalabrutinib, outside the intended use as specified in the protocol and includes deliberate administration of the product by the wrong route.

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Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

3.9.5.4 Reporting Timeline

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is completed within **one** (initial fatal/life-threatening or follow-up fatal/life-threatening) **or 5** (other serious initial and follow-up) **calendar days** if there is an SAE associated with the event of medication error, drug abuse, or misuse and **within 30 days** for all other events.

3.9.5.5 Vaccination Guidance

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

3.10 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

The investigator may withdraw any subject from study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Any subject has the right to withdraw from the study at any time. In addition, subjects may be withdrawn from study treatment for the following reasons:

- Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the investigator.
- Any subject who starts new systemic immunosuppressive therapy for the treatment of chronic GVHD, becomes pregnant or breastfeeding, is significantly noncompliant, etc. should be withdrawn from study treatment.

Subjects who discontinue study therapy will continue to be followed on study for follow-up of safety and survival unless they withdraw consent for further follow-up. Thus,

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all subjects receiving ≥ 1 dose of study drug will be followed during the immediate post-therapy period according to the study calendar until resolution of treatment-related toxicities or the safety follow up visit, whichever is longer unless the subject withdraws consent for such follow-up to be conducted. Patients will continue to be followed by chart review for survival, relapse and chronic GVHD outcomes unless they withdraw consent.

3.11 REMOVAL FROM STUDY

Reasons for removal of a subject from the study are:

- Subject's withdrawal of consent from study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death

3.12 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the Sponsor's Pharmacovigilance procedures. Adverse events, and SAEs will be reviewed internally as part of ongoing safety surveillance.

Monthly conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs, and deaths).

In addition, an independent Data and Safety and Monitoring Board (DSMB) will monitor this study starting from 6 months after the first enrollment, and at least annually.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 2. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

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

4.1 DESCRIPTION OF PROCEDURES

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4.1.1 Informed Consent

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

4.1.2 Medical History

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

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. Important additional requirements for reporting SAEs are explained in Section 6.2.4.

4.1.4 Concomitant Medications and Therapy

Document all concomitant systemic medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.3.1 and 3.3.2. All screening procedures, unless otherwise indicated, should be completed within 28 days of the first dose of study drug.

4.1.6 Karnofsky Performance Status

The Karnofsky performance index is provided in Appendix 6 and must be captured at enrollment to confirm eligibility.

4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the height (screening only) and weight, blood pressure and general physical examination.

Symptom-directed and response assessment physical exams will be done during the

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treatment period and at the safety follow-up visit.

4.1.8 Electrocardiogram

Subjects should be in supine position and resting for at least 5 minutes before any study-related ECGs. ECG must be performed at screening.

4.1.9 Urine or Serum Pregnancy Test

Pregnancy tests will be required for women of childbearing potential prior to starting the study drug and at the end of treatment.

4.1.10 Hematology

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

4.1.11 Serum Chemistry

Chemistry panel must include alkaline phosphatase, ALT, AST, creatinine, and total bilirubin.

4.1.12 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (anti-HBs), anti-HBc, and HCV antibody. 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. 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.

4.1.13 Pulmonary Function Tests

Pulmonary Function Tests will be required for Day 1, Cycle 1, then spirometry on Day 1, Cycle 4, 7, and every 3 months or if clinically indicated.

4.1.14 Patient-Reported Outcomes

Subjects will complete the Lee Chronic GVHD Symptom Scale and the PROMIS-29 (Appendix 7) survey on day 1 +/- 7 days of Cycles 1, 4, 7 and every 3 months thereafter.

4.1.15 GVHD Response Assessment Measures

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Clinical providers will complete the NIH Consensus response measures (Appendix 8) at study visits based on physical exam finding, testing and patient interviews.

4.1.16 Pharmacodynamics Studies

Peripheral blood samples (20 mL EDTA tubes) will be collected, processed into PBMC and plasma and frozen for future testing at 3 time points: (1) between signed consent and first dose of acalabrutinib; (2) Day 1, cycle 2; and (3) Day 1, cycle 4.

4.1.17 Study Drug Accountability

Subjects will return unused medications at each study visit.

4.2 ASSESSMENT OF RESPONSE TO TREATMENT

Response assessments will be evaluated based on NIH Criteria (refer to Appendix 9).

4.3 SUSPECTED DRUG TOXICITY OR PROGRESSIVE DISEASE VISITS

Please see section 4.4 below.

4.4 TREATMENT TERMINATION AND SAFETY FOLLOW-UP VISITS

A treatment termination (TT) visit is required for safety assessments for any subjects who permanently discontinue study drug for any reason, including disease progression. The TT visit should be scheduled within 7 days of the last dose of study drug, if possible, and is not required for subjects who discontinue from the study within 10 days of a scheduled study visit.

Each subject should be followed until the safety follow-up (SFU) visit at 30 (+ 7) days after his or her last dose of study drug to monitor for resolution or progression of AEs and to document the occurrence of any new events, regardless of whether the subject receives a new cGVHD therapy or demonstrates disease progression within this timeframe. If a patient is not able to return for evaluation, study staff will call the patient to document any new events. Subjects who withdraw consent for study treatment should still be encouraged to complete the SFU assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. The Schedule of Assessments (Appendix 2 describes the procedures required for the TT and SFU visits.

