

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210259Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA, 505(b)(1)
Application Number(s)	210259
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Division/Office	CDER/OHOP/DHP
Review Completion Date	October 26, 2017
Established Name	Acalabrutinib
(Proposed) Trade Name	CALQUENCE
Pharmacologic Class	Kinase inhibitor
Code name	ACP-196
Applicant	Acerta Pharma B.V.
Formulation(s)	hard shell capsule
Dosing Regimen	100 mg orally approximately every 12 hours
Applicant Proposed Indication(s)/Population(s)	Treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Ashley Lucci Vaughn
Nonclinical Reviewer	Brenda Gehrke
Nonclinical Team Leader	Christopher Sheth
Office of Clinical Pharmacology Reviewer(s)	Vicky Hsu
Office of Clinical Pharmacology Team Leader(s)	Gene Williams
Clinical Reviewer	Margret Merino
Clinical Team Leader	Tanya Wroblewski
Statistical Reviewer	Jingjing Ye
Statistical Team Leader	Lei Nie
Cross-Disciplinary Team Leader	Tanya Wroblewski
Division Director (DHOT)	John Leighton
Division Director (OCP)	Nam Atiqur Rahman
Division Director (OB)	Rajeshwari Sridhara
Division Director (OHOP)	Albert Deisseroth
Office Director (or designated signatory authority)	Richard Pazdur

Additional Reviewers of Application

OPQ	Sherita McLamore
Microbiology	Not Applicable
OPDP	Nisha Patel
OSI	Anthony Orencia
OSE/DEPI	Not Applicable
OSE/DMEPA	Leeza Rahimi
OSE/DRISK	Ingrid Chapman
DMPP	Sharon Mills

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALT	alanine aminotransferase
ANC	Absolute neutrophil count
AST	aspartate aminotransferase
BCR	B-cell antigen receptor
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BTK	Bruton tyrosine kinase
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLL	Chronic lymphocytic leukemia
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	Complete Response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CSR	Clinical Study Report
CT	Computed tomography
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EORTC	European Organization for Research and Treatment of Cancer
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GALT	gut-associated lymphoid tissue
GCP	good clinical practice

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GD	gestation day
GLP	good laboratory practice
GGT	gamma-glutamyl transferase
GRMP	good review management practice
hERG	human ether-a-go-go related gene
HI	hepatic impairment
ICH	International Conference on Harmonization
IMAP	immobilized metal ion affinity-based fluorescence polarization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MCL	Mantle Cell Lymphoma
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
MIPI	Mantle Cell Lymphoma International Prognostic Index
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NHL	Non-hodgkin's lymphoma
NK	Natural Killer
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
ORR	Overall Response Rate
PBRER	Periodic Benefit-Risk Evaluation Report
PET	Positron-emission topography
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
RI	renal impairment
SAE	serious adverse event

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SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TDAR	T-cell dependent antigen response
TEAE	treatment emergent adverse event
TK	toxicokinetics

1 Executive Summary

1.1. Product Introduction

Established Name: Acalabrutinib, ACP-196

Proprietary Name: CALQUENCE®

Applicant: Acerta Pharma B.V.

Pharmacologic Class: Kinase inhibitor

Mechanism of Action: Forms a covalent bond with cysteine residue (Cys481) in the Bruton Tyrosine Kinase(BTK) active site, leading to inhibition of BTK enzymatic activity.

Applicants Proposed Indication: For the treatment of patients with mantle cell lymphoma who have received at least one prior therapy.

Proposed Dosage and Administration: 100mg orally twice daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of acalabrutinib under 21 CFR 314.510 Subpart H for the indication “for treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.” The recommended dose is 100mg orally approximately every twelve hours.

The recommendation is based on the findings of ACE-LY-004 a single-arm, multicenter study (NCT02213926) that enrolled 124 patients with relapsed or refractory mantle cell lymphoma. The median age was 68 years (range, 42 to 90 years) and the median number of prior therapies was 2 (range, 1 to 5). Patients who received prior treatment with BTK inhibitors were excluded from the study. Acalabrutinib was administered orally at 100mg twice daily until disease progression or unacceptable toxicity. Tumor response was assessed according to the 2014 Lugano Classification for Non-Hodgkin’s Lymphoma. The determination of efficacy was based on the overall response rate of 80.6% (95% CI: 72.6, 87.2) per investigator assessment. The median duration of response in months was not reached (range 1+, 20+) with median follow-up of 15.2 months. Thirty-nine and half percent of patients (95% CI: 30.9, 48.7) achieved a complete response (CR). There was 91% concordance between the Independent Review Committee and investigator assessment for ORR and 93% concordance for CR.

Section 21 CFR 314.510 addresses approval based on clinical endpoints other than survival or irreversible morbidity. Accelerated approval is subject to the requirement that the Applicant study the drug further to verify and describe its clinical benefit where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcome.

The rationale for the recommendation of accelerated approval for acalabrutinib is founded upon the following considerations:

- Uncertainty as to the relationship of ORR and DOR to the ultimate outcome of overall survival. Although the ORR was 80.6% per investigator assessment, 37.1% of patients discontinued treatment due to progressive disease.
- Because multiple therapies are approved for mantle cell lymphoma, a comprehensive characterization of the efficacy of anti-neoplastic agents, targeted agents, disease course, and determination of adequacy of long-term follow up is important. Questions remain regarding the treatment of mantle cell lymphoma such as optimal use of single and combination treatments, characterization of disease course (nodal, extranodal sites, BM involvement), and evaluation of treatment effect on time-to-event endpoints including progression free survival and overall survival.

All disciplines agreed with the approval recommendation of acalabrutinib or did not identify any outstanding issues that precluded the approval recommendation. In summary, the review team concluded that the overall response rate of 80.6% (95% CI: 72.6, 87.2) demonstrated in Study ACE-LY-004 with a median duration of response that has not been reached with 15.2 months of follow-up constitutes substantial evidence of effectiveness. A clinical benefit has not been confirmed and verification and description of the clinical benefit will need to be demonstrated in a confirmatory trial.

1.3. **Benefit-Risk Assessment**

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Benefit-Risk Summary and Assessment

Acalabrutinib is a Bruton's Tyrosine Kinase (BTK) inhibitor which forms a covalent bond with cysteine residue (Cys481) in the BTK active site, leading to inhibition of BTK enzymatic activity.

Mantle cell lymphoma is a rare and aggressive subtype of B-cell non-Hodgkin lymphoma. Current therapeutic options for patients with relapsed or refractory disease consists of single-agent or combination regimens with overall response rates ranging from approximately 20% to 90%. However, the median PFS and OS are generally less than two years. More recently, a first generation BTK inhibitor received accelerated approval for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy based on overall response rate of 66% and median duration of response of 17.5 months; however, the clinical benefit remains to be verified and described in an ongoing confirmatory trial. Effective agents are still needed for the treatment of relapsed or refractory mantle cell lymphoma.

The effectiveness of acalabrutinib was demonstrated in a single-arm, multicenter study (ACE-LY-004) of single-agent acalabrutinib administered twice daily until disease progression or unacceptable toxicity in patients with relapsed or refractory mantle cell lymphoma who had failed to achieve a partial response to prior therapy. Efficacy was evaluated in 124 patients enrolled in Study ACE-LY-004. The median age was 68 years (range, 42 to 90 years) and the median number of prior therapies was 2 (range, 1 to 5). Patients who received prior treatment with BTK inhibitors were excluded from the study. Tumor response was assessed according to the Lugano Classification for Non-Hodgkin's Lymphoma (2014). The overall response rate, which was the primary endpoint, was 80.6% (95% CI: 72.6, 87.2) per investigator assessment. The median duration of response in months was not reached (range 1+, 20+) with median follow-up of 15.2 months. Thirty-nine and half percent of patients (95% CI: 30.9, 48.7) achieved a complete response (CR). There was 91% concordance between the IRC and investigator assessment for ORR and 93% concordance for CR. At 12 months, the percentage of patients who achieved a CR or PR and who were still in remission was 72.1% (95% CI: 61.6%, 80.2%) by investigator assessment.

Acalabrutinib demonstrated an acceptable safety profile for the intended population. The safety profile was supported by analysis of a combined safety database of 612 patients (includes 2 patients from 90-day safety follow-up) with hematological malignancies. In Study ACE-LY-004(n=124), the median duration of treatment was 16.6 months (range, 0.1 to 26.6) and the most common adverse reactions ($\geq 20\%$ of patients) were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. Dose reductions or dose discontinuations due to any adverse reactions were reported in 1.6% and 6.5% of patients, respectively.

Events of clinical interest were identified based on preclinical findings, emerging data from clinical studies relating to acalabrutinib by the Applicant, and pharmacological effects associated with BTK inhibitors, including hemorrhage, infection, cytopenias, atrial fibrillation or flutter, and second primary malignancies. In the combined safety database (n=612), overall bleeding events, including bruising and

petechiae of any grade, occurred in approximately 50% of patients. Grade 3 or higher infections occurred in 18% of patients. Grade 3 or 4 cytopenias, including neutropenia (23%), anemia (11%) and thrombocytopenia (8%) based on laboratory measurements, also occurred. Second primary malignancies, including non-skin carcinomas, occurred in 11% of patients, and atrial fibrillation and flutter occurred in 3% (combined) of patients in the combined safety database population (n=612).

