PROTOCOL

TITLE:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma
PROTOCOL NUMBER:	ACE-LY-002
STUDY DRUG:	ACP-196 (acalabrutinib)
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SPONSOR MEDICAL MONITOR:	PPD Acerta Pharma BV Phone: PPD Email:
SPONSOR:	Acerta Pharma BV PPD 5349 AB Oss The Netherlands
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Amendment 2 Date:	Version 2.0: 10 March 2015
Amendment 3 Date:	Version 3.0: 13 January 2016
Amendment 4 Date:	Version 4.0: 16 March 2020

Confidentiality Statement

This document contains proprietary and confidential information of Acerta Pharma BV that must not be disclosed to anyone other than the recipient study staff and members of the institutional review board/independent ethics committee. This information cannot be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Acerta Pharma BV.

PROTOCOL APPROVAL: AMENDMENT 4

I have carefully read Protocol ACE-LY-002 entitled "An Open-label, Phase 1b Study of ACP-196 in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Acerta Pharma, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma BV requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

SUMMARY OF AMENDMENT 4

This protocol is being amended to add Second Primary Malignancy information, add rollover protocol language, and align protocol with the Investigator Brochure.

Inclusion/Exclusion criteria have not been modified because enrollment closed.

Clarifying edits and typographical changes have been made throughout the protocol. In addition, the following substantive changes were made as part of this amendment.

Change	Rationale
Global Change ACP-196 has been changed to acalabrutinib as appropriate throughout the document.	Acalabrutinib is the name of the clinical study drug.
Title Page Updated medical monitor.	Medical Monitor information has been updated. Amendment number and date updated.
Synopsis Updated to reflect changes made throughout the protocol.	Updated to ensure consistency between the body of the protocol and the synopsis.
Section 1.3.4 Drug-drug Interaction Potential Added caution statement when coadministering with narrow therapeutic index breast cancer resistance protein (BCRP) substrates.	Updated to align with IB update.
Section 1.4 Clinical Experience Added Calquence® approval language. Added reference to Investigator Brochure for latest information.	Added Calquence® approval language. Deleted detailed information regarding pharmacokinetics, pharmacodynamics, and clinical experience. Added statement to refer to the Investigator Brochure for latest information.
Section 3.1 Description of Study Updated rollover language.	Updated rollover language for acalabrutinib studies.
Section 3.5.3 Administration of Study Drug Removed language regarding avoiding grapefruit juice and Seville oranges.	Removed text to align with IB update.
Section 3.6.2 Guideline for Use of CYP Inhibiting/Inducing Drugs Updated language regarding CYP3A inhibitors/inducers.	Updated to align with IB update, CDS, and other protocols.
Section 3.6.3 Guideline for Use of Drugs that Affect Gastric pH Updated guidelines.	Updated to align with IB update, CDS, and other protocols.
Section 3.7.1 Reference Safety Information Added Reference Safety information.	Added section to align with IB update.
Section 3.7.2 Dietary Restrictions Updated dietary restriction information.	Updated to align with IB update.

Change	Rationale
Section 3.7.3 Hemorrhage Added hemorrhage information.	Added section to align with IB update.
Section 3.7.4 Infections Added information regarding infections.	Added section to align with IB update.
Section 3.7.4.2 Progressive Multifocal Leukoencephalopathy Added information regarding progressive multifocal leukoencephalopathy (PML).	Added section to align with IB update.
Section 3.7.5 Cytopenias Added information regarding cytopenias.	Added section to align with IB update.
Section 3.7.6 Second Primary Malignancies Added information regarding second primary malignancies.	Added section to align with IB update.
Section 3.7.7 Atrial Fibrillation Added information on atrial fibrillation.	Added section to align with IB update.
Section 3.7.9 Reproductive Toxicity Updated definition of women of non-reproductive potential. Updated highly effective methods of contraception.	Updated to align with IB update.
Section 3.7.10 Overdose Instructions Updated overdose information.	Updated to align with IB update.
Section 6.1.4 Adverse Events of Special Interest Added section on adverse events of special interest to include ventricular arrhythmias.	Added section to align with IB update.
Section 6.2.1 Adverse Event Reporting Period Updated adverse event reporting period.	Updated to align with IB update.
Section 6.2.2 Assessment of Adverse Events Added information regarding symptomatic deterioration.	Updated to align with IB update
Section 6.2.3 Second Primary Malignancies Added section on reporting adverse events of second primary malignancies.	Added section to align with IB update.
Section 6.2.5 Expedited Reporting Requirement for Serious Adverse Events Added adverse events of special interest (AESI).	Added AESI to align with IB update
Section 6.2.7 Hy's Law Added section with information regarding Hy's law.	Added section to align with IB update.
Appendix 2 Examples of Coadministered Drugs that Need Additional Consideration Title of the appendix was changed, and contents updated.	Updated to align with IB update, CDS, and other protocols.

Change	Rationale
Appendix 5 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law Information regarding Hy's law added.	Added appendix to align with IB update.

TABLE OF CONTENTS

PROTOCOL APPROVAL: AMENDMENT 4 ..... **2**
SUMMARY OF AMENDMENT 4 ..... **3**
TABLE OF CONTENTS **6**
ABBREVIATIONS **10**
STUDY SYNOPSIS **13**
1.0 BACKGROUND INFORMATION **21**
1.1 Diffuse Large B-Cell Lymphoma 21
1.2 Role of Btk in Lymphoid Cancers 23
1.3 Preclinical Studies 24
1.3.1 Chemistry 24
1.3.2 Efficacy Pharmacology 24
1.3.3 Safety Pharmacology 25
1.3.4 Drug-drug Interaction Potential 26
1.3.5 In Vivo General Toxicology 26
1.4 Clinical Experience 27
1.5 Benefit/Risk 27
1.6 Summary and Conclusions 28
2.0 STUDY OBJECTIVES **28**
2.1 Primary Objective 28
2.2 Secondary Objectives: 28
3.0 STUDY DESIGN **28**
3.1 Description of Study 28
3.2 Study Parameters 29
3.2.1 Efficacy Parameters 29
3.2.2 Safety Parameters 30
3.2.3 Pharmacokinetic and Pharmacodynamic Parameters 30
3.3 Rationale for Study Design and Dosing Regimen 30
3.4 Selection of Study Population 31
3.4.1 Inclusion Criteria 31
3.4.2 Exclusion Criteria 32
3.4.3 Replacement of Subjects 33
3.4.4 Enrollment Procedures 33
3.5 Study Drug 34
3.5.1 Premedications 34
3.5.2 Formulation, Packaging, and Storage 34
3.5.3 Administration of Study Drug 34

3.5.4 Assuring Subject Compliance ... 35
3.5.5 Dose Delays ... 35
3.5.6 Dose Modification and Discontinuation ... 35
3.6 Concomitant Therapy ... 36
3.6.1 Permitted Concomitant Therapy ... 36
3.6.2 Guideline for Use of CYP Inhibiting/Inducing Drugs ... 36
3.6.3 Guideline for Use of Drugs that Affect Gastric pH ... 37
3.6.4 Prohibited Concomitant Therapy ... 37
3.7 Precautions ... 37
3.7.1 Reference Safety Information ... 37
3.7.2 Dietary Restrictions ... 38
3.7.3 Hemorrhage ... 38
3.7.4 Infections ... 38
3.7.4.1 Hepatitis B Virus Reactivation ... 38
3.7.4.2 Progressive Multifocal Leukoencephalopathy ... 39
3.7.5 Cytopenias ... 39
3.7.6 Second Primary Malignancies ... 39
3.7.7 Atrial Fibrillation ... 39
3.7.8 Surgery ... 40
3.7.9 Reproductive Toxicity ... 40
3.7.10 Overdose Instructions ... 41
3.8 Stopping Rules ... 42
3.9 Data and Safety Monitoring ... 43
4.0 STUDY ACTIVITIES AND ASSESSMENTS ... 43
4.1 Description of Procedures ... 44
4.1.1 Informed Consent ... 44
4.1.2 Medical History ... 44
4.1.3 Adverse Events ... 44
4.1.4 Concomitant Medications and Therapy ... 44
4.1.5 Confirmation of Eligibility ... 44
4.1.6 Archival Tumor Sample ... 44
4.1.7 ECOG Performance Status ... 44
4.1.8 Physical Examination, Vital Signs, Height & Weight ... 45
4.1.9 Bone Marrow Aspirate and Biopsy ... 45
4.1.10 Electrocardiogram ... 45
4.1.11 Urine Pregnancy Test ... 45
4.1.12 Hematology ... 45
4.1.13 Serum Chemistry ... 46
4.1.14 Urinalysis ... 46

4.1.15 T/B/NK Cell Count ... 46
4.1.16 Serum Immunoglobulin ... 46
4.1.17 Hepatitis B and C Testing ... 46
4.1.18 Pharmacodynamics ... 46
4.1.19 Pharmacokinetics ... 47
4.1.20 Tumor Assessment ... 47
4.1.21 Routine Clinical Assessments ... 48
4.1.22 Study Drug Accountability ... 49
4.2 Investigator's Assessment of Response to Treatment ... 49
4.3 Early Termination/Safety Follow-up Visit ... 52
4.4 Time-to-Next Treatment ... 52
4.5 Missed Evaluations ... 52
5.0 STATISTICAL METHODS OF ANALYSIS ... 53
5.1 General Considerations ... 53
5.1.1 Response Assessment ... 53
5.1.2 Safety Monitoring ... 53
5.2 Definition of Analysis Sets ... 53
5.3 Missing Data Handling ... 53
5.4 Determination of Sample Size ... 54
5.5 Data Analysis ... 54
5.5.1 Safety Parameters ... 54
5.5.2 Demographics and Baseline Characteristics ... 54
5.5.3 Study Treatment Administration and Compliance ... 54
5.5.4 Analysis of Efficacy Parameters ... 55
5.5.5 Analysis of Pharmacokinetic/Pharmacodynamic Parameters ... 56
5.5.6 Explorative or Correlative Analyses ... 57
6.0 ASSESSMENT OF SAFETY ... 57
6.1 Definitions ... 57
6.1.1 Adverse Events ... 57
6.1.2 Serious Adverse Event ... 58
6.1.3 Severity ... 58
6.1.4 Adverse Events of Special Interest ... 59
6.2 Documenting and Reporting of Adverse and Serious Adverse Events ... 59
6.2.1 Adverse Event Reporting Period ... 59
6.2.2 Assessment of Adverse Events ... 60
6.2.3 Second Primary Malignancies ... 60
6.2.4 Pregnancy ... 61
6.2.5 Expedited Reporting Requirements for Serious Adverse Events ... 61