4.5 FOLLOW-UP FOR NEW SYSTEMIC TREATMENT, DISEASE RELAPSE, AND SURVIVAL

4.5.1 Long-term Follow-up

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Once subjects discontinue acalabrutinib and complete the SFU, they will be followed through medical records for new systemic chronic GVHD treatment, disease relapse and survival, in order to calculate FFS.

4.6 MISSED EVALUATIONS

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

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

This is a Phase 2, single-arm trial designed to assess the safety and efficacy of acalabrutinib in subjects with chronic GVHD.

5.2 RATIONALE FOR SAMPLE SIZE

With a sample size of 50 patients, the best ORR will be estimated with a 95% exact binomial confidence intervals (CIs).[29] If acalabrutinib is more effective than ibrutinib as a historic control, the lower bound of the CIs will be used to provide evidence that the true ORR is greater than a specific response rate. With 50 patients evaluable for response, we would have 92% power to rule out a response rate of 67% at the 1-sided 5% level, if the true response rate were 85%. The observation of at least 39 patients with a response would be considered evidence to rule out a response rate of 67% or smaller. However, even if acalabrutinib is not statistically more effective than ibrutinib, it may still be a preferable treatment if the response rate is similar but the toxicity is less.

5.3 ANALYSIS POPULATIONS

All efficacy and safety analysis will be performed using the treated population, which consists of all subjects who receive any amount of study treatment. The characteristics of this population will be described. The analysis of duration of response will only include subjects who have achieved objective response.

We will also report efficacy in a modified intention-to-treat population (mITT), defined as subjects who receive at least 30 days of acalabrutinib and at least one response assessment. The 30 days of acalabrutinib dosing does not need to be consecutive.

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5.4 MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of acalabrutinib cycles completed and the number and timing of prescribed dose delays, reductions and interruptions.

5.5.2 Analysis of Efficacy Parameters

5.5.2.1 Primary Endpoint

The primary endpoint is the best response (complete and partial response [CR + PR]) of all subjects following initiation of acalabrutinib, calculated according to the proposed response definitions of the 2014 NIH Consensus Conference. Exact 95% CIs will be calculated for the objective response rate using the Clopper and Pearson method. With 50 patients, the estimated best response probability will be within +/- 0.14 of the true response probability with 95% confidence. The primary analysis will be conducted when the best RR is known for each patient within the first 6 months of treatment.

Since acalabrutinib is anticipated to be similar to ibrutinib but less toxic, we will compare the observed best ORR with the published efficacy of ibrutinib (67%) and provide the 95% CI for the difference.

5.5.2.2 Secondary Endpoints

The secondary endpoints are the safety and tolerability of acalabrutinib, the best response of the evaluable subjects, the duration of response, patient-reported outcomes, failure-free survival (FFS, duration of relapse-free survival without adding another systemic treatment for chronic GVHD), and organ-specific response rates.

Safety and tolerability

Grade 3 and above AEs according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, and all SAEs will be described for the population receiving at least one dose of acalabrutinib at least from the time of consent through the safety follow-up period. Any AE/SAE at least possibly related to acalabrutinib therapy will be reported for the duration of the study.

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Best response in modified Intention-To-Treat (mITT) population

The best response (CR+PR) of subjects who received at least one response assessment (response-evaluable population) and received at least 30 days of acalabrutinib (do not need to be consecutive) will be estimated with an exact 95% CI.

Duration of response (DOR)

The DOR will be described for the group achieving at least a partial response, defined as the number of weeks the subject maintains a partial or complete response, calculated from the date the response is documented until loss of the response or start of another systemic immunosuppressive treatment for chronic GVHD, whichever occurs first. Patients who maintain their response or do not return for evaluations will be censored at their last assessment. DOR will be estimated using the Kaplan-Meier method. Approximate 95% CIs for median DOR will be computed using the formula proposed by Brookmeyer and Crowley.[30]

Patient-reported outcomes

Patients will provide assessment of their symptom burden and quality of life using validated instruments recommended by the NIH Consensus Development Project on Chronic GVHD (Lee Chronic GVHD Symptom Scale)[31] and the NIH-endorsed PROMIS-29. Scores will be calculated for each instrument based on published algorithms with absolute changes and clinically meaningful changes described for the population as a whole and based on CR+PR vs. SD+MR+PD.

Failure-free survival

This time-to-event outcome will be estimated with the composite event of death from any cause, relapse and addition of secondary immune suppressive agents using the Kaplan-Meier method. Systemic immune-suppressive agents include orally or intravenously administered systemically active immune-suppressive drugs, as well as procedures including extra-corporeal photopheresis (ECP). Topical or local therapies are not considered systemic agents. FFS will be reported at 6 months and 1 year.

Organ-specific response rates

Response rates by organ will also be calculated and reported as ORR (CR+PR) vs. all other categories (SD, PD, MR).

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6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs.

6.1 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product, regardless of attribution. This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with chronic GVHD that were not present before the AE reporting period (see Section 6.2.1).
- Pre-existing medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.
- Abnormal laboratory values considered clinically significant by the investigator should be reported as an AE.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened**: A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Preplanned hospitalization**: A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the preplanned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before signing the ICF, will not be considered serious if they are performed after signing the ICF for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances are also not SAEs.
- **Diagnostic testing and procedures**: Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should

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be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (eg, routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.