In summary, it is concluded that the overall response rate of 80.6% (95% CI: 72.6%, 87.2%) demonstrated in Study ACE-LY-004 with a median duration of response that has not been reached with 15.2 months of follow-up constitutes substantial evidence of effectiveness. Based on the available evidence, acalabrutinib demonstrated a favorable safety profile for the intended population. The safe use of acalabrutinib can be managed through accurate labeling and routine hematology and oncology care. Therefore, the benefit-risk profile is favorable to support approval of acalabrutinib under 21 CFR 314.510 Subpart H for the indication “for treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy.” A clinical benefit has not been confirmed and verification and description of the clinical benefit will need to be demonstrated in a confirmatory trial.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Relapsed and refractory mantle cell lymphoma is a serious and life-threatening illness with an overall poor prognosis.	Relapsed and refractory mantle cell lymphoma is a fatal disease.
Current Treatment Options	- There is limited disease control with either combination chemotherapy (ORRs of 58%-93%) and median progression free survival of < 2 years or single agents (ORRs of 26%-31%) and median OS < 2 years. - A first generation BTK inhibitor received accelerated approval for patients with mantle cell lymphoma who have received at least one prior therapy based on a demonstrated ORR of 66% with median duration of response of 17.5 months. The clinical benefit remains to be verified and described.	There is a need for effective agents for the treatment of R/R MCL.
Benefit	Study ACE-LY-004 was a single-arm, multicenter trial that enrolled 124	There is substantial evidence of effectiveness

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	patients with mantle cell lymphoma who had received at least one prior therapy showed an ORR of 80.6% (95% CI: 72.6, 87.2) per investigator assessment using the 2014 Lugano Classification for Non-Hodgkin Lymphoma. • The complete response rate was 39.5%(95% CI: 30.9, 48.7). • The median duration of response was not reached with median follow-up of 15.2 months. • At 12 months, the percentage of patients who achieved a CR or PR and who were still in remission was 72.1% (95% CI: 61.6%, 80.2%) by investigator assessment.	for acalabrutinib as a treatment for patients with mantle cell lymphoma who have received at least one prior therapy. The Applicant has an ongoing confirmatory trial which is required to verify and describe the clinical benefit.
<u>Risk</u>	• In Study ACE-LY-004(n=124), the most common adverse reactions (≥20% of patients) were anemia, thrombocytopenia, headache, neutropenia, diarrhea, fatigue, myalgia, and bruising. (Hematological adverse reactions based on both laboratory and hematological adverse reactions) • Dose reductions or discontinuations due to any adverse reactions were reported in 1.6% and 6.5% of patients, respectively. • Serious adverse events occurred in 38.7% of patients with no specific SAE occurring in greater than 5% of patients. The most common SAE was pneumonia (4.0%). • Grade ≥ 3 adverse reactions occurred in 49.2% of patients with neutropenia (10.5%) being the common hematological event and pneumonia (4.8%) the most common non-hematological adverse reaction. • No patient deaths on study were attributed to acalabrutinib therapy. • Adverse events of clinical interest include hemorrhage, infection, cytopenias, atrial fibrillation and flutter and second primary malignancies.	Based on available evidence, the overall safety profile of acalabrutinib is acceptable for the intended population. The current USPI includes warnings and precautions for hemorrhage, cytopenias, atrial fibrillation and atrial flutter and second primary malignancies.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In the combined safety database (n=612), which includes two additional patients based on 90-day safety cut-off, overall bleeding events including bruising and petechiae of any grade occurred in approximately 50% of patients. • Grade 3 or higher infections occurred in 18.0% of patients in combined safety database(n=612). • Grade 3 or 4 cytopenias, including neutropenia (23.0%), anemia (10.9%) and thrombocytopenia (8.2%) based on laboratory measurements occurred in the combined safety database population(n=612). • Second primary malignancies including non-skin carcinomas occurred in 10.6% of patients with hematological malignancies in the combined safety database of 612 patients. • Atrial fibrillation and flutter occurred in 2.9%% of patients in the combined safety database population(n=612).	
Risk Management	• There is no proposal for a formal risk management plan. • The Applicant has a pharmacovigilance plan for adverse events of special interest: major hemorrhage, atrial fibrillation and flutter, cytopenias, infections, and second primary malignancies.	The safe use of acalabrutinib can be managed through accurate labeling and routine hematology and oncology care. No REMS indicated. In addition, confirmatory trials are ongoing to better define the benefit-risk profile.

X

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}

Tanya Wroblewski, M.D.
Cross-Disciplinary Team Leader

APPEARS THIS WAY ON ORIGINAL

2 Therapeutic Context

2.1. Analysis of Condition

Mantle cell lymphoma (MCL) is a rare subtype of non-Hodgkin lymphoma (NHL) with a poor prognosis and represents 3-10% (SEER 2017) of all new non-Hodgkin lymphomas cases per year. The estimated incidence of MCL is 0.51 to 0.55 cases per 100,000 persons in the US. Most patients present with aggressive, disseminated disease and there is a 2.5:1 male-to-female predominance with a median age at diagnosis of 64 years. Generally, MCL is thought to possess the worst characteristics of both indolent and aggressive NHL subtypes due to the incurability of the disease with conventional chemotherapy and a more aggressive disease course.

Recently updated WHO guidelines (Swerdlow, 2016) recognize two subtypes of mantle cell lymphoma: 1) classical MCL which involves lymph nodes and extranodal sites and characterized by immunoglobulin heavy chain (IGHV)-unmuted B cells, and 2) leukemic non-nodal MCL which is generally composed of IGHV-mutated genes and typically involves bone marrow, peripheral blood and spleen, and has a more indolent presentation.

Patients can be classified into low, intermediate, and high-risk categories based on the MCL international prognostic index (MIPI) which incorporates age, performance status, LDH, and leukocyte count. The MIPI as well as the simplified MIPI has been validated in several studies as having prognostic significance for patients with MCL. Patients with intermediate and high risk MIPI scores have a median OS of less than 5 years (Hoster, 2008).

Molecularly, mantle cell lymphoma is characterized by the chromosomal translocation t(11;14)(q13;q32) which juxtaposes the proto-oncogene CCND1 at 11q13 to the immunoglobulin heavy chain complex(IGHV) at chromosome 14q32 and results in over-expression of cyclin D1 and cell cycle dysregulation. Cyclin D1 promotes mantle cell lymphomagenesis due to its function in the cell cycle and regulation of cyclin-dependent kinases (CDK4 and CDK6) (Cheah, 2016).

There is no curative therapy for MCL with the exception of rare patients who achieve long-term disease-free survival after allogeneic stem cell transplantation. The median overall survival in patents with newly diagnosed high-risk MCL is 3-4 years with no plateau in the survival curve. First-line treatments include multi-agent chemotherapy regimens; however, almost all patients will eventually relapse. For patients with relapsed and refractory disease, the median overall survival for these patients treated with monotherapy is 1-2 years. (Cheah, 2016)

2.2. Analysis of Current Treatment Options

Therapeutic options include salvage chemotherapy regimens and targeted therapies. Bortezomib and lenalidomide are the only approved (regular) treatments for relapsed and refractory MCL with overall response rate (ORRs) of 31% and 26%, respectively. Ibrutinib (a first-generation BTK inhibitor) received accelerated approval in 2013 for relapsed and refractory mantle cell lymphoma based on an ORR of 66%. The table below provides summaries of the trials supporting regulatory actions for these agents.

Table 1: FDA Approved Drugs for the Treatment of MCL

Product (s) Name	Relevant Indication	Year of Approval	Dosing/ Administration	Trial Design	Efficacy Information Endpoints
Bortezomib	R/R MCL	2015 Traditional Approval	1.3mg/m ² /dose intravenously twice weekly for two weeks followed by 10 day rest	N=155 Single arm	ORR 31% CR 8% DOR 9.2 mo
Lenalidomide	R/R MCL	2013 Traditional Approval	25mg orally once daily on days 1-21 of repeated 28 day cycles	N=134 Single-Arm	ORR 26% CR 7.5% DOR 16.6 mo
Ibrutinib	R/R MCL	2013 Accelerated Approval	560 mg orally daily until disease progression or unacceptable toxicity	N=111 Single Arm	ORR 66% CR 21% DOR 17.5 mo

Source: USPI, Bortezomib, Lenalidomide, Ibrutinib

There are several other therapies that are used in both the front-line and relapsed setting. The decision as to which therapeutic option chosen often depends upon underlying co-morbidities, prior therapies, and the patient's potential for stem cell transplant. Accepted therapies include single agents such as bendamustine or rituximab and combination therapies such as bendamustine-rituximab (BR), rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), hyper fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD) alone or in combination with rituximab (R-Hyper CVAD) (NCCN Guidelines, 2017) (Fakhri, 2017).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Acalabrutinib is a new molecular entity and is currently not marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The table below summarizes the key regulatory activities for acalabrutinib. A pre-NDA meeting was held with the Agency in May 2017.

Table 2: Summary of Regulatory Activity for acalabrutinib

Date	Event Summary
July 19, 2013	Pre-IND meeting requested and written advice was provided for the first in human trial of acalabrutinib in patients with CLL.
November 27, 2013	IND 118717 was submitted.
September 21, 2015	Orphan Drug Designation granted for mantle cell lymphoma.
March 21, 2016	And EOP2 meeting was held to discuss the Applicant's plan for clinical development of acalabrutinib in mantle cell lymphoma and plans for study ACE-LY-004 to serve as the pivotal study to support and indication for mantle cell lymphoma. At that time the agency recommended a minimum of 12 month follow up for responders to document durability of response.
January 27, 2017	The Applicant received written responses and feedback was provided to Applicant on the proposed content and format of an NDA for acalabrutinib for the treatment of patients with mantle cell lymphoma who had received at least one prior therapy.
June 2, 2017	Pre-NDA meeting was held with the Agency. The Agency requested that the sponsor submit assessments of response for all disease compartments for patients with extranodal disease.
June 13, 2017	NDA 210259 was submitted.
July 31, 2017	Breakthrough Therapy Designation granted for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy.

Important Issues with Consideration to Related Drugs

- Ibrutinib is a first-in-class BTK inhibitor. The adverse drug reactions associated with ibrutinib (atrial fibrillation, hemorrhage, and infections and cytopenias) were taken into consideration in the evaluation of this application.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations conducted inspections for Study ACY-LY-004 at two clinical sites: Site #034 (M.D. Anderson Cancer Center, Houston, TX) and Site #035 (Hackensack University Medical Center, Hackensack, NJ). These sites were selected based on highest patient accrual and high rate of treatment response. The Applicant Acerta Pharma was also audited.

The final regulatory classification of the Applicant is Voluntary Action Indicated based on delays between 4 and 11 months from the time of a revised version of the protocol until the time of submission to the IRB. Upon review of the details of the revised protocol, the content in these amendments was largely administrative and the delays in the approval of these amendments were not thought to have a significant impact on either safety or efficacy data for the study.

OSI concluded that the study data derived from the inspected clinical sites and the Applicant are considered reliable in support of the requested indication. Please refer to the Clinical Inspection Summary by Dr. Anthony Orencia, M.D. (August 18, 2017) for any additional details.

4.2. Product Quality

Novel excipients: No

Any impurity of concern: No, all impurity concerns have been resolved.

4.1. Clinical Microbiology

There were no clinical microbiology issues with this application.

4.2. Devices and Companion Diagnostic Issues

There were no devices or companion diagnostic issues with this application.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The nonclinical development program for acalabrutinib was conducted in various cellular assay systems, and in the mouse, rat, rabbit, and dog, to evaluate the pharmacology, pharmacokinetics, general toxicology, reproductive and developmental effects, and the genotoxic potential of acalabrutinib. Acalabrutinib is an inhibitor Bruton tyrosine kinase (BTK). BTK is a signaling molecule of the B-cell antigen receptor (BCR) and cytokine receptor pathways that is expressed in B-cells, myeloid cells, mast cells, and platelets. BTK's role in signaling through the B-cell surface receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Chronic activation of the BCR pathway is involved in the proliferation and cell survival of various B-cell malignancies. The established pharmacological class for acalabrutinib is kinase inhibitor.