6.2.6 Type and Duration of Follow-up of Subjects After Adverse Events ... 62
6.2.7 Hy's Law ... 62
7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS ... 62
7.1 Regulatory and Ethical Compliance ... 63
7.2 Institutional Review Board and Independent Ethics Committee ... 63
7.3 Informed Consent and Protected Subject Health Information Authorization ... 63
7.4 Subject Screening Log ... 64
7.5 Case Report Forms ... 64
7.6 Study Monitoring Requirements ... 64
7.7 Investigational Study Drug Accountability ... 65
7.8 Record Retention ... 66
7.9 Protocol Amendments ... 66
7.10 Publication of Study Results ... 67
7.11 Clinical Trial Insurance ... 67
7.12 General Investigator Responsibilities ... 68
8.0 REFERENCES ... 69
9.0 APPENDICES ... 71

In–Text Tables

Table 1-1. Assessment of ACP-196 Active-site Occupancy in Fine Needle Aspirates of Canine Lymph Node Tumors (N=4) ... 25
Table 3-1. Drug Discontinuation Actions for *Acalabrutinib* ... 36
Table 4-1. Pharmacokinetic Sample Schedule ... 47
Table 4-2. Response Assessment Criteria for DLBCL (Cheson 2014) ... 50

Appendices

Appendix 1. Performance Status Scores ... 72
Appendix 2. Examples of Coadministered Drugs That Need Additional Consideration ... 73
Appendix 3. Adverse Event Assessment of Causality ... 75
Appendix 4. Schedule of Assessments ... 76
Appendix 5. Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law ... 78

ABBREVIATIONS

Abbreviation	Definition
ABC	activated B-cell (DLBCL subtype)
ACP-196	acalabrutinib
AE(s)	adverse event(s)
AESIs	*adverse events of special interest*
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplantation
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BCRP	*breast cancer resistance protein*
BID	twice per day (dosing)
Btk	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CHOP	cyclophosphamide/doxorubicin/vincristine/prednisone
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete remission (response)
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLCO	diffuse lung capacity for carbon monoxide
DOR	duration of response

Abbreviation	Definition
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
GCB	germinal-cell B cell (DLBCL subtype)
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	immunoglobulin
IPI	International Prognostic Index
IRB	Institutional Review Board
IVIG	intravenous immunoglobulins
LDH	lactate dehydrogenase
LTFU	long-term follow up
MALT	mucosa-associated lymphoid tissue (lymphoma)
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
ORR	overall response rate
OS	overall survival
PBMC(s)	peripheral blood mononuclear cells

Abbreviation	Definition
PCR	polymerase chain reaction
PI3K	phosphoinositide-3 kinase
PMBL	primary mediastinal (thymic) large B-cell lymphoma
PD	pharmacodynamics
PET	positron-emission tomography
PFS	progression-free survival
PFT	pulmonary function test
PK	pharmacokinetics
PR	partial remission (response)
QD	once per day (dosing)
QM	every month
QTc	corrected QT interval
R-CHOP	rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone
R-DHAP	rituximab/cisplatin/cytarabine/dexamethasone
R-ICE	rituximab/ifosamide/etoposide/carboplatin/mesna
SAE(s)	serious adverse event(s)
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase (also called AST)
SGPT	serum glutamic pyruvic transaminase (also called ALT)
SPD	sum of the product of the diameters
SUSAR	Suspected Unexpected Serious Adverse Reaction (report)
$t_{½}$	terminal elimination half-life (whenever possible)
λ_z	terminal elimination rate constant (whenever possible)
T_{max}	time to maximum drug concentration
ULN	upper limit of normal
WHO	World Health Organization

STUDY SYNOPSIS

Protocol Number:	ACE-LY-002
Study Drug:	ACP-196 (acalabrutinib)
Protocol Title:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Relapsed or Refractory de Novo Activated B-cell (ABC) Subtype of Diffuse Large B-Cell Lymphoma
Phase:	Phase 1b
Comparator:	None
Background and Rationale for Study	Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton tyrosine kinase (Btk) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL) including diffuse large B-cell lymphoma (DLBCL). Ibrutinib, a first generation Btk inhibitor, has been approved for the treatment of chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL). Interim results from a Phase 2 study of ibrutinib 560 mg once per day (QD) in subjects with relapsed/refractory GCB and ABC DLBCL reported an objective tumor response rate of 41% (complete response [CR] 17% and partial response [PR] 24%) for subjects with ABC DLBCL versus 5% (no CRs) in subjects with germinal-cell B-cell (GCB) DLBCL (de Vos 2013). Similar results were observed with ONO-4059 (160 to 480 mg QD), a second generation Btk inhibitor in a Phase 1 dose-escalation study in subjects with ABC DLBCL. In both studies, the Btk inhibitors were well tolerated. Acerta Pharma BV (Acerta Pharma) has developed a novel second generation Btk inhibitor, ACP-196 *(also known as acalabrutinib)*, that achieves significant oral bioavailability and potency in preclinical models. Phase 1/2 clinical studies have shown that *acalabrutinib* is an orally bioavailable Btk inhibitor with fast absorption and rapid clearance that maintains optimal target coverage over 24 hours with a dosage of 100 mg BID. *Acalabrutinib* has been well tolerated in healthy volunteers and subjects with CLL or Richter's syndrome. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and activity of *acalabrutinib* administration in subjects with ABC DLBCL.

Study Design:	This study is a multicenter, open-label study. Twenty subjects, 10 refractory and 10 relapsed, will be enrolled and will take 100 mg of *acalabrutinib* twice per day (BID). The study will be conducted at approximately 9 sites in up to 4 countries. Relapsed subjects will be defined as subjects who have had a PR or better (Cheson 2007 or Cheson 2014 criteria) from the previous anticancer therapy and now have progressed. Refractory subjects will be defined as subjects whose best response to the previous anticancer therapy was stable disease or did not respond to therapy. Twenty-eight days of study drug administration is 1 cycle. Treatment with *acalabrutinib* may be continued for >28 days until disease progression or an unacceptable drug-related toxicity occurs. Dose modification provisions are provided in the study protocol. Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to *the protocol* for more information on assessing disease progression under these circumstances. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. Radiologic tumor assessments will be done at 8- to 12-week intervals during the trial. [Note: For sites in Germany, radiologic tumor assessments will not include positron emission tomography (PET) assessments and radiologic tumor assessments will be done at screening and at the end of Cycle 2 OR Cycle 4 depending on each subject's individual response; thereafter they will be done at investigator discretion]. All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1 and Cycle 2. Refer to protocol for a comprehensive list of study assessments and their timing. Subjects showing clinical benefit and who are tolerating *acalabrutinib* may remain on study through the end of Cycle 12. The end of trial is defined as the point when the last subject enrolled completes the end of Cycle 12 or withdraws for any reason and completes the 30-day follow-up visit (if applicable), whichever occurs first. *Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff (DCO) and database closure, subjects who remain in this study may*

	be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs per protocol. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.
Study Objectives:	**Primary Objective:** To characterize the safety profile of *acalabrutinib* in subjects with relapsed or refractory ABC DLBCL **Secondary Objective:** • To characterize the PK of *acalabrutinib* • To evaluate the PD effects of *acalabrutinib* • To evaluate the activity of *acalabrutinib* as measured by response rate, duration of response, time-to-next treatment, and progression-free survival
Efficacy Parameters:	• Overall response rate (ORR) • Duration of response • Progression-free survival • Time-to-next treatment
Safety Parameters:	Type, frequency, severity, timing of onset, duration, and relationship to study drug of any *treatment-emergent* adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation *or dose reduction* of study treatment.

Pharmacokinetic Parameters:	The plasma PK of *acalabrutinib* will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of *acalabrutinib*: • AUC_{0-t}: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (Ct). • AUC_{0-12}: Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation. • $AUC_{0-\infty}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant. • $AUC_{0-24calc}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}. • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • CL/F: Oral clearance
Pharmacodynamic Parameters:	The occupancy of Btk by *acalabrutinib* will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged *acalabrutinib* analogue probe. The effect of *acalabrutinib* on biologic markers of B-cell function will also be evaluated.
Sample Size:	Twenty subjects that consist of 10 subjects who are refractory to and 10 subjects who have relapsed from the previous anticancer therapy.
Inclusion Criteria:	• Men and women ≥ 18 years of age. • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. • Pathologically confirmed de novo ABC DLBCL, and subjects **must have** available archival tissue for central pathology review to be eligible. • Relapsed or refractory disease, defined as either: 1) recurrence of disease after a CR,

	or 2) PR, stable disease (SD), or progressive disease at completion of the treatment regimen preceding entry to the study (residual disease): ○ Subjects must have previously received a standard anthracycline and rituximab-based first-treatment regimen (eg, rituximab/cyclophosphamide/ doxorubicin/vincristine/prednisone [R-CHOP]). ○ Subjects with suspected residual disease after the treatment regimen directly preceding study enrollment must have biopsy demonstration of residual DLBCL. ○ Subjects who have not received high-dose chemotherapy/autologous stem cell transplantation (HDT/ASCT) must be ineligible for HDT/ASCT as defined by meeting any of the following criteria: ▪ Age ≥ 70 years ▪ Diffuse lung capacity for carbon monoxide (DLCO) < 50% by pulmonary function test (PFT) ▪ Left ventricular ejection fraction (LVEF) < 50% by ECHO ▪ Other organ dysfunction or comorbidities precluding the use of HDT/ASCT on the basis of unacceptable risk of treatment-related morbidity ▪ Subject refusal of HDT/ASCT ○ Subjects who are intolerant to anthracycline-based first-line therapy and meet all other eligibility criteria including recurrent or refractory disease are also eligible. • Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension and ≥ 1.0 cm in the longest perpendicular dimension as assessed by computed tomography [CT] scan). • Agreement to use acceptable forms of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children. • Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug. • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.

	• Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).
Exclusion Criteria:	• Transformed DLBCL or DLBCL with coexistent histologies (eg, follicular lymphoma [FL] or mucosa-associated lymphoid tissue [MALT]). • Primary mediastinal (thymic) large B-cell lymphoma (PMBL). • Known central nervous system (CNS) lymphoma. • Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the medical monitor. • A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of *acalabrutinib*, or put the study outcomes at undue risk. • 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, or QTc > 480 msec. • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Any immunotherapy within 4 weeks of first dose of study drug. • The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s). • Radio- or toxin-immunoconjugates within 10 weeks of the first dose of study drug. • Prior exposure to a B-cell receptor (BCR) inhibitor (eg, Btk, phosphoinositide-3 kinase [PI3K], or Syk inhibitors) or BCL-2 inhibitors (eg, ABT-199).

	• Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
	• Known history of human immunodeficiency virus (HIV), serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
	• Major surgery within 4 weeks before first dose of study drug.
	• History of stroke or intracranial hemorrhage within 6 months before the first dose of *acalabrutinib*.
	• History of bleeding diathesis (eg, hemophilia or von Willebrand disease)
	• Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug.
	• Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)
	• Any of the following laboratory abnormalities:
	  ○ Absolute neutrophil count (ANC) < 750 cells/mm^3 (0.75 x 10^9/L). For subjects with documented bone marrow involvement, ANC < 500 cells/mm^3 (0.50 x 10^9/L)
	  ○ Platelet count < 50,000 cells/mm^3 (50 x 10^9/L) independent of transfusion support. For subjects with documented bone marrow involvement, < 30,000 cells/mm^3 (30 x 10^9/L)
	  ○ Serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN)
	  ○ Creatinine > 2.5 x ULN
	  ○ Total bilirubin > 2.5 x ULN
	• Breast feeding or pregnant.
	• Concurrent participation in another therapeutic clinical trial.

Dosage Form and Strength:	*Acalabrutinib* is provided as 100-mg hard gelatin capsules prepared using standard pharmaceutical grade excipients.
Dose Regimen/Route of Administration:	*Acalabrutinib* is an orally administered product. *Acalabrutinib* may be administered with or without food. <u>Regimen:</u> 100 mg *acalabrutinib* (1 x 100-mg capsules) administered 12 hours apart (BID dosing = 200-mg total daily dose)
Concomitant Medications:	*Use of proton-pump inhibitors, H2-receptor antagonists, or antacids while taking acalabrutinib is not recommended due to a potential decrease in study treatment exposure. If treatment with a gastric acid reducing agent is required, use of a H2-receptor antagonist (2 hours after acalabrutinib) or antacid (2 hours before or 2 hours after acalabrutinib) should be considered. Co-administration of acalabrutinib with proton pump inhibitors should be avoided.* *The concomitant use of acalabrutinib with breast cancer resistance protein (BCRP) substrates (e.g., prazosin, glyburide, nitrofurantoin, dipyridamole, statins, and cimetidine) may increase exposure to the BCRP substrates by inhibition of intestinal BCRP, and therefore should be avoided.* Concomitant use of strong inhibitors/inducers of CYP3A should be avoided when possible. *Subjects requiring long-term (>1 week) treatment with a strong CYP3A inhibitor/inducer are excluded from the study. In addition, the use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of study drug is prohibited. If a subject requires short-term treatment (≤7 days) with a strong CYP3A inhibitor, acalabrutinib treatment should be interrupted. If the subject requires treatment with a moderate CYP3A inhibitor, the acalabrutinib dose should be reduced to 100 mg QD. Co-administration of strong CYP3A inducers should be avoided. If a subject requires treatment with a strong CYP3A inducer, the acalabrutinib dose should be increased to 200 mg BID.*
Statistics:	No formal statistical tests of hypotheses will be performed as is typical for a Phase 1b study. The trial design is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data, as appropriate.

1.0 BACKGROUND INFORMATION

1.1 DIFFUSE LARGE B-CELL LYMPHOMA

Diffuse large B-cell lymphoma (DLBCL) is the most common of the aggressive NHL in the United States, with an annual incidence that has been rising gradually since the 1990s. While approximately half of the incremental rise in incidence of DLBCL is attributable to identifiable factors—such as the increase in the incidence of HIV-related DLBCL, the evolution of more specific diagnostic techniques, and revisions in lymphoma classification schemes—much of the rising incidence remains unexplained. A very aggressive malignancy in its untreated natural history, DLBCL is a potentially curable disease, with a significant proportion of patients cured with modern standard chemoimmunotherapy. Nonetheless, for those patients not cured by standard initial therapy, the prognosis remains generally poor, and DLBCL still accounts for the highest number of deaths per year of all the NHL histologies.

Treatment for DLBCL

Anthracycline-based combination chemotherapy, eg, CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone), has been the standard approach to initial therapy for DLBCL for decades. While several variants to the CHOP regimen have been developed, often varying by the addition of other agents or dose-intensification of the agents, a large multi-arm Phase 3 trial demonstrated no differences in disease-free or overall survival (OS) with these “second-generation” variants as compared with CHOP (Fisher 1993). The addition of rituximab to CHOP (R-CHOP) or CHOP-like regimens, however, has resulted in improvement in both disease-free and OS in DLBCL in 3 large randomized Phase 3 trials (Coiffier 2002, Habermann 2006, Pfreundschuh 2006). Long-term follow-up of the GELA LNH-98.5 study confirmed that a greater proportion of patients are cured using R-CHOP compared with CHOP alone (Coiffier 2010).

For patients with either residual or recurrent DLBCL following initial therapy, the approach of re-induction chemotherapy, followed by high-dose chemotherapy with autologous stem cell support (HDT/ASCT) for responding patients, remains the current standard of care. Such an approach was demonstrated to result in superior disease-free survival compared with re-induction chemotherapy-alone in a randomized Phase 3 trial (Philip 1995). However, the results of a more recently reported Phase 3 trial comparing rituximab, ifosfamide, carboplatin, and etoposide (R-ICE) to rituximab, cisplatin, cytarabine, and dexamethasone (R-DHAP) as re-induction therapy suggests that this standard salvage

approach may be less efficacious in the era of rituximab-based first-line therapy, as 3-year event-free survival rates were significantly lower for patients who had received rituximab-based first-line therapy (Gisselbrecht et al 2010). In addition, HDT/ASCT is associated with considerable treatment-related morbidity and occasional treatment-related mortality. Advanced age and suboptimal baseline pulmonary or cardiac function are risks for excessive morbidity during and after HDT/ASCT. Therefore, effective and tolerable therapies are needed in relapsed or refractory DLBCL, particularly in the era of rituximab-based initial chemoimmunotherapy.

Clinical and Molecular Markers of Prognosis

The major clinical prognostic factors for NHL are well described and have been incorporated into the International Prognostic Index (IPI) scoring system. The specific factors are: age > 60 years, stage III or IV disease, performance status ≥ 2, and elevated lactate dehydrogenase (LDH) levels. These factors are combined in the IPI into 4 categories, with 5-year progression-free survival (PFS) ranging from 40% to 70% and 5-year OS ranging from 26% to 73% among patients treated with CHOP (International Non-Hodgkin's Lymphoma Prognostic Factors Project, 1993). Regarding applicability of the IPI in the era of modern chemoimmunotherapy (eg, R-CHOP), a recent report of a large series of patients treated with rituximab-based regimens found the IPI remains predictive for disease-free and overall survival (Ziepert 2010).

DLBCL is a heterogeneous disease not only clinically, but also morphologically and molecularly. Recent progress has been made in terms of understanding and categorizing the molecular heterogeneity of DLBCL. In a retrospective analysis of a large series of patients with DLBCL, The Leukemia and Lymphoma Molecular Profiling Project used DNA microarray to identify distinct gene-expression profiles on the basis of hierarchical clustering (Rosenwald 2002). Two principal independent gene-expression subgroups were identified: germinal-center B cell (GCB) and activated B cell (ABC). When outcome after standard chemotherapy was analyzed, the GCB and ABC subgroups were not only prognostically distinct in direct comparison (with superior outcome in the GCB subgroup), but this prognostic distinction was also independent of the IPI. Therefore, it may be possible to distinguish prognostic subgroups of DLBCL on a molecular as well as clinical basis.

1.2 ROLE OF BTK IN LYMPHOID CANCERS

Bruton tyrosine kinase (Btk) is a non-receptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Mohamed 2009, Bradshaw 2010). Functional null mutations of Btk in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells (Vihinen 2000). Conversely, Btk activation is implicated in the pathogenesis of several B-cell malignancies (Buggy 2012). Taken together, these findings have suggested that inhibition of Btk may offer an attractive strategy for treating B-cell neoplasms.

Ibrutinib (IMBRUVICA™), a first generation oral, small-molecule Btk inhibitor has been approved for the treatment for CLL and MCL. Interim results from a Phase 2 study of ibrutinib 560 mg QD in subjects with relapsed/refractory GCB and ABC DLBCL reported an objective tumor response rate of 41% (CR 17% and PR 24%) for subjects with ABC DLBCL (N=29) versus 5% (no CRs) in subjects with GCB DLBCL (N=20) (de Vos 2013). In a Phase 1 dose-escalation study (160 to 480 mg QD) of ONO-4059, a second generation Btk inhibitor, in subjects with ABC DLBCL an ORR of 47% (7/15) was observed (Dyer 2014). Also subjects who were refractory to the prior anticancer therapy had an ORR of 33% (3/9) compared with an ORR of 67% (4/6) for subjects who had relapsed after the prior therapy. In both studies, the Btk inhibitors were well tolerated.

While highly potent in inhibiting Btk, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in Btk to which the drug covalently binds. The inhibition of epidermal growth factor receptor (EGFR) is also observed in cellular assays and may be the cause of ibrutinib-related adverse events (AEs) of diarrhea and rash (IMBRUVICA® package insert). In addition, ibrutinib is a substrate for CYP3A4; inhibition of CYP3A causes a 29-fold increase in maximum concentration (C_{max}) and 24-fold increase in area under the curve (AUC) for ibrutinib (IMBRUVICA® package insert). This increases the possibility of drug-drug interactions in combination therapies with drugs currently used in management of subjects with cancer. These liabilities support the development of alternative Btk inhibitors for use in the therapy of B-cell malignancies.