- **Abnormal laboratory results that the investigator considers to not be clinically significant**: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Signs/symptoms of chronic GVHD due to GVHD progression**. These events are captured elsewhere as efficacy data.

Patients will be monitored for AEs through 30 days following their last dose of acalabrutinib. Any toxicity with at least 5% true prevalence is likely to be observed (with 92% probability) in a trial of 50 patients.

6.1.2 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 6.2 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

6.1.3 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see Section 6.1.4). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the

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subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).

- It requires or prolongs inpatient hospitalization (Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE).
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

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

Adverse Events (AEs) for malignant tumors reported during a study should be assessed as Serious AEs. If no other seriousness criteria apply, the 'Important Medical Event' criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a Non-Serious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as Serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

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

6.1.4 Severity

The study site will grade the severity of adverse events experience by study participants according to CTCAE version 5. Grade 1 and grade 2 non-serious adverse events do not

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require reporting. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.1.5 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The study will collect all Grade 3 and above adverse events, regardless of relationship to study therapy or study procedures. Severity grading will be based on the current version of the Common Terminology Criteria for Adverse Events (CTCAE). Grade 1 and 2 non-serious events will not be collected.

All non-serious, Grade 3 and above adverse events must be recorded in the database within 20 days of becoming aware of the event. Non-serious adverse events collected in the database will be compiled by the coordinating center and reported to the DSMB at regularly scheduled meetings.

All serious adverse events (Grade 1 and above) must be reported in the database within 24 hours of becoming aware of the event and the coordinating center notified. Significant and relevant follow-up information should also be reported as soon as possible. The sponsor-investigator and coordinating center will work with the site to

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prepare the IND safety report for reporting to Acerta/AstraZeneca, FDA and the IRB and others as required.

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study drug and ends with the SFU visit. Exception to this reporting period are (a) any AE occurring due to a protocol-defined screening procedure; and (b) if any SAE occurs beyond 30 days after the last dose of acalabrutinib ***AND*** it is assessed by the investigator as related to acalabrutinib, it must be reported as an SAE.

All SAEs that occur during the reporting period should be followed to resolution or until the investigator assesses the subject as stable, or until the subject is lost to follow up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the investigator does not expect any further improvement or worsening of the event.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE CRF.

Chronic GVHD disease progression itself is not considered an AE.

Each recorded AE or SAE will be described by its diagnostic term, duration (eg, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' per FDA guidance on safety reporting requirements (FDA Guidance 2012).

See Appendix 10 for more detail on assessing relationship.

6.2.3 Pregnancy

The Sponsor-Investigator should report all pregnancies and pregnancies in the partners of subjects to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta Pharma/AZ per contractual guidelines. Investigators should report any occurrences to Sponsor-Investigator within 24 hours.

Any uncomplicated pregnancy that occurs with the subject or with the partner of a

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treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of 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. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

6.2.4 Expedited Reporting Requirements for Serious Adverse Events

Investigators should report any SAEs to Sponsor-Investigator within 24 hours. The Sponsor-Investigator should report all SAEs to the IRB and Regulatory Authorities per institutional and/or regulatory guidelines, and to Acerta Pharma/AZ per contractual guidelines. The Sponsor will notify Acerta Pharma/AZ in parallel with submission to the IRB and concerned Regulatory Authority for Suspected Unexpected Serious Adverse Reactions (SUSARs) and within fifteen (15) calendar days of awareness for other SAEs or Special Situation Reports using individual unblinded or blinded case reports (Institution's Standard SAE Report Form, MedWatch, or CIOMS). New information will be submitted to Acerta Pharma/AZ within the same timeframe as initial reports.

Whenever possible, SAEs should be reported by diagnosis term not as a constellation of symptoms. All deaths should be reported with the primary cause of death as the AE term, including if due to GVHD, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

All SAEs are to be submitted to AstraZeneca Product Safety mailbox:

AEMailboxClinicalTrialTCS@astrazeneca.com

6.2.5 Type and Duration of Follow-up of Subjects after Adverse Events

All Grade 3 and higher AEs and SAEs that are encountered during the protocol-specified

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AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, or the subject is lost to follow-up or withdraws consent.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

The Sponsor retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, current Investigator Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study. Inter-IRB authorization agreements may substitute for local IRB oversight.

This clinical study was designed and will be implemented in accordance with the protocol, the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations (CFR) Title 21 and European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.

7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

The investigator, or designee, must explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21 Code of Federal Regulations (CFR) Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's

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legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with regulatory agencies and IRBs/IECs. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.3 DATA COLLECTION

Authorized study site personnel will collect and enter data for this study according to the completion guidelines that will be provided. The investigator will ensure that data collection is accurate and completed promptly.

7.4 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib tablets must be kept in a limited access cabinet or space in the research pharmacy. The study drug must not be used outside the context of the protocol.

7.5 RECORD RETENTION

The investigators and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each Form FDA 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE information, subject files (source documentation) that substantiate database entries, all relevant correspondence and other documents pertaining to the conduct of the study.

The investigator shall retain study records in accordance with institutional and/or national/local regulations, whichever is longer.