Acalabrutinib and its active metabolite ACP-5862 inhibited BTK with IC_{50} values of 3.0 nM and 5.0 nM, respectively. Covalent binding for BTK was demonstrated in adenosine triphosphate (ATP) competition assays and data from the BTK-wild type compared to the BTK Cys481Ser mutant confirmed that acalabrutinib and ACP-5862 bind covalently to C481 in the ATP pocket of BTK. In the kinase selectivity screens, compared to the inhibition of BTK at 1 μ M, acalabrutinib and/or ACP-5862 showed >65% inhibition for BMX, BRK (PTK6), ERBB2, ERBB4, LIMK1, MEK5, TEC, and TXK based on K_d values.

The in vitro activity of acalabrutinib and ACP-5862 on BTK in cells was evaluated in Ramos B lymphoma cells, human peripheral blood mononuclear cells (PBMCs), and human whole blood. Both acalabrutinib and ACP-5862 showed binding to BTK in the Ramos (Burkitt's lymphoma) cell line, with a 3-fold difference between acalabrutinib (EC_{50} =13 nM) and ACP-5862 (EC_{50} =39 nM). Acalabrutinib and ACP-5862 inhibited BCR-mediated CD69 up regulation in both PBMCs and whole blood with EC_{50} values ranging from 6 nM to 64 nM and 4-fold and 7-fold greater potency with acalabrutinib in PBMCs and whole blood, respectively. The effects of acalabrutinib on CD86 and CD69 cell surface expression in gated B cells were evaluated following ex vivo B cell activation in splenocytes from mice administered a single oral dose of acalabrutinib. The ED_{50} of acalabrutinib administered orally ranges between 0.34 and 1.8 mg/kg for the inhibition of CD86 expression and 0.16 and 1.3 mg/kg for the inhibition of CD69 expression. Additionally, the in vivo activity of acalabrutinib against malignant B cells was assessed in human xenograft models in mice. Treatment with acalabrutinib at a dose of 12.5 mg/kg twice daily (BID) resulted in tumor growth inhibition in models of diffuse large B cell lymphoma and mantle cell lymphoma.

Other pharmacology studies compared the effects of acalabrutinib and ibrutinib on other types of immune cells and platelet function and thrombus formation. In studies conducted to compare the effects of acalabrutinib and ibrutinib on T cells and natural killer (NK) cells, results

showed that while ibrutinib had multiple effects including decreases in T helper cell development, NK cytolytic function, and IFN γ production in CD8 T cells, acalabrutinib had either no effect or modest effects on T cells and NK cells. Based on the results of the in vitro and in vivo assays evaluating and comparing the effects of acalabrutinib and ibrutinib on platelet function, acalabrutinib appears to have fewer effects than ibrutinib on platelets in aggregometry assays and in a humanized mouse model of thrombus formation.

Safety pharmacology studies assessed the effects of acalabrutinib on the cardiovascular, central nervous system (CNS), and respiratory function. Following single oral doses, acalabrutinib had no toxicologically-significant effects on cardiovascular function in a cardiovascular study in telemetered dogs, and had no effects on neurobehavioral function, rectal temperature, or respiratory function in CNS and respiratory studies conducted in male rats.

Both acalabrutinib and ACP-5862 bound to protein in the plasma of various species in a concentration-independent manner. In human plasma, binding averaged 97.5% for acalabrutinib and 98.6% for ACP-5862. The blood cell partitioning for acalabrutinib was highest in the mouse and dog (~45-58%), the species with the lowest protein binding, and averaged 26% in humans. In a quantitative whole-body autoradiography study in rats following a single oral administration of radiolabeled acalabrutinib, the drug was widely distributed with the highest radioactivity observed in the large intestine, liver, uveal tract, kidney cortex, extraorbital lacrimal gland, intra-orbital lacrimal gland, kidney medulla, kidney, adrenal glands, cecum, and small intestine. Acalabrutinib was extensively metabolized with primary metabolites representing carbon oxidation, glutathione conjugation, amide hydrolysis, *N*-dealkylation, and alkyne hydration. Pyrrolidine oxidation appears to be the major metabolic pathway with the active metabolite ACP-5862 observed at the highest levels in all species tested. Levels of ACP-5862 were greater in human plasma than in rat and dog plasma. Elimination studies showed that acalabrutinib was mainly excreted through the fecal route in both rats (~90%) and dogs (~70%) with some elimination through the urine (~3% in rats and ~15% in dogs).

Repeat-dose toxicology studies were conducted to assess the chronic toxicity of acalabrutinib. While acalabrutinib is clinically administered twice daily as flat dose (mg) in patients, acalabrutinib was administered once daily in mg/kg in rats and dogs. Sprague-Dawley rats were administered doses up to 300 mg/kg in the 26-week study and Beagle dogs were administered doses up to 30 mg/kg in the 91-day (3-month) and 39-week studies. The studies were conducted using the oral route of administration, which is consistent with the intended clinical route of administration. For the purposes of this review the 39-week repeat-dose study in dogs is summarized here in Section 5.1, and the 91-day study was fully reviewed in Section 5.5.1 as there were more pronounced toxicities in the 91-day dog study. In rats, the effects of acalabrutinib on T-cell dependent antigen responses (TDAR) were evaluated in the 91-day (primary TDAR) and in the 26-week (secondary (recall) TDAR) studies. The primary TDAR response (as measured by the generation of IgM antibody to keyhole limpet hemocyanin (KLH)) was mildly diminished at sporadic timepoints in males and females. The secondary TDAR

response (anti-KLH IgG antibodies) was only sporadically statistically significantly decreased in females. There was no other evidence to suggest the TDAR findings were biologically or pathologically relevant.

In the 26-week study in rats, acalabrutinib was administered by oral gavage at 0, 20, 100, or 300/200 mg/kg/day once daily with a 4-week recovery period. The highest dose was initially 300 mg/kg/day; however, mortality was observed at 300 mg/kg/day during the first 2 weeks of treatment and the highest dose was decreased to 200 mg/kg/day. Additional mortality was observed in animals treated with 300/200 mg/kg/day following the dose reduction. Findings in animals with early mortality included clinical signs of decreased activity, rapid or difficulty breathing, ataxia, hunched posture, pale skin, discolored skin, skin cold to touch, thin, vocalization, and/or hypersensitive to touch, and body weight loss. Marked increases in urea nitrogen, creatinine, potassium, and phosphorus with moderate decreases in sodium, chloride, and total protein indicated severe renal insufficiency and injury and correlated with tubular degeneration/necrosis in the kidney. Other microscopic findings in these animals included hepatocyte degeneration/necrosis in the liver, and hemorrhage/inflammation/necrosis in the heart. The causes of mortality were determined to be uremia/acute kidney failure and myocardial necrosis. In surviving animals, clinical pathology changes included increases in lymphocytes, monocytes, total bilirubin, gamma-glutamyl transferase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), urea nitrogen, and creatinine, and decreases in triglycerides. The organs of toxicity of acalabrutinib in surviving animals included the kidney, liver, lung, mesenteric lymph node, and pancreas.

In the 39-week study in dogs, acalabrutinib was administered orally via gelatin capsules at doses of 0, 10, or 30 mg/kg/day once daily for 39 weeks with a 4-week recovery period. Toxicities were limited to changes in clinical pathology consisting of reversible effects on red blood cell parameters including decreases in red cell mass and decreases in albumin. Acalabrutinib produced more toxicity in the 3-month (91-day) dog study when administered at doses of 0, 5, 10, or 30 mg/kg/day for 91-days with a 28-day recovery period. At the highest dose of 30 mg/kg/day, one female had increases in clinical chemistry parameters (ALT, alkaline phosphatase, urea nitrogen, and creatinine) and clinical signs that lead to a 1-week dosing interruption of acalabrutinib (Days 46-52) in this animal. Dosing was resumed at 30 mg/kg/day and the animal finished the study. Decreased body weight and food consumption were observed in females at all doses compared to vehicle controls. Hematology changes were consistent with the findings in the 9-month study and included decreases in red cell mass (erythrocytes, hemoglobin, and hematocrit) with corresponding increases in mean cell volume (MCV) and reticulocytes. Organs of toxicity of acalabrutinib observed in the 91-day study included the gut-associated lymphoid tissue (GALT), kidney, liver, mandibular and mesenteric lymph nodes, spleen, and thyroid/parathyroid.

A combination fertility and embryo-fetal development study was conducted in rats with acalabrutinib administered once daily at doses of 0, 30, 100, or 300 mg/kg/day starting 28 days prior to pairing through mating and a postmating period (77-79 days total) in males and at

doses of 0, 30, 100, or 200 mg/kg/day starting 14 days prior to pairing through Gestation Day (GD) 17 in females. No effects on fertility or embryo-fetal development were observed at any dose level. Exposures at the doses of 300 mg/kg/day in males and 200 mg/kg/day in females were approximately 18 times and 16 times, respectively, the human clinical exposure based on AUC at the recommended human dose. The pharmacokinetic analysis from a pilot pre- and post-natal development study in which acalabrutinib was administered orally to pregnant female rats from GD 6 through delivery until lactation day (LD) 12 confirmed the presence of acalabrutinib and its active metabolite in fetal rat plasma on GD 18 and in maternal milk and pup plasma on LD 18.

In an embryo-fetal development study in female rabbits, once daily administration of acalabrutinib at doses of 0, 50, 100, or 200 mg/kg/day on GD 6-18 resulted in maternal toxicity at 100 and 200 mg/kg/day characterized by decreased food consumption, body weight gain, and body weight leading to mortality. Mortality was observed in all the animals in the 200 mg/kg/day group; therefore, developmental toxicity could not be assessed at this dose. Fetal toxicity characterized by decreased fetal body weights and delayed fetal skeletal ossification was observed at the maternally toxic dose of 100 mg/kg/day. Maternal exposures at the 100 mg/kg/day dose were approximately 4 times the human clinical exposure based on AUC at the recommended human dose.

Acalabrutinib was not mutagenic in the in vitro bacterial reverse mutation test or clastogenic in the in vitro chromosomal aberrations assay in peripheral human lymphocytes or in the in vivo bone marrow micronucleus assay in rats. No carcinogenicity studies have been conducted or are required to support marketing of acalabrutinib for the current indication.

Seven drug substance and two drug product impurities needed to be qualified based on the proposed specifications. There was one impurity in the drug substance and one in the drug product that could not be toxicologically qualified based on animal studies, and the Applicant agreed to reduce the specifications for those two impurities to acceptable levels.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of acalabrutinib for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

A. In vitro studies

Kinase profiling was conducted for acalabrutinib and its metabolite ACP-5862 (also referred to as M27) to determine the activity at Bruton tyrosine kinase (BTK) and the kinase selectivity profile. Both acalabrutinib and ACP-5862 inhibited BTK in an immobilized metal ion affinity-based fluorescence polarization (IMAP) assay with IC₅₀ values of 3.0 nM for acalabrutinib and 5.0 nM for ACP-5862. To demonstrate covalent binding for BTK, BTK IMAP adenosine triphosphate (ATP) competition assays were conducted with variable pre-incubation times (0, 30, and 60 minutes) and ATP concentrations (5, 25, and 100 µM).