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of ACP-196 *(also known as acalabrutinib),* an orally bioavailable, new chemical entity that covalently inhibits Btk and shows encouraging activity and acceptable safety in nonclinical studies. Within the class of Btk inhibitors, *acalabrutinib* is a more

selective inhibitor of Btk than ibrutinib. Key nonclinical differentiators of *acalabrutinib* versus ibrutinib are:

- *Acalabrutinib* has been evaluated against ibrutinib in EGFR expressing cell lines. Ibrutinib is a potent covalent inhibitor of EGFR (EC50 = 50 to 70 nM). *Acalabrutinib* does not inhibit EGFR even at the highest concentration tested (10 μM).
- *Acalabrutinib* has been evaluated against ibrutinib in in vitro antibody-dependent cell-mediated cytotoxicity (ADCC) assays. At physiologic concentrations, ibrutinib, but not *acalabrutinib*, reduced natural killer (NK) cell-mediated lysis of Raji and autologous CLL tumor cells and significantly inhibited rituximab-induced NK cell cytokine secretion ($P<0.05$).
- *Acalabrutinib* has been evaluated against ibrutinib in an in vivo thrombus formation model. At physiologic concentrations, ibrutinib, but not *acalabrutinib*, significantly inhibited thrombus formation ($P=0.001$).

The nonclinical and toxicology results of *acalabrutinib* suggest it may have an improved therapeutic window relative to ibrutinib; it may be more readily combined with other agents for the treatment of cancer.

1.3 PRECLINICAL STUDIES

Summaries of preclinical studies are provided below. For more detailed information please refer to the Investigator Brochure.

1.3.1 Chemistry

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. For clinical testing, *acalabrutinib* has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

1.3.2 Efficacy Pharmacology

Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to Btk inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). ACP-196 is currently being evaluated in an ongoing dose-escalation study in canine spontaneous B-cell lymphoma. Fourteen dogs, all of which had DLBCL confirmed by histology, have been treated with ACP-196 for at least

2 weeks. The dosages have ranged from 2.5 to 20 mg/kg QD or BID. To date, per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), PRs been observed in 4 of 14 dogs (29%) and stable disease (SD) has been observed in 8 of 14 dogs (57%) (Gardner 2014). No ACP-196 related AEs have been reported to date in this study. These findings are preliminary and similar to the clinical responses (ie, 1 dog with PR out of 5 dogs treated with suspected or confirmed DLBCL) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

Preliminary results assessing Btk occupancy using a biotin-tagged analogue of ACP-196 show near complete Btk occupancy over 24 hours with BID versus QD dosing in canine tumor tissue (Table 1-1).

Table 1-1. Assessment of ACP-196 Active-site Occupancy in Fine Needle Aspirates of Canine Lymph Node Tumors (N=4)

Timing	Dog Identification and ACP-196 Dosing Regimen			
	DL-10	DL-12	DL-14	DL-16
	5 mg/kg QD	10 mg/kg BID	20 mg/kg QD	20 mg/kg QD
	Btk Occupancy (% versus predose)			
Day 1 (3 hours after morning dose)	98%	99%	98%	99%
Day 7 (before morning dose)	80%	98%	77%	93%

BID = twice per day; Btk = Bruton tyrosine kinase; ND = not determined; QD = once per day

1.3.3 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with ACP-196 have demonstrated a favorable nonclinical safety profile.

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, ACP-196 shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a IC_{50} of 2.7 µM, suggesting a low clinical risk of off-target effects. ACP-196 at 10 µM showed no inhibition of in vitro epidermal growth factor receptor (EGFR) phosphorylation in an A431 human epidermoid cancer cell line, whereas ibrutinib had an IC_{50} of 66 nM.

The in vitro effect of ACP-196 on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with

hERG. ACP-196 inhibited hERG channel activity by 25% at 10 µM, suggesting a low clinical risk that ACP-196 would induce clinical QT prolongation as predicted by this assay.

ACP-196 was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of ACP-196 at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that ACP-196 is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.3.4 Drug-drug Interaction Potential

The in vitro studies suggest CYP-mediated metabolism of ACP-196 appears to be catalyzed predominantly by CYP3A4/5. However, in elimination studies in preclinical species, the metabolic fate of ACP-196 is dominated by direct conjugation of ACP-196 with glutathione, providing evidence for a significant non-CYP mechanism of elimination. In a healthy volunteer study (ACE-HV-001), the effect of coadministration of a potent CYP3A and P-gP inhibitor, itraconazole, on the plasma levels of ACP-196 was evaluated. The mean plasma ACP-196 C_{max} and $AUC_{0\text{-last}}$ values increased 3.7- and 5.1-fold, respectively, in the presence of itraconazole relative to no pretreatment. In vitro studies also show that ACP-196 is a substrate for P-gp.

ACP-196 is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms.

Results from drug transporter studies suggest that ACP-196 is not anticipated to alter the PK of other therapeutic agents that are substrates for MDR1, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2. ACP-196 (200 mg QD) may alter the PK of *breast cancer resistance protein (*BCRP) substrates by inhibition of intestinal BCRP*. Caution should be taken when coadministered with narrow therapeutic index BCRP substrates.*

1.3.5 In Vivo General Toxicology

To date, the toxicology program has included 28-day GLP evaluations in rats and dogs. In the 28-day study in male and female Sprague-Dawley rats, animals received oral gavage ACP-196 dosages of 30, 100, and 300 mg/kg/day. In the 28-day study in male and female

beagle dogs, animals received oral ACP-196 dosages of 3, 10, and 30 mg/kg/day. Both studies had 28-day recovery periods.

The no observable adverse effect level in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, 100 mg/kg/day was selected to conservatively represent the highest nonseverely toxic dose (HNSTD). The pancreatic findings were investigated in subsequent rat toxicology studies and found to be treatment related, non-adverse at lower doses, and not associated with systemic toxicity or changes in biomarkers of pancreatic function. The islet cell changes resemble a spontaneous pancreatic lesion that is described as an age-related finding in male rats of this strain. In dogs at 30 mg/kg/day, no adverse effects on the pancreas were observed; there were no microscopic findings in the pancreas, and all clinical biomarkers of pancreatic function were normal.

In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the 28-day toxicology studies. However, in 5 of 6 rats from the 300-mg/kg group that died early in the study, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts. These findings were most likely incidental postmortem changes.

1.4 CLINICAL EXPERIENCE

Calquence® has been approved in the United States and other markets for the treatment of adult patients with MCL who have received at least one prior therapy, CLL, and small lymphocytic lymphoma (SLL).

For the latest information for pharmacokinetics and pharmacodynamics and clinical experience, see the Investigator Brochure.

1.5 BENEFIT/RISK

Acalabrutinib is a potent, orally available small-molecule inhibitor of Btk. A PK/PD study has been completed with *acalabrutinib* in healthy volunteers (ACE-HV-001; *see Investigator Brochure*). The safety results showed no identified safety risks in healthy subjects receiving 1 or 2 days of *acalabrutinib* ≤ 100 mg. In study ACE-CL-001, a study of *acalabrutinib* in subjects with relapsed/refractory or previously untreated CLL or Richter's

syndrome, no DLTs have been reported at dosages of ≤ 400 mg QD or 100 and 200 mg BID. The overall response rate in the evaluable subjects for this study is currently 94% with some subjects obtaining PRs after only 2 cycles of therapy. Based on these robust results in subjects with CLL, the evaluation of *acalabrutinib* in subjects with relapsed or refractory ABC DLBCL is warranted.

1.6 SUMMARY AND CONCLUSIONS

The design and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with lymphoid cancers; knowledge of the efficacy and safety of other Btk inhibitors (eg, ibrutinib and ONO-4059) in subjects with hematologic cancers; and the available nonclinical and clinical information regarding *acalabrutinib*.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To characterize the safety profile of *acalabrutinib* in subjects with relapsed or refractory ABC DLBCL

2.2 SECONDARY OBJECTIVES:

- To characterize the PK of *acalabrutinib*
- To evaluate the PD effects of *acalabrutinib*
- To evaluate the activity of *acalabrutinib* as measured by response rate, duration of response, time-to-next treatment, and progression-free survival

3.0 STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This study is a multicenter and open-label study. Twenty subjects, 10 relapsed and 10 refractory, will be enrolled and will take 100 mg of *acalabrutinib* BID. The study will be conducted at approximately 9 sites in up to 4 countries.

Relapsed subjects will be defined as subjects who have had a PR or better (Cheson 2014 or Cheson 2007 criteria) from the previous anticancer therapy and now have progressed. Refractory subjects will be defined as subjects whose best response to the previous anticancer therapy was SD or did not respond to therapy.

Treatment with *acalabrutinib* may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. Tumor assessments will be performed at 8- to 12-week intervals during the trial. Dose modification provisions are provided in

Section 3.5.5. Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe.

All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1 and Cycle 2.

Refer to Appendix 4 for a comprehensive list of study assessments and their timing. Subjects showing clinical benefit and who are tolerating *acalabrutinib* may remain on study through the end of Cycle 12. The end of trial is defined as the point when the last subject enrolled completes the end of Cycle 12 or withdraws for any reason and completes the 30-day follow-up visit (if applicable), whichever occurs first.

Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff (DCO) and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs per Section 6.2.5. Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.

3.2 STUDY PARAMETERS

3.2.1 Efficacy Parameters

Standardized response and progression criteria have been established for lymphoma (Cheson 2014); assessments of *acalabrutinib* efficacy in this study will be based on these Lugano criteria. Efficacy endpoints will include:

- ORR

- Duration of response
- Progression-free survival
- Time-to-next treatment

3.2.2 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 AEs or abnormalities of laboratory tests; SAEs; or AEs leading to discontinuation or dose reduction of study treatment.

For consistency of interpretation, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Standard definitions for seriousness will be applied (see Section 6.1).

3.2.3 Pharmacokinetic and Pharmacodynamic Parameters

Standard PK parameters for *acalabrutinib* in plasma will be evaluated in this study. A full description of the PK parameters is provided in Section 5.5.5.

The occupancy of Btk by *acalabrutinib* will be measured in peripheral blood mononuclear cells (PBMCs) with the aid of a biotin-tagged *acalabrutinib* analogue probe. The effect of *acalabrutinib* on biologic markers of B-cell function will also be evaluated.

PK/PD assessments will only be done in subjects at sites in the United States only.

3.3 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

*P*reliminary data from the ongoing Phase 1/2 study in subjects with CLL have shown that *acalabrutinib* is well tolerate at dosages of 100 to 400 mg QD and 100 to 200 mg BID. In addition, preliminary PD data from ACE-CL-001 show that Btk occupancy > 95% in peripheral blood is observed 4 hours after dosing but decreases to < 95% occupancy at 24 hours, while with BID dosing complete Btk occupancy (95% to 99%) is maintained over 24 hours at steady state. These data suggest that de novo synthesis of Btk can occur within 24 hours in peripheral blood cells. BID dosing may ensure Btk inhibition for the entire 24 hours and thus may be beneficial in terms of increased efficacy and/or decreased development of resistance to *acalabrutinib*. In addition, having information regarding the safety and pharmacology of a BID schedule may support future combination studies with

other drugs that are given BID. Therefore, this study has been designed to evaluate the safety, PK, PD, and activity of dosing with 100 mg BID dosing in subjects with ABC DLBCL.