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Appendix 1. NIH Global Severity of Chronic GVHD

Mild chronic GVHD

1or 2 organs involved with no more than score 1 *plus*
Lung score 0

Moderate chronic GVHD

3 or more organs involved with no more than score 1

OR

At least 1 organ (not lung) with a score of 2

OR

Lung score 1

Severe chronic GVHD

At least 1 organ with a score of 3

OR

Lung score of 2 or 3

Key points:

1. In skin: higher of the two scores to be used for calculating global severity.
2. In lung: FEV1 is used instead of clinical score for calculating global severity.
3. If the entire abnormality in an organ is noted to be unequivocally explained by a non-GVHD documented cause, that organ is not included for calculation of the global severity.
4. If the abnormality in an organ is attributed to multifactorial causes (GVHD plus other causes) the scored organ will be used for calculation of the global severity regardless of the contributing causes (no downgrading of organ severity score).

Appendix 2. Schedule of Assessments

Procedures	Screening[j]	Treatment Period (28 day cycles)		PD/toxicity visit	Treatment termination (TT)[m]	Safety follow-up (SFU)[n]	Long-term follow-up
		Cycles 1 through 6	Cycles 7, 10, 13, 16, 19, 22[l]				
Day in cycle	-28 to 0	1[k]	1[k]				
Informed consent	X						
Eligibility criteria[a]	X						
Medical history	X						
Karnofsky Performance Score	X						
Height	X						
Pregnancy test[b]	X				X	X	
ECG[c]	X						
Physical exam	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	
Hematology and chemistry	X	X	X	X	X	X	
cGVHD severity scoring	X						
cGVHD response assessment measures[d]		X	X	X			

Footnotes defined on last page of table.

Procedures	Screening[j]	Treatment Period (28 day cycles)		PD/toxicity visit	Treatment termination (TT)[m]	Safety follow-up (SFU)[n]	Long-term follow-up
		Cycles 1 through 6	Cycles 7, 10, 13, 16, 19, 22[l]				
Day in cycle	-28 to 0	1[k]	1[k]				
Patient- reported outcomes[e]		X[e]	X	X			
- Lee symptom scale							
- PROMIS-29							
Record systemic immune suppressive agents[f]	X	X	X	X	X	X	X
Pharmacodynamic sample[g]		X[g]					
Pulmonary Function Tests[h]		X					
Spirometry[h]		X	X				
Acalabrutinib Dispensing		X	X				
Collect study drug diary		X	X	X	X		
Survival and malignancy relapse							X
Adverse events[i]		X	X	X	X	X	X

[a]Eligibility includes the following: review of patient records for compliance with all inclusion and exclusion criteria; laboratory tests to meet laboratory criteria; confirmation of no history of HIV or hepatitis B/C

[b]Urine or serum pregnancy tests required for women of childbearing potential prior to starting the study drug and at the end of treatment. Only one pregnancy test is required after acalabrutinib discontinuation (TT or SFU visit).

[c]Subjects must be in a supine position and resting for at least 5 minutes prior to ECG.

[d]Clinical providers will complete the NIH Consensus response measures at enrollment and monthly study visits measures based on physical exam findings, testing, and patient interviews.

[e]Patient reported outcomes collected at enrollment (Cycle 1 Day 1), Cycle 4 Day 1, Cycle 7 Day 1, and every 3 months thereafter.

[f]Document all concomitant systemic medications and procedures from within 21 days before the start of study drug through 30 days after the last dose of study drug. After the SFU, record any new systemic cGVHD treatments as part of long term follow-up.

[g]Peripheral blood samples for pharmacodynamic studies between informed consent and first dose; Cycle 2 Day 1; and Cycle 4 Day 1.

[h]Full pulmonary function tests (FEV_1, FVC, DL_{CO} (corrected for Hb), TLC, and RV) required at Cycle 1. Spirometry (FEV_1, FVC) required on Cycle 4 Day 1, Cycle 7 Day 1, and every 3 months or if clinically indicated.

[i]AEs/SAEs are monitored from the time the subject receives the first dose of study drug and ends with the SFU visit. Exceptions listed in 6.2.1. After the SFU, only SAEs assessed by the investigator as related to acalabrutinib must be reported.

[j]If screening visit occurs $\leq$7 days prior to Cycle 1 Day 1, then Cycle 1 Day 1 studies do not have to be repeated.

[k]Acceptable window for study visits during the treatment period is +/- 7 days.

[l]Subjects who are responding to and tolerating the drug have option to continue treatment for up to 24 cycles.

[m]Treatment termination (TT) visit is required for any subjects who permanently discontinue study drug for any reason (including cGVHD progression). TT visit should be scheduled within 7 days of the last dose. TT visit not required for subjects who discontinue from study within 10 days of scheduled study visit.

[n]Each subject should be followed until the Safety follow-up (SFU) visit at 30 +7 days after the last dose of study drug.

Appendix 3. Subject Drug Diary

FH 8801 ACALABRUTINIB

Acalabrutinib Study Participant Self-Administration Diary – 100mg Capsules

Subject ID:		Cycle #:	
Assigned dose:	☐ 100mg twice a day ☐ 100mg once a day (dose reduction)	Date Dispensed:	

Your MD: _____ MD Contact Information: _____

SUBJECT DRUG INSTRUCTIONS:

Storage:

Keep the study drug (acalabrutinib) at room temperature. It should be stored according to the storage conditions as indicated on the label.