Table 3 Variation in half-maximal inhibitory concentrations (IC₅₀) of acalabrutinib and ACP-5862 in BTK IMAP ATP competition assay

ATP (µM)	IC ₅₀ (nM)					
	Acalabrutinib			Metabolite ACP-5862		
	0 minutes	30 minutes	60 minutes	0 minutes	30 minutes	60 minutes
5	11.6	4.6	3.2	27.3	12.6	6.9
25	27.6	7.6	3.9	72.4	18.1	9.5
100	61.0	9.0	4.4	101.0	23.7	10.8

To confirm the covalent inhibition of acalabrutinib and ACP-5862, the inhibitory activity was investigated on BTK-WT and the BTK Cys481Ser mutant (BTK-C481S) using the LanthaScreen assay technology. Results confirm the covalent binding to BTK; the increase in potency observed with BTK-WT compared to BTK-C481S results from the capacity of acalabrutinib and ACP-5862 to bind covalently to C481 in the ATP pocket of BTK. The binding kinetics show that while the affinity of ACP-5862 for BTK-WT is similar to acalabrutinib (K_i=300 nM for acalabrutinib and 188 nM for ACP-5862), the inactivation rate of ACP-5862 is about 3 times lower (kinact= 0.0102 s⁻¹ for acalabrutinib and 0.0031 s⁻¹ for ACP-5862), leading to a higher potency for BTK for acalabrutinib than ACP-5862.

The kinase selectivity profiling was conducted at a single concentration of 10 µM on a panel of 282 wildtype human kinases, at a single concentration of 1 µM on a panel of 384 wild type kinases, and on a select panel of kinases that have a cysteine in the identical position in the ATP pocket as Cys481 in BTK (3F-Cys kinases). Results in the 384 kinase panel showed that compared to the inhibition of BTK at 1 µM, >65% inhibition was shown for the following kinases for acalabrutinib and/or ACP-5862:

Table 4 Kd Values of kinases with >65% inhibition at 1 μ M for Acalabrutinib and ACP-5862

Kinase	Kd (nM)	
	Acalabrutinib	ACP-5862 (metabolite)
BTK	15	29
BMX	570	190
BRK (PTK6)	1600	150
ERBB2	56	120
ERBB4	140	970
LIMK1	190	400
MEK5	930	69
TEC	16	40
TXK	540	1100

In the selective panel with 3F-Cys kinases, compared to the inhibition of BTK, acalabrutinib and ACP-5862 showed the most inhibition of BMX, ERBB4, and TEC.

Table 5 Potency of Acalabrutinib and ACP-5862 on 3F-Cys Kinases

Kinase	IC ₅₀ (nM)	
	Acalabrutinib	ACP-5862 (metabolite)
BTK	3	5
BMX	58	15
ERBB4	19	343
TEC	139	345

The in vitro potency of acalabrutinib and ACP-5862 on BTK in cells was evaluated in Ramos B lymphoma cells, human peripheral blood mononuclear cells (PBMCs), and human whole blood. Both acalabrutinib and ACP-5862 showed binding to BTK in the Ramos (Burkitt's lymphoma) cell line in an ELISA assay, and acalabrutinib (EC₅₀=13 nM) was 3-fold more potent than ACP-5862 (EC₅₀=39 nM). The effects of acalabrutinib and ACP-5862 on CD69 expression following B cell receptor (BCR) activation with anti-IgM or anti-IgD was evaluated in PBMC and whole blood using flow cytometry. Acalabrutinib was 4-fold more potent than ACP-5862 in inhibiting BCR-mediated CD69 up-regulation in PBMCs both with (EC₅₀=13 nM for acalabrutinib and 51 nM for ACP-5869) and without (EC₅₀=6 nM for acalabrutinib and 26 nM for ACP-5869) washout. The finding of only a 2-fold shift in the EC₅₀ values following washout of acalabrutinib or ACP-5869 confirms that both compounds bind covalently to BTK. In whole blood, acalabrutinib (EC₅₀=9 nM) was 7-fold more potent than ACP-5862 (EC₅₀=64 nM) in inhibiting BCR-mediated CD69 up-regulation.

The effects of acalabrutinib on CD86 and CD69 cell surface expression in gated B cells were evaluated using flow cytometry following ex vivo B cell activation with anti-IgM in splenocytes from mice administered a single oral dose of acalabrutinib. In one study, mice were administered a single dose of acalabrutinib (0.1 to 30 mg/kg) and euthanized 3 hours after dosing. In this assay, the ED₅₀ of acalabrutinib administered orally ranges between 0.34 and 1.8 mg/kg for the inhibition of CD86 expression and 0.16 and 1.3 mg/kg for the inhibition of CD69

expression across multiple experiments. In another study, the timecourse of the inhibition of CD86 and CD69 induction by acalabrutinib was measured with a single dose of 25 mg/kg acalabrutinib administered to mice euthanized at various times between 3 and 40 hours after dosing. Acalabrutinib inhibited CD86 and CD69 induction to near baseline levels at the 3-hour time point and over time, both surface receptor readouts increased towards control levels with partial inhibition still observed at 24 hours after dosing.

Table 6 Return of Function Profile of CD86 and CD69 Expression in Response to Ex Vivo BCR Stimulation in mouse splenocyte B cells

Measure	Mean % of inhibition from vehicle control				
	3 hr	6 hr	12 hour	18 hour	24 hr
CD86 expression	92.1	87.4	77.5	49.4	44.5
CD69 expression	104.9	106.9	84.7	78.4	67.3

Studies were conducted to compare the effects of acalabrutinib and ibrutinib on T helper cell development, natural killer (NK) cell function, CD8 T cell function, and dendritic cell maturation (summarized in the table below). T cell studies used mouse splenic lymphocytes and NK cell studies used human PBMCs. Additional studies have shown that in contrast to ibrutinib, acalabrutinib does not affect the in vitro proliferation of primary CD8 cytotoxic T cells of human or murine origin and has minimal or no effect on trastuzumab-mediated NK-antibody-dependent cell-mediated cytotoxicity (NK-ADCC) activity in vitro in human NK cells ($EC_{50} > 4 \mu M$).

Table 7 Summary of Effects of Acalabrutinib and Ibrutinib on T Cells and NK cells

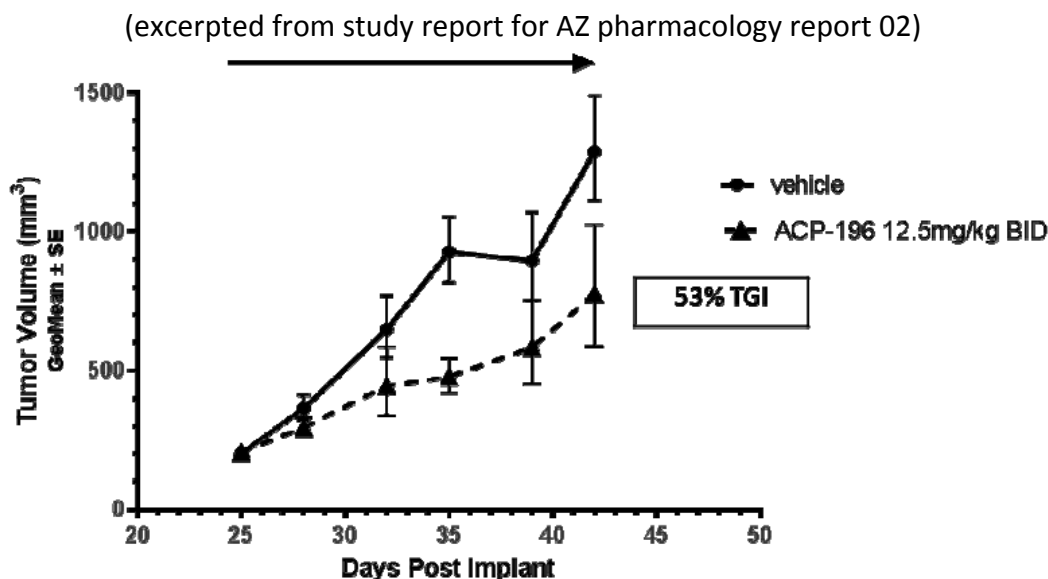
Assay	Ibrutinib	Acalabrutinib
Th2 cultures (IL-4 secretion measured)	Decreased	Modest decrease
Th17 cell frequency (IL-17 expression measured)	Decreased	No effect
Treg	Decreased	Modest decrease
NK killing	Decreased	Modest decrease
NKT cells	No effect	No effect
CD8 Cytotoxic T lymphocytes	No effect	No effect
CD8 IFN γ production	Decreased	No effect
Mouse dendritic cells	Increases maturation	Modest increased maturation
Human dendritic cells	Modest increased maturation (CD86)	No effect

B. In vivo studies

The in vivo activity of acalabrutinib against malignant B cells was assessed in human xenograft models in mice. Acalabrutinib (12.5 mg/kg BID) was administered orally to female CB.17 SCID mice for 28 consecutive days in a model of diffuse large B cell lymphoma (OCI-LY10) and for 17 consecutive days in a model of mantle cell lymphoma (Jeko-1). In the OCI-LY10 xenograft

model, treatment with acalabrutinib for 28 days resulted in 100% tumor growth inhibition. As shown in the figure below, treatment with acalabrutinib for 17 days in the Jeko-1 model resulted in 53% tumor growth inhibition.

Figure 1 Effects of Acalabrutinib on Tumor Growth in the Jeko-1 Model of Mantle Cell Lymphoma



Acalabrutinib was also tested in a chronic lymphocytic leukemia (CLL) xenograft model in NSG mice. Mice were treated with acalabrutinib (0.006, 0.06, 0.15, or 0.3 mg/mL) or vehicle alone in the drinking water. Acalabrutinib inhibited tumor proliferation as measured by Ki67 expression in CLL cells from the spleen of the mice with a mean decrease in Ki67 of 58%, 70%, and 73% at 0.006 mg/mL, 0.06 mg/mL, and 0.15 mg/mL acalabrutinib, respectively, compared to vehicle.