3.4 SELECTION OF STUDY POPULATION

3.4.1 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. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
3. Pathologically confirmed de novo ABC DLBCL, and subjects **must have** available archival tissue for central pathology review to be eligible.
4. Relapsed or refractory disease, defined as either: 1) recurrence of disease after a CR, or 2) PR, SD, or progressive disease at completion of the treatment regimen preceding entry to the study (residual disease):
    - Subjects must have previously received a standard anthracycline and rituximab-based first-treatment regimen (eg, R-CHOP).
    - Subjects with suspected residual disease after the treatment regimen directly preceding study enrollment must have biopsy demonstration of residual DLBCL.
    - Subjects who have not received HDT/ASCT must be ineligible for HDT/ASCT as defined by meeting any of the following criteria:
        - Age ≥ 70 years
        - Diffuse lung capacity for carbon monoxide (DLCO) < 50% by PFT
        - Left ventricular ejection fraction (LVEF) < 50% by ECHO
        - Other organ dysfunction or comorbidities precluding the use of HDT/ASCT on the basis of unacceptable risk of treatment-related morbidity
        - Subject refusal of HDT/ASCT
    - Subjects who are intolerant to anthracycline-based first-line therapy and meet all other eligibility criteria including recurrent or refractory disease are also eligible.
5. Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of ≥ 1 lesion that measures ≥ 2.0 cm in the longest dimension and ≥ 1.0 cm in the longest perpendicular dimension as assessed by CT scan).
6. Agreement to use acceptable forms of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children.

7. Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug.
8. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
9. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

3.4.2 Exclusion Criteria

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

1. Transformed DLBCL or DLBCL with coexistent histologies (eg, FL or MALT)
2. Primary mediastinal (thymic) large B-cell lymphoma (PMBL)
3. Known central nervous system (CNS) lymphoma
4. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the medical monitor.
5. A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of *acalabrutinib*, or put the study outcomes at undue risk.
6. 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, or QTc > 480 msec.
7. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
8. Any immunotherapy within 4 weeks of first dose of study drug.
9. The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s).
10. Radio- or toxin-immunoconjugates within 10 weeks of the first dose of study drug
11. Prior exposure to a B-cell receptor (BCR) inhibitor (eg, Btk phosphoinositide-3 kinase [PI3K], or Syk inhibitors) or BCL-2 inhibitors (eg, ABT-199).
12. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
13. Known history of human immunodeficiency virus (HIV), serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
14. Major surgery within 4 weeks before first dose of study drug.

15. History of stroke or intracranial hemorrhage within 6 months before the first dose of *acalabrutinib*.
16. History of bleeding diathesis (eg, hemophilia or von Willebrand disease)
17. Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 28 days of first dose of study drug.
18. Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole)
19. Any of the following laboratory abnormalities:
    a. Absolute neutrophil count (ANC) < 750 cells/mm^3 (0.75 x 10^9/L). For subjects with documented bone marrow involvement, ANC < 500 cells/mm^3 (0.50 x 10^9/L)
    b. Platelet count < 50,000 cells/mm^3 (50 x 10^9/L) independent of transfusion support. For subjects with documented bone marrow involvement, < 30,000 cells/mm^3 (30 x 10^9/L)
    c. Serum AST/SGOT or ALT/SGPT ≥ 3.0 x ULN
    d. Creatinine > 2.5 x ULN
    e. Total bilirubin > 2.5 x ULN
20. Breast feeding or pregnant.
21. Concurrent participation in another therapeutic clinical trial.

3.4.3 Replacement of Subjects

Any subject who does not complete Cycle 2 may be replaced at the discretion of the study investigator and sponsor.

3.4.4 Enrollment Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- 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 officially enrolled in the study.
- To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the form is faxed/emailed to the sponsor.
- An Enrollment Confirmation Form will be completed and faxed/emailed to the study center by the sponsor within 24 hours.

Treatment must begin within the screening window (Section 4.1) and after the site has received notification from the sponsor. Study treatment is not blinded on this study.

3.5 STUDY DRUG

3.5.1 Premedications

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

3.5.2 Formulation, Packaging, and Storage

Acalabrutinib should be stored according to the instructions on the label that is affixed to the package containing the drug product.

Acalabrutinib capsules contain100 mg drug substance. *Acalabrutinib* will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative.

Refer to the Investigator Brochure for additional information.

3.5.3 Administration of Study Drug

Investigators are prohibited from supplying *acalabrutinib* to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators on FDA Form 1572. The investigator must ensure that subjects receive *acalabrutinib* only from personnel who fully understand the procedures for administering the drug.

Acalabrutinib is intended to be administered orally with 8 ounces (approximately 240 mL) of water. Subjects may take study drug with or without food. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Dietary restrictions are provided in Section 3.7.1.

Doses should be taken BID with the second dose 11-13 hours after the first.

If a dose is missed, it can be taken within 3 hours after the scheduled time with a return to the normal schedule with the following dose. If the time from the scheduled time of administration 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.

3.5.4 Assuring Subject Compliance

Subjects will receive their Day 1 and Day 8 doses in the clinic. For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other treatments will be taken at home. Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.7. Returned capsules must not be redispensed to another subject. The study staff will resupply the subject with the correct number of capsules needed for use until the next visit.

3.5.5 Dose Delays

Treatment with *acalabrutinib* should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the medical monitor. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the medical monitor.

Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances.

3.5.6 Dose Modification and Discontinuation

The actions in Table 3-1 should be taken for the following toxicities:

- Grade 4 ANC (< 500/µL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded on the electronic case report form [eCRF]).
- Grade 3 platelets in presence of significant bleeding
- Grade 4 platelets

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

Table 3-1. Drug Discontinuation 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 100 mg once daily
4th	Discontinue *acalabrutinib*

Whenever possible, any dose adjustment of *acalabrutinib* should be discussed between the investigator and the Acerta Pharma medical monitor before implementation. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level. Any changes to the dosing regimen must be recorded in the Dosage Administration eCRF.

3.6 CONCOMITANT THERAPY

3.6.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

For subjects considered at risk for tumor lysis syndrome: Administer appropriate hydration, alkalinization of urine, and allopurinol or rasburicase per institutional standards before initiating treatment.

3.6.2 Guideline for Use of CYP Inhibiting/Inducing Drugs

At the systemic exposure levels expected in this study, *acalabrutinib* inhibition of CYP metabolism is not anticipated. However, concomitant administration of *acalabrutinib* with a strong CYP3A4 inhibitor increased exposure by approximately 5-fold (*see Investigator Brochure*). Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (Appendix 2) should be avoided when possible. *Subjects requiring long-term (>1 week) treatment with a strong CYP3A inhibitor/inducer are excluded from the study. In addition, the use of strong or moderate CYP3A inhibitors or inducers within 7 days of the first dose of study drug is prohibited. If a subject requires short-term treatment (≤7 days) with a strong*

CYP3A inhibitor, acalabrutinib treatment should be interrupted. If the subject requires treatment with a moderate CYP3A inhibitor, the acalabrutinib dose should be reduced to 100 mg QD. Co-administration of strong CYP3A inducers should be avoided. If a subject requires treatment with a strong CYP3A inducer, the acalabrutinib dose should be increased to 200 mg BID.

3.6.3 Guideline for Use of Drugs that Affect Gastric pH

Use of proton-pump inhibitors, H2-receptor antagonists, or antacids while taking acalabrutinib is not recommended due to a potential decrease in study treatment exposure. If treatment with a gastric acid reducing agent is required, use of a H2-receptor antagonist (2 hours after acalabrutinib) or antacid (2 hours before or 2 hours after acalabrutinib) should be considered. Co-administration of acalabrutinib with proton pump inhibitors should be avoided.

The concomitant use of acalabrutinib with BCRP substrates (e.g., prazosin, glyburide, nitrofurantoin, dipyridamole, statins, and cimetidine) may increase exposure to the BCRP substrates by inhibition of intestinal BCRP, and therefore should be avoided.

3.6.4 Prohibited Concomitant Therapy

Any chemotherapy, immunotherapy, corticosteroids (> 10 mg of prednisone or equivalent), kinase inhibitors, bone marrow transplantation, experimental therapy, warfarin, and radiotherapy are prohibited.

3.7 PRECAUTIONS

3.7.1 Reference Safety Information

For the purpose of reporting AEs and serious adverse events (SAEs):

> *The Investigator Brochure contains the Reference Safety Information (RSI) for acalabrutinib.*

3.7.2 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 a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.*

3.7.3 Hemorrhage

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

The mechanism for hemorrhage is not well understood. Subjects receiving antithrombic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. Consider the benefit-risk of withholding acalabrutinib for at least 3 days pre- and post-surgery. Subjects with hemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations as clinically indicated.

3.7.4 Infections

Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequent reported Grade ≥3 infection was pneumonia (preferred term).

Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Refer to Section 3.7.4.1 and Section 4.1.17 for additional information and monitoring guidance for viral hepatitis and Section 3.7.4.2 for additional information and management guidance for signs and symptoms of PML.

3.7.4.1 Hepatitis B Virus Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with *acalabrutinib*. Therefore, subjects who are hepatitis B core antibody (anti-HBc) positive or have a known history of hepatitis B virus (HBV) infection, should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of *acalabrutinib*. Any subject with a rising viral load (above lower limit of detection) should discontinue *acalabrutinib* and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming *acalabrutinib* in subjects who develop HBV reactivation.

3.7.4.2 Progressive Multifocal Leukoencephalopathy

Cases of progressive multifocal leukoencephalopathy (PML) have occurred in clinical studies with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties.

If PML is suspected, hold further treatment with acalabrutinib treatment until PML is excluded. A diagnostic evaluation may include (but is not limited to):

- *Neurologic consultation*
- *Brain magnetic resonance imaging (MRI)*
- *PCR analysis for John Cunningham virus DNA in cerebrospinal fluid*

If PML is confirmed, permanently discontinue acalabrutinib.

3.7.5 Cytopenias

Grade 3 or 4 cytopenias including neutropenia, anemia, and thrombocytopenia have occurred in clinical studies with acalabrutinib. Monitor blood counts as medically appropriate.