Dosing Instructions:

100mg twice a day: You will take 1 capsule by mouth twice a day at around the same time each day.

100mg once a day: You will take 1 capsule by mouth daily at around the same time each day.

Special Instructions:

The capsules must be swallowed whole. Do NOT try to open the capsules or dissolve them in water. Acalabrutinib can be taken with or without food.

If you miss a dose, you can take it up to 3 hours after the scheduled time with a return to the normal schedule at the next dose. If it has been more than 3 hours, do not take the missed dose. Take the next dose as the scheduled time. Do not take extra capsules to make up the missed dose.

Please bring the bottle(s) and all unused capsules to the clinic or hospital at each visit (even if the bottle is empty).

Diary Instructions:

Please record all entries in **INK.** Correct mistakes with single-line strikethrough, initials and date.

Please complete the form every day. This form will help you keep track of your study treatment doses.

If you miss a dose, write the reason. If you have any abnormal symptoms while taking the study drugs, record them on the form.

*** YOU MUST BRING THIS FORM AND YOUR BOTTLES OF STUDY DRUG TO THE STUDY STAFF AT EACH VISIT TO THE CLINIC OR HOSPITAL.**

Version 07JAN2019

Day	Date	omin.gdose'.11umber of capsules taken	Evening dose: numlber of capsules taken	Reason for missed or changed d'.ose/ Abnormal symptoms/Commems (if anyl
1	*Example 01-Jan-2019*	*1*	*1*	*none*
]				
2				
3				
4				
5				
6				
7				
8				
9				
10				
1]				
12				
13				
14				
15				
16				
17				
18				
19				
20				
2]				
2:2				
2:3				
24				
25				
216				
27				
28				

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Appendix 4. Known Strong in Vivo Inhibitors or Inducers of CYP3A

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	carbamazepine
Cobicistat[b]	enzalutamide
conivaptan[b]	mitotane
Danoprevir and ritonavir[c]	phenytoin
elvitegravir and ritonavir[c]	rifampin
grapefruit juice[d]	St John's wort[f]
indinavir and ritonavir[c]	
itraconazole[b]	
ketoconazole	
lopinavir/ritonavir[b] (combination drug) [b, c]	
Paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) [c]	
posaconazole	
ritonavir[b, c]	
saquinavir and ritonavir [b, c]	
Telaprevir[b]	
Tipranavir and ritonavor[b, c]	
Troleandomycin	
Voriconazole	
Clarithromycin[b]	
diltiazem[b]	
idelalisib	
nefazodone	
nelfinavir[b]	

a. A strong inhibitor is defined as an inhibitor that increases the AUC of a substrate by ≥ 5-fold.
b. Inhibitor of P-gp (defined as those increasing AUC of digoxin to ≥1.25-fold).
c. Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.
d. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
e. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.
f. The effect of St. John’s wort varies widely and is preparation-dependent.

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

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers . Web link Accessed 16 May 2019 http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

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Appendix 5. Contraceptive Guidance

Definitions

Woman of Childbearing Potential

WOCBP are women who are fertile following menarche and until becoming postmenopausal unless permanently sterile; permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Subjects of Non-Reproductive Potential

Women are considered to be of non-reproductive potential if they meet any of the below criteria:

- Postmenopausal, defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age a high follicle-stimulating hormone (FSH)level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy, or bilateral tubal ligation/occlusion, at least 6 weeks before Screening
- Have a congenital or acquired condition that prevents childbearing

Men are considered to be of non-reproductive potential if they are permanently sterile due to bilateral orchidectomy.

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 maybe 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.

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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 (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

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

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Appendix 6. Karnofsky Performance Status Scale Definitions Rating (%) Criteria

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

References:

Crooks, V, Waller S, et al. The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. J Gerontol. 1991; 46: M139-M144.
de Haan R, Aaronson A, et al. Measuring quality of life in stroke. Stroke. 1993; 24:320- 327.
Hollen PJ, Gralla RJ, et al. Measurement of quality of life in patients with lung cancer in multicenter trials of new therapies. Cancer. 1994; 73: 2087-2098.
O'Toole DM, Golden AM. Evaluating cancer patients for rehabilitation potential. West J Med. 1991; 155:384-387.
Oxford Textbook of Palliative Medicine, Oxford University Press. 1993;109.
Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193.

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Appendix 7. Patient-Reported Outcomes

A. Lee cGVHD Symptom Scale

Please let us know whether you have been bothered by any of the following problems in the past 7 days.