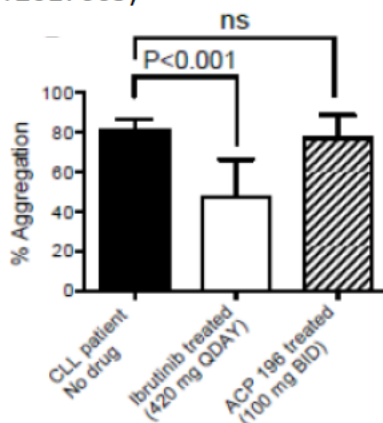
C. Effects on platelet function

In vitro and in vivo assays were conducted to assess and compare the effects of acalabrutinib and ibrutinib on platelet function and thrombus formation. Platelet activity was assessed using light transmitted aggregometry (LTA) to measure aggregation in vitro and a humanized genetically modified mouse model (VWF^{HA1} mouse) to measure the ability of human platelets to support thrombus formation in vivo at sites of a laser-induced arterial injury. Platelets obtained from healthy volunteers and patients with chronic lymphocytic leukemia (CLL) treated with acalabrutinib or ibrutinib were used in these assays. In the LTA assay for platelet aggregation, acalabrutinib or ibrutinib were added to platelet suspensions and incubated for 10 minutes before the induction of aggregation. In the in vivo thrombosis model, freshly isolated platelets from healthy volunteers were prepared and then treated in vitro with acalabrutinib or ibrutinib prior to evaluation in the mouse model. Additionally, platelets (harvested 1 hour postdose)

from patients with CLL treated at steady state with ibrutinib (420 mg once daily) or acalabrutinib (100 mg twice daily) were compared with platelets from healthy volunteers. Results in the LTA assay showed that platelet aggregation following convulxin snake venom (CVX) stimulation in platelets from healthy volunteers was inhibited by both acalabrutinib and ibrutinib; however, there was a 7-fold difference in inhibitory activity with IC_{50} values of 0.12 μ M for ibrutinib and 0.85 μ M for acalabrutinib. The activation of tyrosine kinases is involved in the mechanism for CVX-induced platelet aggregation and the higher potency of ibrutinib is consistent with the higher potency of ibrutinib on TEC kinase in biochemical assays. At the concentrations tested (including 1 μ M), acalabrutinib and ibrutinib did not influence the platelet aggregation induced by thrombin receptor agonist peptide (TRAP-6; 15 μ M) or adenosine diphosphate (ADP; 20 μ M), which induce activation through binding of the thrombin receptor and purinergic receptors, respectively. In another experiment conducted with platelets from patients with CLL (6 patients prior to any treatment, 8 patients treated with ibrutinib, and 19 patients treated with acalabrutinib), ibrutinib treatment significantly inhibited CVX-induced aggregation, while the percentage of CVX-induced aggregation was similar in platelets from patients treated with acalabrutinib and untreated patients.

Figure 2 Convulxin-induced aggregation of platelets harvested from patients with CLL

(excerpted from study report for r2017005)

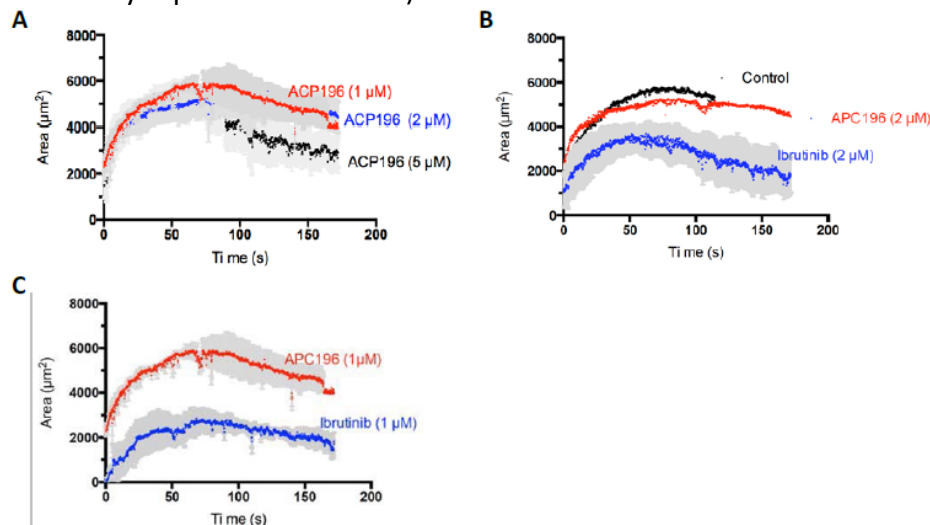


In the in vivo thrombosis model, a concentration-response in the reduction of thrombus formation was observed in platelets from healthy volunteers treated with acalabrutinib. At concentrations of 1 and 2 μ M, treatment with ibrutinib had a significantly reduced capacity to support thrombus growth compared to platelets treated with acalabrutinib (~50% reduction in maximal thrombus size). Platelets from patients with CLL treated with acalabrutinib for >1 month showed similar thrombogenic properties to the platelets of healthy volunteers, and platelets from ibrutinib-treated patients formed significantly smaller thrombi with a >40% reduction in the maximal thrombus size. Additionally, when platelets from patients with CLL treated with acalabrutinib were incubated ex vivo with ibrutinib (2 μ M), decreases in both CVX-induced aggregation and in vivo thrombus formation in the VWF^{HA1} mice were observed compared to the same platelets without ibrutinib incubation (data not shown). Based on the results of the in vitro and in vivo assays evaluating and comparing the effects of acalabrutinib

and ibrutinib on platelet function, acalabrutinib appears to have fewer effects than ibrutinib on platelets in aggregometry assays and in a humanized mouse model of thrombus formation.

Figure 3 Effect of ibrutinib vs. acalabrutinib on human platelet thrombus formation

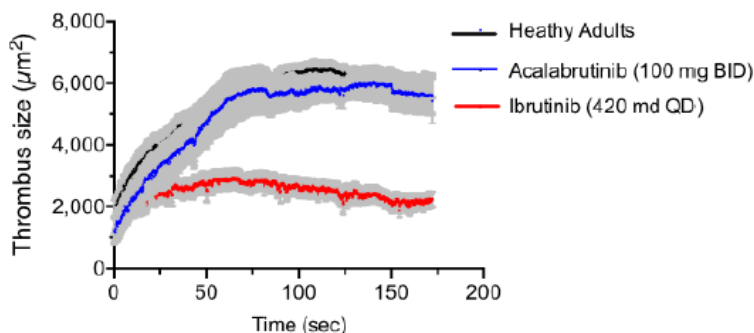
(excerpted from study report for r2017005)



Notes: (A) Thrombus during 3 minutes after laser-induced arteriole injury in the cremaster muscle of VWF^{HA1} mice. Platelets isolated from healthy adults were pre-treated with ACP-196 at the indicated concentrations prior to infusion. (B) Comparison of ACP-196 and ibrutinib treatments (2 μM) with an untreated control sample. (C) Comparison of ACP-196 and ibrutinib treatments (1 μM). Mean $\pm$ SEM ($n=5$ for each drug) are shown. The same data for ACP-196 1 μM are shown in panels A and C.

Figure 4 Pharmacodynamic properties of acalabrutinib and ibrutinib

(excerpted from study report for r2017005)



Notes: Platelets from healthy adults ($n=5$), or CLL patients on ACP-196 ($n=5$) or ibrutinib ($n=5$) were fluorescently labeled and their interactions with injured arterioles visualized by intravital microscopy. Results represent median $\pm$ SD of integrated fluorescence per μm^2 , after evaluation of a minimum of 4 arterioles per mouse. A subset of these data was published in Byrd 2016 ($n=3$ relapsed/refractory CLL patients treated with ACP-196).

Secondary Pharmacology

Acalabrutinib and ACP-5862 were evaluated in radioligand binding assays across a diverse set of 80 receptors, ion channels, and transporters. The summary data was reviewed, and $\geq 50\%$ inhibition of specific ligand binding was only observed for adenosine A2A and A3 receptors and neurokinin 2 (NK2). The K_i values were all above the observed peak clinical concentrations for

acalabrutinib and ACP-5862, indicating a low potential for physiologically relevant effects in patients treated with the intended clinical dose regimen.

Safety Pharmacology

A. Central Nervous System (CNS)

In a modified Irwin test conducted with good laboratory practice (GLP), male Sprague Dawley rats (8/group) were administered a single oral dose of acalabrutinib (30, 100, or 300 mg/kg), vehicle (0.4% hydroxypropyl methylcellulose with 0.2% Tween 80 in water), or the positive control chlorpromazine (20 mg/kg). Detailed clinical signs with CNS functional assessments including sensory, motor, and behavioral endpoints and rectal temperatures were measured at predose and 1, 2, 4, 6, and 24 hours after dosing, mortality was checked twice daily, and body weight was measured predose. Acalabrutinib had no effects on neurobehavioral function or rectal temperature following a single oral administration at doses up to 300 mg/kg.

B. Respiratory

In a GLP study, male Sprague Dawley rats (10/group) were administered a single oral dose of acalabrutinib (30, 100, or 300 mg/kg), vehicle (0.4% hydroxypropyl methylcellulose with 0.2% Tween 80 in water), or the positive control baclofen (40 mg/kg). Respiratory parameters (breathing frequency, tidal volume, minute volume, peak inspiratory flow, and peak expiratory flow) were evaluated at 30 minute intervals during the first 4 hours after dosing using head out plethysmography. Acalabrutinib had no effects on respiratory function following a single oral administration at doses up to 300 mg/kg.

C. Cardiovascular

The potential for acalabrutinib to inhibit the human ether-a-go-go related gene (hERG) potassium channel was assessed in two separate in vitro GLP studies. In one study, acalabrutinib at a concentration of 10 μ M showed an inhibition of 25.1% of the hERG tail current measured in HEK-293 cells stably transfected with hERG-1 cDNA. In the second study, the effects of acalabrutinib (1 and 10 μ M) and ACP-319 (a PI3K δ inhibitor; 1, 3, 10, and 30 μ M) both separately and in combination on the hERG tail currents were measured in CHO-K1 cells expressing the hERG channel. Acalabrutinib alone inhibited the hERG tail current by 8.2% at 1 μ M and 24.9% at 10 μ M. In the presence of acalabrutinib (10 μ M), ACP-319 inhibited the hERG tail current in a concentration dependent manner with an IC₅₀ value of 10.3 μ M for ACP-319. The IC₅₀ values for the inhibition of the hERG current for acalabrutinib were not determined in either study.

In an in vivo GLP cardiovascular assessment study, radiotelemetry-instrumented Beagle dogs (4 males) were administered single oral doses of vehicle (0.4% hydroxypropyl methylcellulose with 0.2% Tween 80 in water) and acalabrutinib (3, 10, and 30 mg/kg) per an escalating dose design with approximately 3 to 7 days between doses. Cardiovascular function assessments including heart rate, arterial blood pressure (mean, systolic, and diastolic), pulse pressure, and ECG waveforms from which ECG intervals (PR, QRS, RR, QT, and heart rate-corrected QT) were

derived and body temperature were collected continuously from approximately 1 hour prior to administration of vehicle or acalabrutinib through 24 hours after dosing. Acalabrutinib had no toxicologically-significant effects on cardiovascular function following single oral doses up to 30 mg/kg in this study.