Subjects with cytopenias should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated. Subjects should be closely monitored as appropriate.

3.7.6 Second Primary Malignancies

Second primary malignancies, including solid tumors and skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma). Subjects should be monitored for signs and symptoms of malignancy. For Subjects who develop a second primary malignancy, subjects should be managed according to institutional guidelines with diagnostic evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor. Please refer to Section 6.2.3 for second primary malignancy reporting guidance.

3.7.7 Atrial Fibrillation

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

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

3.7.8 Surgery

Susceptibility to bleeding has been observed with the first generation Btk inhibitor, ibrutinib (IMBRUVICA® package insert). As a precaution, it is suggested that *acalabrutinib* be held for 3 days before and after any major surgical procedure.

3.7.9 Reproductive Toxicity

Definition of Women of Non-reproductive Potential

Women will be considered of non-reproductive potential if they are either:

1) 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 post-menopausal 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.);

OR

2) Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3) Have a congenital or acquired condition that prevents childbearing.

Highly Effective Methods of Contraception‡

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

- *Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal*
- *Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable*
- *Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)*
- *Bilateral tubal occlusion*
- *Vasectomy of a female subject's male partner (with medical assessment and confirmation of vasectomy surgical success)*

- *Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)*

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

Periodic abstinence[†] (eg, 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 as an effective method of contraception.

[†]Abstinence (relative to heterosexual activity) can only be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and IECs/IRBs. Periodic abstinence (eg, calendar, ovulation, sympto-thermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

[‡]If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Developmental and reproductive toxicology studies in rats have not identified acalabrutinib-related toxicities for fertility, reproductive success, embryofetal development, or embryofetal survival. In rabbits, at dose levels which resulted in maternal toxicities, skeletal variations were associated with reductions in fetal weights. Effects on parturition and post-natal development are pending. For additional details, refer to the Acalabrutinib Investigator Brochure.

Subjects should promptly notify the investigator if they, or their partners, become pregnant during this period. Female subjects must also notify the investigator if they become pregnant 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 described in Section 6.2.4.

3.7.10 Overdose Instructions

In the event of ingestion of more than the recommended dosage per protocol, additional clinical monitoring is recommended by the sponsor. For any subject experiencing an *acalabrutinib* overdose, observation for any symptomatic side effects should be instituted,

and vital signs and 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 is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

The Acerta Pharma medical monitor should be contacted if a study drug overdose occurs.

3.8 STOPPING RULES

All study participants may receive *acalabrutinib* indefinitely as long as they are safely benefitting. However:

- Any subject has the right to withdraw from the study at any time.
- Any subject who has objective evidence of definitive DLBCL progression while receiving study treatment at the highest individual tolerable dose level allowed in the protocol (see Section 3.5.5) should be withdrawn from the study treatment. Note: If there is uncertainty regarding whether there is DLBCL progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 4- to 8-week intervals) pending confirmation of progression. In particular, transient worsening of disease during temporary interruption of study therapy (eg, for intercurrent illness, drug-related toxicity, or surgery) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.
- Any subject who is unable to tolerate rechallenge with the lowest protocol-described, dose-modified levels (see Section 3.5.5) should be withdrawn from the study treatment unless continued therapy is permitted by the Acerta Pharma medical monitor.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the Acerta Pharma medical monitor. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in

circumstances that increase risk or substantially compromise the interpretation of study results.

- The investigator, in consultation with the Acerta Pharma medical monitor, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Subjects who discontinue study therapy will continue on study for safety (Section 4.3) and time-to-next therapy (Section 4.4) unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted or enrolls in an *acalabrutinib* maintenance study. The date the subject is withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation will be recorded and also should be described on the appropriate eCRF.

3.9 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Quarterly conference calls with the investigators 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).

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 4. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are required. 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. Such unscheduled assessments will be captured in the protocol-specific database as appropriate.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand and sign the IRB/IEC approved ICF 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.

4.1.2 Medical History

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

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

Document all concomitant 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 3.4. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug. De-identified copies of all screening radiology results, site pathology report for confirming diagnosis of ABC DLBCL, and a list of prior anticancer therapy and best responses need to be submitted to the sponsor as part of the enrollment process.

4.1.6 Archival Tumor Sample

All subjects must have available archival tissue for central pathology review. Either unstained slides (minimum of 10 slides) or a paraffin block will be acceptable for central pathology review. Please refer the study manual for a more detailed description of the procedures and for information on where to send the archival tissue samples.

4.1.7 ECOG Performance Status

The ECOG performance index is provided in Appendix 1.

4.1.8 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams, including tumor assessments by palpation, will be done during the treatment period and at the safety follow-up visits.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.

4.1.9 Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at screening. Subjects who have a bone marrow aspirate and biopsy result since completion of their last therapy for DLBCL may use those bone marrow results in lieu of the baseline bone marrow aspirate/biopsy required for this study provided the biopsy/aspirate was done within 60 days of the first dose of study drug. Per the current response criteria (Cheson 2014), a bone marrow aspirate/biopsy will also be required at any time on study to confirm complete remission (CR). A bone marrow aspirate and biopsy will also be done at end of Cycle 12. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

4.1.10 Electrocardiogram

Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.

4.1.11 Urine Pregnancy Test

Pregnancy tests will be required only for women with childbearing potential. If positive, pregnancy must be ruled out by ultrasound. Testing will be done by the central laboratory.

4.1.12 Hematology

Hematology studies must include complete blood count (CBC) with differential and platelet and reticulocyte counts. Testing will be done by the central laboratory.

4.1.13 Serum Chemistry

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by the central laboratory.

4.1.14 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be done by the central laboratory.

4.1.15 T/B/NK Cell Count

Flow cytometry testing will include $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD16/56^+$ cells. Testing will be done by the central laboratory.

4.1.16 Serum Immunoglobulin

Testing for IgG, IgM, and IgA will be done by the central laboratory.

4.1.17 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and hepatitis C (HCV) antibody. Since intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see Appendix 4 and exclusion criterion #13). Testing will be done by local or central laboratory.

Refer to Section 3.7.4.1 and Appendix 4 regarding monitoring of subjects who are anti-HBc positive or have a known history of HBV.

4.1.18 Pharmacodynamics

Blood samples will be used for PD testing (eg, Btk occupancy and B-cell activation). Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be done by the sponsor.

4.1.19 Pharmacokinetics

Refer to the laboratory manual for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory. Leftover plasma samples may be used for exploratory *acalabrutinib* metabolite analyses. The predose sample can be taken up to 1 hour before dosing.

Table 4-1. Pharmacokinetic Sample Schedule

		HOURS POSTDOSE						
Cycle	**Day**	**Predose**	**0.5 (±5 min)**	**1 (±5 min)**	**2 (±5 min)**	**4 (±10 min)**	**6 (±10 min)**	**24 (±30 min)**
1	**1**	X	X	X	X	X	X	X*before Day 2 first dose
	8	X	X	X	X	X	X	
	15, 22, 28	Predose and 1 h (±5 min) postdose and 5 to 15 min before electrocardiogram (ECG)						

Note: All timepoints are relative to the morning dose.

4.1.20 Tumor Assessment

A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (eg, neck) within 30 days before the first dose of study drug. A pretreatment positron-emission tomography (PET)/CT scan within 90 days before the first dose is also required. Information on extranodal involvement will also be recorded.

During treatment, CT scans with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) will be done for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6 (± 7 days); and then every 3 cycles (12 weeks, ± 7 days) thereafter or more frequently at investigator discretion. On-study tumor assessments will also be done by physical exam and laboratory results. Bone marrow and PET/CT are only required for confirmation of CR per clinical guidelines (see Section 4.2).

Note: For sites in Germany, radiologic tumor assessments will not include PET. Radiologic tumor assessments will be done at Screening and at the end of Cycle 2 (± 7 days) OR Cycle 4 (± 7 days) depending each on subjects' individual response; thereafter they will be done at investigator discretion. On-study tumor assessments will also be done by physical exam and laboratory results.

De-identified copies of all radiology results maybe requested by the sponsor.

Subjects should have radiographic tumor measurements done at the participating study center or an acceptable alternate imaging facility using an identical imaging protocol and similar equipment. The same imaging equipment should be used for all scans whenever possible. The same radiologist should be assigned to read all the scans for a given subject throughout the study.

In the event disease progression is suspected due to physical examination or laboratory test, a CT and PET/CT scan must be performed to confirm disease progression. There must be radiographically measurable disease at screening (≥ 1 lymph node > 2.0 cm in the longest diameter). If the sole lesion lies within the field of prior radiotherapy, there must be evidence of disease progression in that lesion.

Up to 6 measurable lymph nodes (only target lesions > 1.5 cm in the longest diameter may be assessed), clearly measurable in 2 perpendicular dimensions, will be followed as target lesions for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved. If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions followed throughout the study. The cranial-caudal measurement of the spleen and longest diameter of the liver will be assessed at screening and all subsequent response evaluations.

4.1.21 Routine Clinical Assessments

Routine clinical assessments include physical exams, recording of symptoms, and hematologic evaluations to evaluate for both AEs and assessment of disease progression at times when the CT and/or PET/CT scan is not obtained. The investigator should report any suspected disease progression to the sponsor or designee via the electronic data capturing (EDC) system within 24 hours of discovery.

4.1.22 Study Drug Accountability

See Section 7.7.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

The investigator must rate the response of the subject's response to treatment consistent with clinical guidelines (Cheson 2014) as listed in Table 4-2.

Table 4-2. Response Assessment Criteria for DLBCL (Cheson 2014)

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in the marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extra lymphatic sites	Score 4 or5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm ×5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0mm
		For a node > 5 mm × 5 mm, but smaller than the normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable

Footnotes appear after the last page of the table.

Table 4-2. Response Assessment Criteria for DLBCL (Cheson 2014) (continued)

Response and Site	PET-CT-Based Response	CT-Based Response
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

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

consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, and lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measureable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

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

4.3 EARLY TERMINATION/SAFETY FOLLOW-UP VISIT

An early termination visit is required for any subjects who permanently discontinue study drug early for any reason including disease progression. Each subject should be followed for 30 (±7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.6) and to document the occurrence of any new events, unless the subject receives a new anticancer therapy within this timeframe. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Appendix 4) describes the procedures required for the safety follow-up.

4.4 TIME-TO-NEXT TREATMENT

Subjects who discontinue study therapy will continue on study for follow-up of safety (Section 4.3) and time-to-next DLBCL therapy unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate post-therapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from the study and the reason for discontinuation will be recorded and also should be described on the appropriate electronic case report form (eCRF).