		Not at all	Slightly	Moderately	Quite a bit	Extremely
Skin						
1.	Abnormal skin color	○0	○1	○2	○3	○4
2.	Rashes	○0	○1	○2	○3	○4
3.	Thickened skin	○0	○1	○2	○3	○4
4.	Sores on skin	○0	○1	○2	○3	○4
5.	Itchy skin	○0	○1	○2	○3	○4
Eyes and Mouth						
6.	Dry eyes	○0	○1	○2	○3	○4
7.	Need to use eyedrops frequently	○0	○1	○2	○3	○4
8.	Difficulty seeing clearly	○0	○1	○2	○3	○4
9.	Need to avoid certain foods due to mouth pain	○0	○1	○2	○3	○4
10.	Ulcers in mouth	○0	○1	○2	○3	○4
11.	Receiving nutrition from an intravenous line or feeding tube	○0	○1	○2	○3	○4
Breathing						
12.	Frequent cough	○0	○1	○2	○3	○4
13.	Colored sputum	○0	○1	○2	○3	○4
14.	Shortness of breath with exercise	○0	○1	○2	○3	○4
15.	Shortness of breath at rest	○0	○1	○2	○3	○4
16.	Need to use oxygen	○0	○1	○2	○3	○4
Eating and Digestion						
17.	Difficulty swallowing solid foods	○0	○1	○2	○3	○4
18.	Difficulty swallowing liquids	○0	○1	○2	○3	○4
19.	Vomiting	○0	○1	○2	○3	○4
20.	Weight loss	○0	○1	○2	○3	○4

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Please let us know whether you have been bothered by any of the following problems in the past 7 days.

Muscles and Joints	**Not at all**	**Slightly**	**Moderately**	**Quite a bit**	**Extremely**
21. Joint and muscle aches	○0	○1	○2	○3	○4
22. Limited joint movement	○0	○1	○2	○3	○4
23. Muscle cramps	○0	○1	○2	○3	○4
24. Weak muscles	○0	○1	○2	○3	○4
Energy					
25. Loss of energy	○0	○1	○2	○3	○4
26. Need to sleep more/take naps	○0	○1	○2	○3	○4
27. Fevers	○0	○1	○2	○3	○4
Mental and Emotional					
28. Depression	○0	○1	○2	○3	○4
29. Anxiety	○0	○1	○2	○3	○4
30. Difficulty sleeping	○0	○1	○2	○3	○4

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Please respond to each question or statement by marking one box per row.

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANXD1	I felt fearful	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANXH0	I found it hard to focus on anything other than my anxiety	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANXH1	My worries overwhelmed me	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEPH1	I felt hopeless	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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	Fatigue In the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
FATEXP41	How run-down did you feel on average? ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Sleep Disturbance **In the past 7 days…**	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER18_CaPS	I have trouble doing all of the family activities that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER23_CaPS	I have trouble doing all of my usual work (include work at home)	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER45_CaPS	I have trouble doing all of the activities with friends that I want to do	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Pain Interference **In the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities? .	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ24	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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Pain Intensity

In the past 7 days…

Global07	How would you rate your pain on average?.....	☐ 0 **No pain**	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10 **Worst pain imaginable**

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Acalabrutinib for Chronic GVHD

Response Assessment
Provider Survey

Instructions:

Please score all signs and symptoms. If you believe the sign or symptom is **DEFINITELY NOT** related to chronic GVHD (e.g., C difficile diarrhea, shingles rash, shortness of breath due to pulmonary embolus) then you should STILL score it, but indicate the true diagnosis.

Subjective symptoms can be scored. For example, joint tightness can be scored based on subjective findings despite the absence of objective limitations.

Please score signs and symptoms present in the *last week*.

Date of Visit: _____

Subject ID: _____

Your Name: _____

Current Visit: _____

Target Date for Next Visit: _____

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SKIN & ROM

	0	1	2	3
Skin *GVHD features to be scored by BSA:* **Check all that apply:** ☐ Maculopapular rash / erythema ☐ Lichen planus-like features ☐ Sclerotic features ☐ Papulosquamous lesions or ichthyosis ☐ Keratosis pilaris-like	❑ No BSA involved	❑ 1-18% BSA	❑ 19-50% BSA	❑ >50% BSA
	☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Skin Features Score	❑ No sclerotic features		❑ Superficial sclerotic features "not hidebound" (able to pinch)	*Check all that apply* ❑ Deep sclerotic features ❑ "Hidebound" (unable to pinch) ❑ Impaired mobility ❑ Ulceration

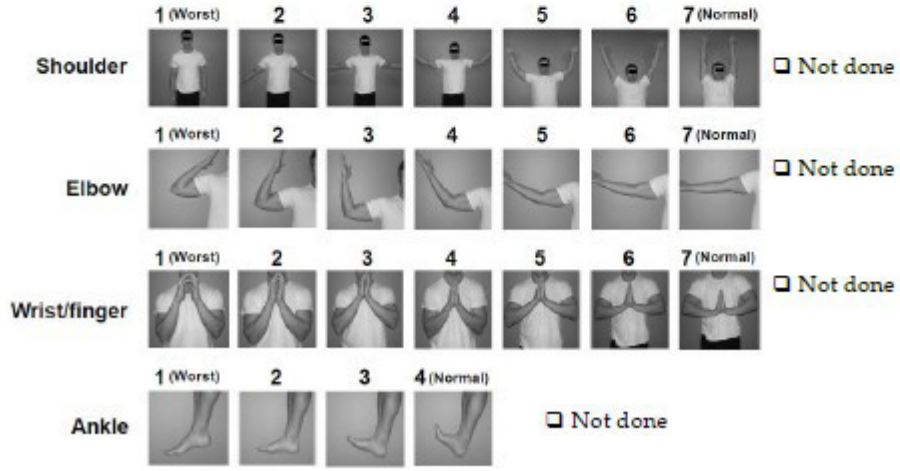
If skin features score = 3, BSA% of non-moveable sclerosis/fasciitis _____