5.4. ADME/PK

Table 8 ADME/PK

Type of Study	Major Findings																																																																																																																		
Absorption	Systemic exposures in various key studies are listed in the table below. Oral bioavailability of acalabrutinib free base in the fasted state was 62%, 21%, 53%, 9.9%, and 25% in mice, rats, dogs, monkeys and humans, respectively. T_{max} ranged from 0.25 hours to 0.5 hours in animals T_{1/2} ranged from 0.63 hours (mouse) to 2.6 hours (dog)																																																																																																																		
Distribution	<table><tr><td rowspan="10">In vitro assessment of ACP-196 protein binding in mouse, rat, dog, monkey, human plasma, human serum albumin, and α-1 acid glycoprotein; and blood cell partitioning of ACP-196 in mouse, rat, dog, monkey and human blood /Study XS-0850</td><td colspan="4">Plasma Protein Binding of Acalabrutinib</td></tr><tr><td rowspan="2">Matrix</td><td colspan="3">Protein Binding (% Bound)</td></tr><tr><td>1 μM ACP-196</td><td>3 μM ACP-196</td><td>10 μM ACP-196</td></tr><tr><td>Mouse plasma</td><td>74.9</td><td>76.3</td><td>75.0</td></tr><tr><td>Rat plasma</td><td>91.4</td><td>92.5</td><td>92.2</td></tr><tr><td>Dog plasma</td><td>62.0</td><td>72.1</td><td>71.1</td></tr><tr><td>Monkey plasma</td><td>94.4</td><td>94.3</td><td>93.9</td></tr><tr><td>Human plasma</td><td>97.4</td><td>97.9</td><td>97.3</td></tr><tr><td>Human serum albumin</td><td>93.5</td><td>93.9</td><td>93.8</td></tr><tr><td>α-1 acid glycoprotein</td><td>43.2</td><td>43.1</td><td>37.1</td></tr><tr><td colspan="5"> </td></tr><tr><td rowspan="10">In vitro assessment of ACP-5862 protein binding in mouse, rat, dog, and human plasma /Study XS-0912</td><td colspan="4">Blood Cell Partitioning of Acalabrutinib</td></tr><tr><td rowspan="2">Matrix</td><td colspan="3">Distribution into Blood Cells (%)</td></tr><tr><td>1 μM ACP-196</td><td>3 μM ACP-196</td><td>10 μM ACP-196</td></tr><tr><td>Mouse blood</td><td>57.9</td><td>54.8</td><td>55.8</td></tr><tr><td>Rat blood</td><td>34.8</td><td>24.6</td><td>29.5</td></tr><tr><td>Dog blood</td><td>49.8</td><td>53.6</td><td>45.3</td></tr><tr><td>Monkey blood</td><td>29.5</td><td>23.0</td><td>29.8</td></tr><tr><td>Human blood</td><td>26.2</td><td>23.5</td><td>29.4</td></tr><tr><td colspan="5"> </td></tr><tr><td rowspan="6">Pharmacokinetics, Distribution, Metabolism, and Excretion of [14C]ACP-196 Following Oral</td><td colspan="4">Plasma Protein Binding of ACP-5862</td></tr><tr><td rowspan="2">Matrix</td><td colspan="2">Protein Binding (% Bound)</td></tr><tr><td>1 μM ACP-5862</td><td>10 μM ACP-5862</td></tr><tr><td>Mouse plasma</td><td>98.6</td><td>98.7</td></tr><tr><td>Rat plasma</td><td>99.9</td><td>99.8</td></tr><tr><td>Dog plasma</td><td>94.6</td><td>94.0</td></tr><tr><td>Human plasma</td><td>98.7</td><td>98.6</td></tr><tr><td colspan="5"> </td></tr><tr><td colspan="5">A single dose of 100 mg/kg of [14C]acalabrutinib at a radioactive dose of 50 μCi/kg was administered orally to Long Evans rats (7 males; 1 animal/time point). Blood was collected at sacrifice at 0.5, 4, 8, 24, 48, 72, and 168 hours after dosing and carcasses were prepared for quantitative whole-body</td></tr></table>	In vitro assessment of ACP-196 protein binding in mouse, rat, dog, monkey, human plasma, human serum albumin, and α-1 acid glycoprotein; and blood cell partitioning of ACP-196 in mouse, rat, dog, monkey and human blood /Study XS-0850	Plasma Protein Binding of Acalabrutinib				Matrix	Protein Binding (% Bound)			1 μM ACP-196	3 μM ACP-196	10 μM ACP-196	Mouse plasma	74.9	76.3	75.0	Rat plasma	91.4	92.5	92.2	Dog plasma	62.0	72.1	71.1	Monkey plasma	94.4	94.3	93.9	Human plasma	97.4	97.9	97.3	Human serum albumin	93.5	93.9	93.8	α-1 acid glycoprotein	43.2	43.1	37.1						In vitro assessment of ACP-5862 protein binding in mouse, rat, dog, and human plasma /Study XS-0912	Blood Cell Partitioning of Acalabrutinib				Matrix	Distribution into Blood Cells (%)			1 μM ACP-196	3 μM ACP-196	10 μM ACP-196	Mouse blood	57.9	54.8	55.8	Rat blood	34.8	24.6	29.5	Dog blood	49.8	53.6	45.3	Monkey blood	29.5	23.0	29.8	Human blood	26.2	23.5	29.4						Pharmacokinetics, Distribution, Metabolism, and Excretion of [14C]ACP-196 Following Oral	Plasma Protein Binding of ACP-5862				Matrix	Protein Binding (% Bound)		1 μM ACP-5862	10 μM ACP-5862	Mouse plasma	98.6	98.7	Rat plasma	99.9	99.8	Dog plasma	94.6	94.0	Human plasma	98.7	98.6						A single dose of 100 mg/kg of [14C]acalabrutinib at a radioactive dose of 50 μCi/kg was administered orally to Long Evans rats (7 males; 1 animal/time point). Blood was collected at sacrifice at 0.5, 4, 8, 24, 48, 72, and 168 hours after dosing and carcasses were prepared for quantitative whole-body				
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Type of Study	Major Findings																																
Administration to Rats /Study 8338525	autoradiography. Drug related radioactivity was widely distributed at 0.5 and 4 hours after dosing with maximum concentrations occurring at these timepoints for most tissues; maximum concentrations were at 8 hours for the intra-orbital lacrimal gland, large intestine, and skin. Concentrations were still detected in the uveal tract and eye at 168 hours after dosing. Highest concentrations of radioactivity (>10000 ng equivalents [¹⁴C]acalabrutinib/g) were observed in the following tissues: <table><tr><th colspan="2">Concentrations of Radioactivity in Tissues</th></tr><tr><th>Tissue</th><th>ng equivalents [¹⁴C]acalabrutinib/g</th></tr><tr><td>Large intestine</td><td>58000</td></tr><tr><td>Liver</td><td>56900</td></tr><tr><td>Uveal tract</td><td>39500</td></tr><tr><td>Kidney cortex</td><td>27400</td></tr><tr><td>Exorbital lacrimal gland</td><td>22200</td></tr><tr><td>Intra-orbital lacrimal gland</td><td>19900</td></tr><tr><td>Kidney medulla</td><td>16500</td></tr><tr><td>Kidney</td><td>15800</td></tr><tr><td>Adrenal glands</td><td>15300</td></tr><tr><td>Cecum</td><td>12300</td></tr><tr><td>Small intestine</td><td>12200</td></tr></table>	Concentrations of Radioactivity in Tissues		Tissue	ng equivalents [¹⁴ C]acalabrutinib/g	Large intestine	58000	Liver	56900	Uveal tract	39500	Kidney cortex	27400	Exorbital lacrimal gland	22200	Intra-orbital lacrimal gland	19900	Kidney medulla	16500	Kidney	15800	Adrenal glands	15300	Cecum	12300	Small intestine	12200						
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ACP-196 (acalabrutinib) Metabolite Profiling and Identification in Rat, Dog, and Human Plasma /Study 8320562	Acalabrutinib metabolite profiles were assessed in plasma from rats (10 mg/kg iv, 6/sex and 2/time point), dogs (100 mg oral, 3 males), and humans at steady state (8 days at 100 mg BID, N=6, from Protocol ACE-CL-001). Acalabrutinib was extensively metabolized with at least 27 distinct drug-related peaks measured by LC-MS with primary metabolites representing carbon oxidation, glutathione conjugation, amide hydrolysis, <i>N</i>-dealkylation, and alkyne hydration. Pyrrolidine oxidation appears to be the major metabolic pathway. Acalabrutinib underwent oxidation in the pyrrolidine moiety to produce metabolite M27 (also known as ACP-5862), and M27 was the predominant metabolite in human, rat, and dog.																																
Table information from Pharmacokinetic Written Summary; Source: Studies 8340639, ACE-HV-113, and 17-RS-426CL	Cross-species comparison of Total Exposure to Acalabrutinib and Major Metabolite CP-5862 following a Single Oral Dose <table><tr><th rowspan="2">Species, Sex</th><th rowspan="2">Dose</th><th colspan="2">Acalabrutinib (Parent)</th><th colspan="2">ACP-5862 (Metabolite)</th><th rowspan="2">AUC Ratio (M/P)</th></tr><tr><th>C_{max} (ng/mL)</th><th>AUC_{0-t} (ng·h/mL)</th><th>C_{max} (ng/mL)</th><th>AUC_{0-t} (ng·h/mL)</th></tr><tr><td>Rat, male</td><td>100 mg/kg</td><td>1790</td><td>4570</td><td>3510</td><td>23300</td><td>4.93</td></tr><tr><td>Rat, female</td><td>100 mg/kg</td><td>4110</td><td>6070</td><td>3770</td><td>22600</td><td>3.57</td></tr><tr><td>Dog, male</td><td>30 mg/kg</td><td>6830</td><td>17800</td><td>797</td><td>2350</td><td>0.10</td></tr></table>	Species, Sex	Dose	Acalabrutinib (Parent)		ACP-5862 (Metabolite)		AUC Ratio (M/P)	C _{max} (ng/mL)	AUC _{0-t} (ng·h/mL)	C _{max} (ng/mL)	AUC _{0-t} (ng·h/mL)	Rat, male	100 mg/kg	1790	4570	3510	23300	4.93	Rat, female	100 mg/kg	4110	6070	3770	22600	3.57	Dog, male	30 mg/kg	6830	17800	797	2350	0.10
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NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}