4.5 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the

investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

This proof-of-concept study is designed to assess the safety, PK/PD, and activity of *acalabrutinib* 100 mg BID in subjects with relapsed/refractory de novo ABC DLBCL.

5.1.1 Response Assessment

Response assessments will be done by the investigators.

5.1.2 Safety Monitoring

The safety plan includes quarterly conference calls between Acerta and investigators to discuss study-specific issues including adverse events and serious adverse events.

5.2 DEFINITION OF ANALYSIS SETS

The following definitions will be used for the efficacy and safety analysis sets.

Safety analysis set: All enrolled subjects who receive ≥ 1 dose of study drug.

Per-protocol (PP) analysis set: All enrolled subjects who receive ≥ 1 dose of study drug, have sufficient baseline measurements, and undergo ≥ 1 assessment for the endpoint of interest (eg, response and PK/PD parameters) after treatment.

Intent-to-treat (ITT) population: All subjects who have enrolled in the protocol.

The safety analysis set will be used for evaluating the safety and efficacy, except duration of response, parameters in this study. The PP and ITT analysis sets will be analyzed for efficacy and PK/PD parameters in this study.

5.3 MISSING DATA HANDLING

General Considerations: Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation.

Duration of Response and Progression-free Survival: Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy.

Safety: Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules. No other imputation of values for missing data will be performed.

5.4 DETERMINATION OF SAMPLE SIZE

No formal statistical tests of hypotheses will be performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate.

The trial design is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. The sample size of 20 subjects in a Phase 1b study is considered adequate to evaluate the initial safety, PK/PD, and activity of *acalabrutinib* in this patient population.

5.5 DATA ANALYSIS

5.5.1 Safety Parameters

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will also be presented by the severity of the AE (per CTCAE, v4.03) and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments, ECGs, and physical exams will be tabulated and summarized.

5.5.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

5.5.3 Study Treatment Administration and Compliance

Descriptive information will be provided regarding the number of *acalabrutinib* doses prescribed, the total number of doses taken, the number of days of treatment, and the number and timing of prescribed dose reductions and interruptions.

For each patient, *acalabrutinib* compliance will be described in terms of the proportion of study drug actually taken based on returned pill count relative to the amount that was dispensed (taking into account physician-prescribed modifications and interruptions).

5.5.4 Analysis of Efficacy Parameters

Response Rate

The individual and composite endpoints of response and progression will be determined. Tumor control will be documented at each assessment by response category (eg, CR, PR, SD, PD) as defined for each response parameter, date that response is first documented, and date of DLBCL disease progression.

Overall response rate will be defined as the proportion of subjects who achieve a CR or PR. Overall response rate will be calculated and the corresponding 97.5% one-sided confidence interval will be derived.

Duration of Response

The duration of response (DOR) defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quantiles (including the median). Data from surviving, nonprogressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of definitive DLBCL progression was objectively documented. Data from subjects who have DLBCL progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time before the missing assessments that lack of DLBCL progression was objectively documented.

Progression-free Survival

Progression-free survival (PFS) is defined as the interval from the start of acalabrutinib therapy to the earlier of the first documentation of objective DLBCL disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of DLBCL progression was objectively documented. Data from subjects who have DLBCL progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the

last time prior to the missing assessments that lack of FL progression was objectively documented.

Time-to-Next Treatment

Time-to-next treatment defined as the time from start of *acalabrutinib* therapy for DLBCL on this protocol to the start of the next treatment for DLBCL. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from subjects who have not received subsequent therapy for DLBCL will be censored at the earliest of death or the last time that lack of administration of a new therapy for DLBCL was objectively documented.

5.5.5 Analysis of Pharmacokinetic/Pharmacodynamic Parameters

The plasma PK of *acalabrutinib* will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of *acalabrutinib*:

- AUC_{0-t} Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t).
- AUC_{0-12} Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.
- $AUC_{0-\infty}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.
- $AUC_{0-24calc}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}.
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- CL/F Oral clearance

Missing dates or times may be imputed for PK and PD samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. If PK and PD sampling for a given subject is not performed according to protocol instructions, the subject may be excluded from the PK and PD analyses.

The PK parameters will be tabulated and summarized using descriptive statistics.

For each PD variable, the concentration at each assessment will be described. The change from baseline to each assessment will be summarized. The best change from baseline during the study will also be summarized. As appropriate, the on-treatment values will be compared with the pretreatment baseline values using paired t-tests. P-values of ≤ 0.05 will be considered significant.

5.5.6 Explorative or Correlative Analyses

Additional PK or PD analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques.

6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

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 or other protocol-imposed intervention, 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 DLBCL that were not present before the AE reporting period (see Section 6.2.1)

- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)
- Preexisting 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 should not be reported as AEs; however, any clinically significant laboratory values (defined as requiring treatment, discontinuation from the study, or dose modification) should be reported as AEs.

6.1.2 Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "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 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 in-patient hospitalization.
- 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).

6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities

- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.1.4 Adverse Events of Special Interest

The following events are adverse events of special interest (AESIs) and must be reported to the sponsor 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)*

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on the SAE/Product Compliant form (see Section 6.2.5).

6.2.1 Adverse Event Reporting Period

After the signing of the ICF and prior to the first dose of study drug, all SAEs must be reported. After the first dose of study drug, all AEs/SAEs, irrespective of attribution of causality, must be reported.

All adverse events will be reported until 30 days after the last dose of study drug or the start of new anticancer therapy (whichever comes first). After this period, investigators should report serious adverse events or other adverse events of concern that are believed to be related to prior treatment with study drug.

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 eCRF and, when applicable, on an SAE/Product Compliant form.

Disease progression itself is not considered an AE; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Symptomatic deterioration may occur in some subjects. Symptomatic deterioration is when progression is evident in the subject's clinical symptoms and the investigator may elect not to perform further disease assessments.

Each recorded AE or SAE will be described by its duration (ie, 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?' Answer Yes or No.

See Appendix 3 for more detail on assessing relationship.

6.2.3 Second Primary Malignancies

Adverse events (AEs) for malignant tumors reported during a study should generally be assessed as serious AEs (SAEs). If no other seriousness criteria apply, the "Important Medical Event" criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a nonserious 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 nonserious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the investigational product *[IP] under study and is not the development*

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

6.2.4 Pregnancy

The investigator should report all pregnancies in study subjects and in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported using the SAE report form, according to the usual timelines and directions for SAE reporting (Section 6.2.5).

Any uncomplicated pregnancy that occurs in a study subject or a partner of a treated subject during this study will be reported for tracking purposes only, if agreed to by the subject or the partner of the subject in this study. 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 30 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner is willing to participate in follow-up.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE/Product Complaint form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving *acalabrutinib* 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.

6.2.5 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. All initial SAE/*AESI* reports and follow-up information will be reported using the protocol-specific electronic data capture system. If electronic SAE/*AESI* reporting is not available, paper SAE/Product Complaint forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. Acerta

Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

All deaths should be reported with the primary cause of death as the AE term, 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. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

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

An SAE*/AESI* may qualify for mandatory expedited reporting to regulatory authorities if the SAE*/AESI* is attributable to the investigational product and is not listed in the current Investigator Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the SAE*/AESI* to all investigators. Each investigator must then notify his or her IRB/IEC of the SAE*/AESI*.

Drug Safety Contact Information	
Fax:	PPD
Email:	

6.2.6 Type and Duration of Follow-up of Subjects After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the event as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

6.2.7 Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN may need to be reported as SAEs. Refer to Appendix 5 *for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law*.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma 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 include:

- Unsatisfactory subject enrollment with regard to quality or quantity

- Significant or numerous deviations from study protocol requirements, such as failure to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete, 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 REGULATORY AND ETHICAL COMPLIANCE

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

7.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the ICF, Investigator Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed FDA 1572 form (Statement of Investigator Form) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agencies, as appropriate, before the implementation of changes in this study.

7.3 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved ICF must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.12), **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 § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated ICF 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 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 with individual local and national patient 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 Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study Sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. 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.

7.4 SUBJECT SCREENING LOG

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.5 CASE REPORT FORMS

Authorized study site personnel (see Section 7.12) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed within 5 days of each subject's visit (unless required earlier for SAE reporting). The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed, in accordance with the record retention policies described in Section 7.8.

7.6 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits by the sponsor, regulatory authorities, or ethics committees.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the

investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology, pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.7 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib capsules must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply *acalabrutinib* capsules to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Acerta Pharma.

Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma or regulatory authorities at any time.

Each shipment of study drug will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. If it is used, the Drug Re-order Form (provided in the pharmacy binder) must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of study drug capsules. Then the designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/emailing address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-LY-002)
2. subject identification number
3. lot number(s) of *acalabrutinib* dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's

requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.8 RECORD RETENTION

The investigator 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 FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, and all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or return to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

7.9 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope

of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.10 PUBLICATION OF STUDY RESULTS

Acerta Pharma may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. The study is being conducted as part of a multicenter clinical trial. Data from all study centers shall be pooled and analyzed for publication in a final report (Primary Publication). The investigator agrees that the Primary Publication, which will be coordinated by Acerta Pharma, will be the first publication to present the pooled study results. After the Primary Publication, or if the Primary Publication is not published within 1 year of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement subject to providing Acerta Pharma with the opportunity to review the contents of any proposed presentation, abstract or publication about such work, including any results of this study, 90 days in advance of any presentation or submission for publication. Within that 90-day period, Acerta Pharma may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, Acerta Pharma may elect an additional review period not to exceed 60 days.

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2014).

7.11 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been obtained according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.12 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. Electronic CRF pages are completed within 5 days of each subject's visit (unless required earlier for SAE reporting).
11. All IND Safety Reports/Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge and to the IRB/IEC per their requirements.

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9.0 APPENDICES

Appendix 1. Performance Status Scores

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

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Appendix 2. Examples of Coadministered Drugs That Need Additional Consideration

The lists of drugs in these tables are not exhaustive. Any questions about drugs not on this list should be addressed to the medical monitor of this study.