How would you rate the severity of this patient's skin and/or joint tightening on the following scale, where 0 is not at all severe and 10 is the most severe symptoms possible:

0 1 2 3 4 5 6 7 8 9 10

Symptoms not at all severe — Most severe symptoms possible

Please circle this person's current ROM for each joint below:



❑ Not done

❑ Not done

❑ Not done

❑ Not done

☐ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____

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		0	1	2	3
Mouth		❑ No symptoms	❑ Mild symptoms with disease signs but not limiting oral intake significantly	❑ Moderate symptoms with disease signs with partial limitation of oral intake	❑ Severe symptoms with disease signs on examination with major limitation of oral intake
		❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Mouth	**Ulcers**	❑ None (=+0)		❑ Ulcers involving (≤20%) (=+3)	❑ Severe ulceration (> 20%) (=+6)
	Erythema	❑ None	❑ Mild erythema OR Moderate erythema (<25%)	❑ Moderate (≥25%) OR Severe erythema (<25%)	❑ Severe erythema (≥25%)
	Lichenoid	❑ None	❑ Lichen-like changes (<25%)	❑ Lichen-like changes (25-50%)	❑ Lichen-like changes (>50%)
		Total score for all mucosal changes			
GI Tract *Check all that apply:* o Esophageal web / proximal stricture or ring o Dysphagia o Anorexia o Nausea o Vomiting o Diarrhea o Weight loss ≥5% over past 3 months o Failure to thrive		❑ No symptoms	❑ Symptoms without significant weight loss (<5%) over past 3 months	❑ *Check all that apply* O Symptoms associated with mild to moderate weight loss (5-15%) over past 3 months O Moderate diarrhea without significant interference with daily living	❑ *Check all that apply* O Symptoms associated with significant weight loss >15% over past 3 months, requires nutritional supplement for most calorie needs O Esophageal dilation O Severe diarrhea with significant interference with daily living
		❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Esophagus		❑ No symptoms	❑ Occasional dysphagia or odynophagia with solid food or pills during the past week	❑ Intermittent dysphagia or odynophagia with solid food or pills, but not for liquids or soft foods during the past week	❑ Dysphagia or odynophagia for almost all oral intake, on almost every day of the past week
		❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Upper GI		❑ No symptoms	❑ Mild, occasional symptoms, with little reduction in oral intake during the past week	❑ Moderate, intermitted symptoms, with some reduction in oral intake, during the past week	❑ More severe or persistent symptoms throughout the day, with marked reduction in oral intake, on almost every day of the week
		❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			

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	0	1	2	3
Lower GI ❑ **Diarrhea**	❑ No loose or liquid stools during the past week	❑ Occasional loose or liquid stools on some days during the past week	❑ Intermittent loose or liquid throughout the day, on almost every day of the past week, without requiring intervention to prevent or correct volume depletion	❑ Voluminous diarrhea on almost every day of the past week, requiring intervention to prevent or correct volume depletion
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Eye	❑ No symptoms	❑ Mild dry eye symptoms not affecting ADL (requiring eye drops ≤3x per day)	❑ Moderate dry eye symptoms partially affecting ADL **WITHOUT** new vision impairment due to KCS *Check all that apply* ○ Requiring lubricant eye drops >3x per day ○ Punctual plugs	❑ Severe dry eye symptoms significantly affecting ADL *Check all that apply* ○ Special eyewear to relieve pain ○ Unable to work because of ocular symptoms ○ Loss of vision due to kerato-conjunctivitis sicca
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Joints /Fascia	❑ No symptoms	❑ *Check all that apply* ○ Mild tightness of arms or legs ○ Mild decreased range of motion (ROM) **AND** not affecting ADL	❑ *Check all that apply* ○ Tightness of arms or legs ○ Joint contractures ○ Erythema thought due to fasciitis ○ Moderate decrease ROM **AND** mild to moderate limitation of ADL	❑ Contractures WITH significant decrease of ROM **AND** significant limitation of ADL (unable to tie shoes, button shirts, dress self etc.)
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Genital Tract ❑ **Not Examined**	❑ No signs	❑ Mild signs and females with or without discomfort on exam	❑ Moderate signs and may have symptoms with discomfort on exam	❑ Severe signs with or without symptoms
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			
Lung	❑ No symptoms	❑ Mild symptoms (shortness of breath after climbing one flight of steps)	❑ Moderate symptoms (shortness of breath after walking on flat ground)	❑ Severe symptoms (shortness of breath at rest; requiring O_2)
	❑ Abnormality present but explained entirely by non-GVHD documented cause (specify):_____			

Note: Liver and pulmonary function tests are collected via chart review to calculate those scores

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OVERALL STATUS

Please rate the severity of this person's chronic GVHD (Global)	
on this scale →	❑ No GVHD (0) ❑ Mild (1) ❑ Moderate (2) ❑ Severe (3)
and on this scale → *(circle one)*	cGVHD symptoms are not at all severe … cGVHD symptoms are most severe possible 0 1 2 3 4 5 6 7 8 9 10

Current GVHD Status	❑ Complete response (1)	❑ Partial response (2)	❑ Mixed response (3)	❑ Unchanged (4)	❑ Progressive (5)

Since the enrollment visit on _____, how would you say this patient's chronic GVHD has changed?							
	Very much better (+3)	Moderately better (+2)	A little better (+1)	About the same (0)	A little worse (-1)	Moderately worse (-2)	Very much worse (-3)
cGVHD Overall	❑	❑	❑	❑	❑	❑	❑
What are your reasons for how you rated "chronic GVHD overall"? *Write in* →	(For example, has a specific organ or symptom improved or worsened?)						