Type of Study	Major Findings																										
	<table><tr><td>Dog, female</td><td>30 mg/kg</td><td>8370</td><td>19300</td><td>1310</td><td>3750</td><td>0.19</td></tr><tr><td>Human</td><td>100 mg</td><td>601</td><td>734</td><td>443</td><td>1670</td><td>2.7</td></tr></table> M/P= Metabolite/Parent; AUC ratio values were adjusted for molecular weight of parent (465.5) and metabolite (481.5) 100 mg/kg	Dog, female	30 mg/kg	8370	19300	1310	3750	0.19	Human	100 mg	601	734	443	1670	2.7												
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Pharmacokinetics, Distribution, Metabolism, and Excretion of [¹⁴ C]ACP-196 Following Oral Administration to Rats /Study 8338525	A single dose of 100 mg/kg of [¹⁴C]acalabrutinib at a radioactive dose of 50 μCi/kg was administered orally to Sprague Dawley rats (3/sex). Urine was collected from each animal at 0-8 and 8-24 hours and at 24-hour intervals through 96 hours after dosing; feces were collected at 24-hour intervals through 96 hours after dosing; carcasses were retained for radioanalysis. The main route of elimination for drug-related radioactivity was via feces; fecal elimination was essentially complete by 48 hours after dosing. Elimination of Radioactivity in Rats <table><tr><th rowspan="2">Sample</th><th colspan="2">% of Radioactive Dose (Mean)</th></tr><tr><th>Males</th><th>Females</th></tr><tr><td>Urine</td><td>2.70</td><td>3.61</td></tr><tr><td>Feces</td><td>91.2</td><td>88.3</td></tr><tr><td>Cage Rinse</td><td>0.246</td><td>0.820</td></tr><tr><td>Cage Wash</td><td>1.83</td><td>0.312</td></tr><tr><td>Cage Wipe</td><td>0.112</td><td>0.323</td></tr><tr><td>Carcass (residual)</td><td>0.667</td><td>0.992</td></tr><tr><td>Total</td><td>96.8</td><td>94.3</td></tr></table>	Sample	% of Radioactive Dose (Mean)		Males	Females	Urine	2.70	3.61	Feces	91.2	88.3	Cage Rinse	0.246	0.820	Cage Wash	1.83	0.312	Cage Wipe	0.112	0.323	Carcass (residual)	0.667	0.992	Total	96.8	94.3
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Absorption, Metabolism, and Excretion of [¹⁴ C]ACP-196 Following Oral Administration to Dogs /Study 8338526	A single dose of 30 mg/kg of [¹⁴C]acalabrutinib at a radioactive dose of 10 μCi/kg was administered orally to Beagle dogs (3/sex). Urine was collected from each animal predose, 0-4, 4-8, and 8-24 hours, and at 24-hour intervals through 96 hours after dosing; feces were collected predose and at 24-hour intervals through 96 hours after dosing. Elimination of radioactivity was rapid and essentially complete by 48 hours after dosing. The main route of elimination for drug-related radioactivity was via feces. Elimination of Radioactivity in Dogs <table><tr><th rowspan="2">Sample</th><th colspan="2">% of Radioactive Dose (Mean)</th></tr><tr><th>Males</th><th>Females</th></tr><tr><td>Urine</td><td>15.2</td><td>14.6</td></tr><tr><td>Feces</td><td>71.8</td><td>69.3</td></tr><tr><td>Cage Rinse</td><td>2.53</td><td>1.63</td></tr><tr><td>Cage Wash</td><td>0.0966</td><td>0.125</td></tr><tr><td>Cage Wipe</td><td>0.754</td><td>1.25</td></tr><tr><td>Cage Debris</td><td>0.615</td><td>0.648</td></tr><tr><td>Total</td><td>91.1</td><td>87.5</td></tr></table>	Sample	% of Radioactive Dose (Mean)		Males	Females	Urine	15.2	14.6	Feces	71.8	69.3	Cage Rinse	2.53	1.63	Cage Wash	0.0966	0.125	Cage Wipe	0.754	1.25	Cage Debris	0.615	0.648	Total	91.1	87.5
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Urine	15.2	14.6																									
Feces	71.8	69.3																									
Cage Rinse	2.53	1.63																									
Cage Wash	0.0966	0.125																									
Cage Wipe	0.754	1.25																									
Cage Debris	0.615	0.648																									
Total	91.1	87.5																									
TK data from general toxicology studies																											
26-Week Oral Toxicity Study in Rats with a 4-Week Recovery Period /Study 2219-084	Peak acalabrutinib plasma concentrations (T_{max}) were observed at 0.25 to 0.5 hours after dosing. T_{1/2} values were not calculated/reported. Exposures (C_{max} and AUC_{0-24hr}) were greater in females than males (female:male ratios ranging from 1.18 to 2.31). Summary of Toxicokinetic Values in 26-Weeks Study in Rats <table><tr><th>Dose</th><th>Day</th><th>C_{max} (ng/mL)</th><th>AUC_{0-24hr} (hr·ng/mL)</th></tr></table>	Dose	Day	C _{max} (ng/mL)	AUC _{0-24hr} (hr·ng/mL)																						
Dose	Day	C _{max} (ng/mL)	AUC _{0-24hr} (hr·ng/mL)																								

Type of Study	Major Findings						
	(mg/kg/day)						
			Males	Females	Males	Females	
	30	1	948	1190	1250	2320	
		28	841	1330	1300	2260	
		91	1120	1370	1200	1720	
		182	763	1640	1150	2010	
	100	1	1470	2590	4280	9890	
		28	2900	4000	5160	8520	
		91	4160	6740	8130	10400	
		182	2510	3820	4760	8130	
	300/200*	1	3070	6050	16200	26000	
		28	4180	6370	11600	17000	
		91	5690	7380	13300	15700	
		182	3110	6920	7930	13000	
	300 mg/kg/day on Day 1 and 200 mg/kg/day on Days 28, 91, and 182						
	91-Day Oral Capsule Toxicity Study in Dogs with a 28-Day Recovery Period /Study 2219-030	Individual peak acalabrutinib plasma concentrations (T _{max}) ranged from 0.5 to 8 hours after dosing with the median T _{max} values of 1 to 1.26 hours. T _{1/2} values were not calculated/reported.					
		Summary of Toxicokinetic Values in 26-Weeks Study in Rats					
Dose (mg/kg/day)		Day	C _{max} (ng/mL)		AUC _{0-24hr} (hr·ng/mL)		
			Males	Females	Males	Females	
5		1	998	890	1990	1800	
		29	883	807	1650	1860	
		58	584	691	1390	1470	
		90	623	454	1350	1200	
10		1	1880	1910	3600	4030	
		29	1890	1470	3790	3280	
		58	1120	1020	2410	2170	
		90	762	1230	2380	3280	
30		1	9320	6640	19500	17400	
		29	5400	2540	14300	5770	
		58	6070	731	14200	2280	
		90	4720	2660	10900	6890	
TK data from reproductive toxicology studies							
Fertility and embryo-fetal development in rats /Study 2219-088	TK parameters for fertility in males						
	Dose (mg/kg/day)	Day	C _{max} (ng/mL)		AUC _{0-24hr} (hr·ng/mL)		
	300	1	1840		16300		
		28	5670		19900*		
	TK parameters for fertility and embryo-fetal development in females						
	Dose (mg/kg/day)	GD Day	C _{max} (ng/mL)	AUC _{Tlast} (hr·ng/mL)	AUC _{0-24hr} (hr·ng/mL)		
	30	6	1380	1990	2030		
		17	861	1680	-		
	100	6	5310	10000	10000		
		17	3760	6830	6830		
	200	6	4170	15900	15900		
		17	6650	17500	17500*		
	GD=Gestational Day *: exposure at NOAEL, value used for comparison in label						

Type of Study	Major Findings																																																																										
Embryo-fetal development in rabbits /Study 2219-075	TK for embryo-fetal development in rabbits <table><tr><th>Dose (mg/kg/day)</th><th>GD Day</th><th>C_{max} (ng/mL)</th><th>AUC_{Tlast} (hr·ng/mL)</th><th>AUC_{0-24hr} (hr·ng/mL)</th></tr><tr><td rowspan="2">50</td><td>6</td><td>1600</td><td>2400</td><td>2400</td></tr><tr><td>18</td><td>1620</td><td>2010</td><td>2030</td></tr><tr><td rowspan="2">100</td><td>6</td><td>3650</td><td>6450</td><td>6450</td></tr><tr><td>18</td><td>3470</td><td>4580</td><td>4580*</td></tr><tr><td rowspan="2">200</td><td>6</td><td>6910</td><td>14800</td><td>14800</td></tr><tr><td>18</td><td>3380</td><td>17800</td><td>17800</td></tr></table> GD=Gestational Day *: exposure used for comparison in label	Dose (mg/kg/day)	GD Day	C _{max} (ng/mL)	AUC _{Tlast} (hr·ng/mL)	AUC _{0-24hr} (hr·ng/mL)	50	6	1600	2400	2400	18	1620	2010	2030	100	6	3650	6450	6450	18	3470	4580	4580*	200	6	6910	14800	14800	18	3380	17800	17800																																										
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Pharmacokinetic analysis of acalabrutinib and metabolite ACP-5862 in pilot pre- and postnatal development study/Report R2017011 for Study 2219-109	Acalabrutinib administered orally to pregnant female rats from GD 6 through delivery until lactation day (LD) 12. Maternal and fetal plasma concentrations on GD 18 <table><tr><th rowspan="2">Dose (mg/kg/day)</th><th rowspan="2">Measure</th><th colspan="2">Concentration (ng/mL)</th></tr><tr><th>Maternal plasma</th><th>Fetal plasma</th></tr><tr><td rowspan="2">100</td><td>ACP-196</td><td>946</td><td>381</td></tr><tr><td>ACP-5862</td><td>628</td><td>11.8</td></tr><tr><td rowspan="2">200</td><td>ACP-196</td><td>3720</td><td>1500</td></tr><tr><td>ACP-5862</td><td>1280</td><td>29.1</td></tr><tr><td rowspan="2">300</td><td>ACP-196</td><td>4370</td><td>2110</td></tr><tr><td>ACP-5862</td><td>1610</td><td>58.1</td></tr></table> GD=Gestational Day Maternal and fetal plasma concentrations on LD 18 <table><tr><th rowspan="3">Dose (mg/kg/day)</th><th rowspan="3">Measure</th><th colspan="4">Concentration (ng/mL)</th></tr><tr><th colspan="2">Maternal plasma</th><th>Maternal milk</th><th>Pup plasma</th></tr><tr><th>1 hr</th><th>3 hr</th><th>3 hr</th><th>1 hr</th></tr><tr><td rowspan="2">100</td><td>ACP-196</td><td>252</td><td>125</td><td>1460</td><td>1.11</td></tr><tr><td>ACP-5862</td><td>168</td><td>98.4</td><td>1610</td><td>6.35</td></tr><tr><td rowspan="2">200</td><td>ACP-196</td><td>2090</td><td>719</td><td>2530</td><td>1.44</td></tr><tr><td>ACP-5862</td><td>1080</td><td>409</td><td>2500</td><td>18.2</td></tr><tr><td rowspan="2">300</td><td>ACP-196</td><td>2130</td><td>913</td><td>5050</td><td>8.45</td></tr><tr><td>ACP-5862</td><td>1210</td><td>435</td><td>3160</td><td>20.9</td></tr></table>	Dose (mg/kg/day)	Measure	Concentration (ng/mL)		Maternal plasma	Fetal plasma	100	ACP-196	946	381	ACP-5862	628	11.8	200	ACP-196	3720	1500	ACP-5862	1280	29.1	300	ACP-196	4370	2110	ACP-5862	1610	58.1	Dose (mg/kg/day)	Measure	Concentration (ng/mL)				Maternal plasma		Maternal milk	Pup plasma	1 hr	3 hr	3 hr	1 hr	100	ACP-196	252	125	1460	1.11	ACP-5862	168	98.4	1610	6.35	200	ACP-196	2090	719	2530	1.44	ACP-5862	1080	409	2500	18.2	300	ACP-196	2130	913	5050	8.45	ACP-5862	1210	435	3160	20.9
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5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: ACP-196: A 26-Week Oral Toxicity Study in Rats with a 4-Week Recovery Period/ 2219-084

Key Study Findings

- Mortality was observed at 300 mg/kg/day during the first 2 weeks of treatment and the highest dose was decreased to 200 mg/kg/day. Additional mortality was observed in animals treated with 300/200 mg/kg/day following the dose

reduction. The causes of mortality were uremia/acute kidney failure and myocardial necrosis.