Strong Inhibitors of CYP3A	***Moderate Inhibitors of CYP3A***
boceprevir	*aprepitant*
clarithromycin[a]	*cimetidine*
cobicistat[a]	*ciprofloxacin*
conivaptan[a]	*clotrimazole*
danoprevir and ritonavir[b]	*crizotinib*
diltiazem[a]	*cyclosporine*
elvitegravir and ritonavir[b]	*dronedarone*[a]
grapefruit juice	*erythromycin*
idelalisib	*fluconazole*
indinavir and ritonavir[b]	*fluvoxamine*
itraconazole[a]	*imatinib*
ketoconazole	*tofisopam*
lopinavir and ritonavir[a,b]	*verapamil*[a]
nefazodone	
nelfinavir[a]	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir)[b]	
posaconazole	
ritonavir[a, b]	
saquinavir and ritonavir[a, b]	
telaprevir[a]	
tipranavir and ritonavir[a, b]	
troleandomycin	
voriconazole	

a. *Inhibitor of P-glycoprotein.*

b. *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.*

c. *After discontinuation of the strong or moderate CYP3A inhibitor, wait 3 days before resuming ventoclax or acalabrutinib.*

Strong Inducers of CYP3A	***Moderate Inducers of CYP3A***
carbamazepine	*bosentan*
enzalutamide	*efavirenz*
mitotane	*etravirine*
phenytoin	*modafinil*
rifampin	
St. John's wort[a]	

a. *The effect of St. John's wort varies widely and is preparation-dependent.*

P-gp Inhibitors	***BCRP Inhibitors***	***Narrow Therapeutic Index P-gp Substrates***
amiodarone	*curcumin*	*digoxin*
carvedilol	*cyclosporine A*	*everolimus*
clarithromycin	*eltrombopag*	*sirolimus*
dronedarone		
itraconazole		
lapatinib		
lopinavir and ritonavir		
propafenone		
quinidine		
ranolazine		
ritonavir		
saquinavir and ritonavir		
telaprevir		
tipranavir and ritonavir		
verapamil		

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 18 July 2018:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix 3. 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

Appendix 4. Schedule of Assessments

	Screening[a]	Cycle 1						Cycle 2		Cycle 3	Cycle 4	Cycles 5-12[b]	ET/Safety Follow Up[c]	LTFU[s]
		Days (± 2)						Day(s) (±2)		Day(s) (±2)	Day(s) (±2)	Day(s) (±2)		
		1	2	8	15	22	28	15	28	28	28	28		
Informed consent	x													
Confirm eligibility	x													
Medical history	x													
PE[d]/Vital signs[e]/Weight	x	x		x	x	x	x	x	x	x	x	x	x	
ECOG status	x	x		x	x	x	x	x	x	x	x	x	x	
ECG[f]	x												x	
Lab assessments:														
Urine pregnancy test[g]	x												x	
Hematology[h]	x	x[t]		x	x	x	x	x	x	x	x	x	x	
Serum chemistry[i]	x	x[t]		x	x	x	x	x	x	x	x	x	x	
Urinalysis[j]	x													
T/B/NK/monocyte cell count[k]		x[v]							x			Every 6 mos		
Serum Ig[l]		x[v]							x			Every 6 mos		
Bone marrow (aspirate/biopsy)[m]	x											For CR only		
Hepatitis serology[u]	x													
HBV PCR[v]							x		x	x	x	QM		QM
Pharmacodynamics[n]		x	x	x			x		x				x	
Pharmacokinetics[o]		x	x	x	x	x	x							
Archival tumor sample[p]	x													
Acalabrutinib dispensed[q]		x	x	x	x	x	x	x	x	x	x	x		
Study drug compliance		x	x	x	x	x	x	x	x	x	x	x		
Tumor assessment[r]	x								x		x	x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	
Time-to-next treatment														x

Abbreviations: anti-HBc = hepatitis B core antibody; CR = complete remission; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET = early termination; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; IVIG = intravenous immunoglobulins; LTFU = long-term follow-up; mos = months; PCR = polymerase chain reaction; PE = physical exam; QM = every month.

Footnotes for ACE-LY-002 Schedule of Study Activities*:*

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. Any subjects who have not progressed while receiving study drug treatment, may be eligible to enroll into a long-term follow up study and continue to receive *acalabrutinib*.
c. An early termination visit will be done for subjects who permanently discontinue study drug early for any reason. A 30-day (± 7 days) safety follow-up visit is required when subjects discontinue study drug unless they start another anticancer therapy within that timeframe.
d. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams, including tumor assessments by palpation, are done thereafter.
e. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
f. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.
g. Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
h. Cycle 1 Day 1 testing does not need to be repeated if screening hematology was done within 7 days of first dose of study drug. Hematology includes complete blood count with differential and platelet counts.
i. Cycle 1 Day 1 testing does not need to be repeated if screening serum chemistry was done within 7 days of first dose of study drug. Serum chemistry: albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.
j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
k. T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD16/56). During Cycle 5-12, only done end of Cycle 6 and 12.
l. Serum immunoglobulin: IgG, IgM, IgA. During Cycle 5-12, only done end of Cycle 6 and 12.
m. A bone marrow aspirate and biopsy will be done at screening. Subjects who have a bone marrow aspirate and biopsy result since completion of their last therapy for DLBCL may use those bone marrow results in lieu of the baseline bone marrow aspirate/biopsy required for this study provided the biopsy/aspirate was done within 60 days before the first dose of study drug. Thereafter, bone marrow aspirate and biopsy will only be required to confirm any complete remission.
n. Pharmacodynamic (PD) assessments will be done on subjects at sites in the United States. On Cycle 1 Day 1 AND Day 8 the PD samples are drawn predose and 4 hours (±10 minutes) postdose. On Cycle 1 Day 2, Cycle 1 Day 28, and Cycle 2 Day 28, the PD samples are drawn up to 10 minutes predose (ie, the first dose of that day). At the Safety follow-up visit, a PD sample will be collected. Note: Timepoints are relative to the morning dose.
o. Pharmacokinetic (PK) assessments will be done on subjects at sites in the United States. PK samples for Cycle 1 Day 1 are drawn predose and at 0.5, 1, 2, 4, 6 and 24 h (before first dose on Day 2) postdose. Samples for Cycle 1 Day 8 are drawn predose and at 0.5, 1, 2, 4, and 6 h postdose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn predose and the second PK sample must be drawn 1 hour postdose. Note: Timepoints are relative to the morning dose.
p. Available archival tumor tissue is required to be eligible for this study. Either unstained slides (a minimum of 10 slides) or a paraffin block will be acceptable for central pathology review.
q. ***Acalabrutinib*: For Cycle 1 Day 1, 2, 8, 15, 22, and 28 study drug (first dose of the day) is administered at the site.**
r. A pretreatment CT scan with contrast (unless contraindicated) is required of the chest, abdomen, and pelvis and any other disease sites (eg, neck) within 30 days before the first dose of study drug. A pretreatment positron-emission tomography (PET)/CT scan within 90 days before the first dose is also required. Information on extranodal involvement will also be recorded. During treatment, CT scans with contrast (unless contraindicated) of the chest, abdomen, and pelvis and any other disease sites (eg, neck) will be done for tumor assessments at the end of Cycle 2 (± 7 days), Cycle 4 (± 7 days), and Cycle 6 (± 7 days); and then every 3 cycles (12 weeks, ± 7 days) thereafter or more frequently at investigator discretion. At all other visits, tumor assessments will be done by physical exam and laboratory results. Bone marrow and PET/CT are only required for confirmation of CR per clinical guidelines (see Section 4.2). At all other visits tumor assessments will be done by physical exam and laboratory results.
s. Subjects who discontinue study therapy will continue on study for follow-up of safety and time-to-next therapy for DLBCL unless they withdraw consent for further follow-up.
t. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.
u. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. Subjects who are receiving prophylactic intravenous immunoglobulins (IVIG) and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have polymerase chain reaction (PCR) testing (see exclusion criterion #13).
v. Subjects who are anti-HBc positive (or have a known history of HBV infection) should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of *acalabrutinib*. Any subject with a rising viral load (above lower limit of detection) should discontinue *acalabrutinib* and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.

Appendix 5. 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 potential Hy's law (PHL) cases and Hy's law (HL) cases. 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 subject meets PHL criteria at any point during the study. All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits, including central and all local laboratory evaluations, even if collected outside of the study visits (e.g., PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated total bilirubin from a local laboratory). The investigator will also review adverse event (AE) data (e.g., for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates with the sponsor in the review and assessment of cases meeting PHL criteria to agree whether 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 AEs and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety-reporting processes.

DEFINITIONS

Potential Hy's Law

AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN at any point during the study after the start of study drug, irrespective of an increase in alkaline phosphatase.

Hy's Law

AST or ALT ≥3 x ULN together with total bilirubin ≥2 x ULN, where no reason other than the IMP can be found to explain the combination of increases (e.g., elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or 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 total bilirubin, but there is no specified timeframe within which the elevations in transaminases and total bilirubin must occur.

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

Laboratory data must be comprehensively reviewed by the investigator for each subject to identify laboratory values meeting the following criteria:

- *ALT ≥3 x ULN*
- *AST ≥3 x ULN*
- *Total bilirubin ≥2 x ULN*

When the identification criteria are met from central or local laboratory results, the investigator will perform the following:

- *Notify the sponsor representative/medical monitor by telephone and report the case as an SAE of Potential Hy's law; seriousness criteria "Important medical event" and causality assessment "yes/related" or in accordance with the clinical study protocol as appropriate.*
- *Request a repeat of the test (new blood draw) without delay*
- *Complete the appropriate unscheduled laboratory electronic Case Report Form (eCRF) module(s)*
- *Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol, as applicable*

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this section should be followed by the investigator for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the study medical monitor and the investigator will review available data, to agree whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP and to ensure that timely analysis and reporting to health authorities within 15 calendar days from the date PHL criteria were met.

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

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

- *If the alternative explanation is an AE/SAE, update the previously submitted PHL SAE accordingly with the new information (reassessing event term, causality, and seriousness criteria) following the sponsor's standard processes.*

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

- *Send updated SAE (report term "Hy's law") according to the sponsor's standard processes:*
  - *The "Medically Important" serious criterion should be used if no other serious criteria apply.*
  - *Because 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 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for HL, then it is assumed that there is no alternative explanation until an informed decision can be made:

- *Provide any further update to the previously submitted SAE of PHL (report term now "Hy's law case"), ensuring causality assessment is related to IMP and seriousness criteria are medically important, according to clinical study protocol process.*
- *Continue follow-up and review according to the agreed plan. After the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following the clinical study protocol process, according to the outcome of the review.*

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a subject meets PHL criteria while receiving 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.