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Other complications related to chronic GVHD:					
	Never (0)	Past, not now (1)	Mild (2)	Moderate (3)	Severe (4)
1. Ascites (serositis)	❑	❑	❑	❑	❑
2. Pericardial Effusion	❑	❑	❑	❑	❑
3. Pleural Effusion(s)	❑	❑	❑	❑	❑
4. Nephrotic syndrome	❑	❑	❑	❑	❑
5. Myasthenia Gravis	❑	❑	❑	❑	❑
6. Peripheral Neuropathy	❑	❑	❑	❑	❑
7. Polymyositis	❑	❑	❑	❑	❑
8. Weight loss >5% without GI symptoms	❑	❑	❑	❑	❑
9. Eosinophilia >500/ul	❑	❑	❑	❑	❑
10. Platelets <100,000/ul	❑	❑	❑	❑	❑
11. Other, please specify: a. _____	❑	❑	❑	❑	❑

Baseline Scores from ____/____/____:

Organ	Score	
	Baseline	Current
Skin		
Eyes		
Mouth		
Ulcers		
Erythema		
Lichenoid		
OMRS Sum (total out of 12)		
Esophagus		
Upper GI		
Lower GI		

Organ	Score	
	Baseline	Current
Liver		
ALT		
Alkaline Phosphatase		
Total Bilirubin		
Lung		
%FEV1		
Joints/Fascia		
P-ROM Score (total out of 25)		
Global		

Clinician Signature: _____ Date: _____

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Appendix 9. Response Determination

Response determination for chronic GVHD clinical trials based on clinician assessments

Organ	Complete Response	Partial Response	Progression
Skin	NIH Skin Score 0 after previous involvement	Decrease in NIH Skin Score by 1 or more points	Increase in NIH Skin Score by 1 or more points, except 0 to 1
Eyes	NIH Eye Score 0 after previous involvement	Decrease in NIH Eye Score by 1 or more points	Increase in NIH Eye Score by 1 or more points, except 0 to 1
Mouth	NIH Modified Oral Mucosa Rating Score 0 after previous involvement	Decrease in NIH Modified Oral Mucosa Rating Score of 2 or more points	Increase in NIH Modified Oral Mucosa Rating Score of 2 or more points
Esophagus	NIH Esophagus Score 0 after previous involvement	Decrease in NIH Esophagus Score by 1 or more points	Increase in NIH Esophagus Score by 1 or more points, except 0 to 1
Upper GI	NIH Upper GI Score 0 after previous involvement	Decrease in NIH Upper GI Score by 1 or more points	Increase in NIH Upper GI Score by 1 or more points, except 0 to 1
Lower GI	NIH Lower GI Score 0 after previous involvement	Decrease in NIH Lower GI Score by 1 or more points	Increase in NIH Lower GI Score by 1 or more points, except from 0 to 1
Liver	Normal ALT, alkaline phosphatase, and Total bilirubin after previous elevation of one or more	Decrease by 50%	Increase by 2x ULN
Lungs	-Normal %FEV1 after previous involvement -If PFTs not available, NIH Lung Symptom Score 0 after previous involvement	-Increase by 10% predicted absolute value of %FEV1 -If PFTs not available, decrease in NIH Lung Symptom Score by 1 or more points	-Decrease by 10% predicted absolute value of %FEV1 -If PFTs not available, increase in NIH Lung Symptom Score by 1 or more points, except 0 to 1
Joints and Fascia	Both NIH Joint and Fascia Score 0 and P-ROM score 25 after previous involvement by at least one measure	Decrease in NIH Joint and Fascia Score by 1 or more points or increase in P-ROM score by 1 point for any site	Increase in NIH Joint and Fascia Score by 1 or more points or decrease in P-ROM score by 1 point for any site
Global	Clinician overall severity score 0	Clinician overall severity score decreases by 2 or more points on a 0–10 scale	Clinician overall severity score increases by 2 or more points on a 0–10 scale

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Appendix 10. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug? No_____Yes____

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

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Appendix 11. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

This Appendix describes the process to be followed to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN together **with** TBL ≥ 2xULN, where no other reason, other than acalabrutinib, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in

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combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to Sponsor).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the Sponsor
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the Sponsor
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

Follow-up

Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the Sponsor that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

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Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment
- Notify the Company

The Company contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Company. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Sponsor) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Company contacts the Investigator to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The Sponsor Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

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- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to standard processes.
    - The 'Medically Important' serious criterion should be used if no other serious criteria apply
    - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease?

If No: follow the process described in Potential Hy's Law Criteria met of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[32] compared with when PHL criteria were previously met

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- If there is no significant change no action is required
- If there is a significant change, follow the process described in Section 4.2 of this Appendix

A ‘significant’ change in the patient’s condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Company if there is any uncertainty.