- Organs of toxicity of acalabrutinib in surviving animals included the kidney, liver, lung, mesenteric lymph node, and pancreas.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 20, 100, or 300/200* mg/kg/day once daily for 26 weeks; 4-week recovery period

*Animals in the 300 mg/kg/day group were placed on a 4-day dose holiday starting on Day 10 (main study females and all toxicokinetics animals) or Day 11 (main study males), then the dose was lowered to 200 mg/kg/day starting on Day 14 or Day 15, respectively

Route of administration:

Oral gavage

Formulation/Vehicle:

(b) (4)% (b) (4) (w:v) and (b) (4)% (b) (4) w:v in NANOPure

Diamond Ultrapure water

Species/Strain:

Rat/Wistar Han

Number/Sex/Group:

Main Study: 16/sex/group

Recovery: 6/sex/group

Age:

~5.5 weeks at receipt

Satellite groups/ unique design:

Toxicokinetics: 6/sex for 0 mg/kg/day group and 14/sex/day for 20, 100, and 300/200 mg/kg/day groups

Deviation from study protocol

No

affecting interpretation of results:

Animals found dead or euthanized *in extremis* during the first 17 days of the study were replaced. According to the methods section, a total of 9 rats were used as replacement animals and according to the morality results section, a total of 7 animals were replaced including 1 male prior to initiation of dosing and 6 females at 300 mg/kg/day (5 main study and 1 toxicokinetic).

Table 9 Observations and Results: changes from control

Parameters	Major findings
Mortality	300 mg/kg/day: 6 females (5 in main study and 1 toxicokinetic animal) were found dead or euthanized <i>in extremis</i> during the replacement period (on Days 8, 10, or 13 in the main study animals).

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	300/200 mg/kg/day: 11 animals treated (6 main study females and 5 toxicokinetic animals (4 male and 1 female) were found dead (n=10) or euthanized <i>in extremis</i> (n=1) after the dose reduction to 200 mg/kg/day. Cause of death in main study animals was uremia/acute kidney failure/myocardial necrosis.																																																																																																																			
Clinical Signs	In animals with mortality at 300/200 mg/kg/day: Decreased activity, rapid or difficulty breathing, ataxia, hunched posture, pale skin, discolored skin, skin cold to touch, thin, vocalization, and/or hypersensitive to touch All doses: Salivation																																																																																																																			
Body Weights	300 mg/kg/day: Body weight loss (↓ up to 7.2% compared to Day 1) in main study females with mortality and replaced																																																																																																																			
Ophthalmoscopy	<table><tr><th colspan="9">Incidence of ophthalmic exam findings at end of dosing period</th></tr><tr><th rowspan="3">Finding</th><th colspan="4">Males</th><th colspan="4">Females</th></tr><tr><th colspan="4">Dose level (mg/kg/day)</th><th colspan="4">Dose level (mg/kg/day)</th></tr><tr><th>0</th><th>30</th><th>100</th><th>300/200</th><th>0</th><th>30</th><th>100</th><th>300/200</th></tr><tr><td colspan="9">End of dosing exam</td></tr><tr><td>Number examined</td><td>22</td><td>22</td><td>22</td><td>22</td><td>22</td><td>22</td><td>22</td><td>16</td></tr><tr><td>Uveitis, right eye</td><td>-</td><td>1</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td></tr><tr><td>Retinal atrophy, left eye</td><td>-</td><td>-</td><td>2</td><td>-</td><td>-</td><td>2</td><td>2</td><td>-</td></tr><tr><td>Retinal atrophy, right eye</td><td>-</td><td>-</td><td>1</td><td>-</td><td>-</td><td>2</td><td>2</td><td>-</td></tr><tr><td colspan="9">Recovery exam</td></tr><tr><td>Number examined</td><td>6</td><td>6</td><td>6</td><td>6</td><td>6</td><td>6</td><td>6</td><td>6</td></tr><tr><td>Retinal atrophy, right eye</td><td>-</td><td>-</td><td>1</td><td>-</td><td>-</td><td>1</td><td>1</td><td>-</td></tr><tr><td>Retinal atrophy, right eye</td><td>-</td><td>-</td><td>1</td><td>-</td><td>-</td><td>1</td><td>1</td><td>-</td></tr></table> - = no test-article related changes	Incidence of ophthalmic exam findings at end of dosing period									Finding	Males				Females				Dose level (mg/kg/day)				Dose level (mg/kg/day)				0	30	100	300/200	0	30	100	300/200	End of dosing exam									Number examined	22	22	22	22	22	22	22	16	Uveitis, right eye	-	1	-	-	-	-	-	-	Retinal atrophy, left eye	-	-	2	-	-	2	2	-	Retinal atrophy, right eye	-	-	1	-	-	2	2	-	Recovery exam									Number examined	6	6	6	6	6	6	6	6	Retinal atrophy, right eye	-	-	1	-	-	1	1	-	Retinal atrophy, right eye	-	-	1	-	-	1	1	-
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Hematology	<table><tr><th colspan="8">% Mean differences vs. concurrent controls</th></tr><tr><th rowspan="3">Parameter</th><th rowspan="3">Time point</th><th colspan="3">Males</th><th colspan="3">Females</th></tr><tr><th colspan="3">Dose level (mg/kg/day)</th><th colspan="3">Dose level (mg/kg/day)</th></tr><tr><th>30</th><th>100</th><th>300/200</th><th>30</th><th>100</th><th>300/200</th></tr><tr><td rowspan="2">Lymphocytes</td><td>Week 5</td><td>-</td><td>-</td><td>↑13%</td><td>-</td><td>-</td><td>↑35%</td></tr><tr><td>Week 13</td><td>-</td><td>-</td><td>↑11%</td><td>-</td><td>-</td><td>↑38%</td></tr><tr><td rowspan="3">Monocytes</td><td>Week 5</td><td>↑14%</td><td>-</td><td>↑22%</td><td>↑14%</td><td>↑24%</td><td>↑52%</td></tr><tr><td>Week 13</td><td>↑18%</td><td>-</td><td>↑22%</td><td>↑22%</td><td>↑18%</td><td>↑63%</td></tr><tr><td>Terminal</td><td>-</td><td>↑15%</td><td>↑32%</td><td>↑36%</td><td>↑60%</td><td>↑51%</td></tr></table>	% Mean differences vs. concurrent controls								Parameter	Time point	Males			Females			Dose level (mg/kg/day)			Dose level (mg/kg/day)			30	100	300/200	30	100	300/200	Lymphocytes	Week 5	-	-	↑13%	-	-	↑35%	Week 13	-	-	↑11%	-	-	↑38%	Monocytes	Week 5	↑14%	-	↑22%	↑14%	↑24%	↑52%	Week 13	↑18%	-	↑22%	↑22%	↑18%	↑63%	Terminal	-	↑15%	↑32%	↑36%	↑60%	↑51%																																																		
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Clinical Chemistry	In animal with mortality at 300/200 mg/kg/day: The female euthanized early <i>in extremis</i> on Day 97 had marked increases in urea nitrogen, creatinine, potassium, and phosphorus with moderate decreases in sodium, chloride, and total protein; these findings indicate severe renal insufficiency and injury and correlated with tubular degeneration/necrosis in the kidney. Group data: <table><tr><th colspan="7">% Mean differences vs. concurrent controls at Week 2</th></tr><tr><th rowspan="3">Parameter</th><th colspan="3">Males</th><th colspan="3">Females</th></tr><tr><th colspan="3">Dose level (mg/kg/day)</th><th colspan="3">Dose level (mg/kg/day)</th></tr><tr><th>30</th><th>100</th><th>300/200</th><th>30</th><th>100</th><th>300/200</th></tr></table>	% Mean differences vs. concurrent controls at Week 2							Parameter	Males			Females			Dose level (mg/kg/day)			Dose level (mg/kg/day)			30	100	300/200	30	100	300/200																																																																																									
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	<table><tr><td>Triglycerides</td><td>-</td><td>↓21%</td><td>↓39%</td><td>-</td><td>↓12%</td><td>↓51%</td></tr><tr><td>Total bilirubin</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑84%</td></tr><tr><td>GGT</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑67%</td></tr><tr><td>AST</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑85%</td></tr><tr><td>ALT</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑134%</td></tr><tr><td>Urea nitrogen</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑49%</td></tr><tr><td>Creatinine</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑73%</td></tr></table>	Triglycerides	-	↓21%	↓39%	-	↓12%	↓51%	Total bilirubin	-	-	-	-	-	↑84%	GGT	-	-	-	-	-	↑67%	AST	-	-	-	-	-	↑85%	ALT	-	-	-	-	-	↑134%	Urea nitrogen	-	-	-	-	-	↑49%	Creatinine	-	-	-	-	-	↑73%
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Creatinine	-	-	-	-	-	↑73%																																												
Urinalysis	Unremarkable																																																	
Gross Pathology	300/200 mg/kg/day: White foci in the lungs observed in 2 males and 1 female at main study necropsy and 1 male at the recovery necropsy																																																	
Organ Weights	<table><tr><th colspan="4">% Mean difference relative to body weight vs. concurrent controls</th></tr><tr><th rowspan="3">Organ</th><th colspan="3">Females</th></tr><tr><th colspan="3">Dose level (mg/kg/day)</th></tr><tr><th>30</th><th>100</th><th>300/200</th></tr><tr><td colspan="4">Kidneys</td></tr><tr><td>Main Study: % difference</td><td>-</td><td>↑14%</td><td>↑14%</td></tr><tr><td>Recovery: % difference</td><td>-</td><td>-</td><td>↑20%</td></tr></table>	% Mean difference relative to body weight vs. concurrent controls				Organ	Females			Dose level (mg/kg/day)			30	100	300/200	Kidneys				Main Study: % difference	-	↑14%	↑14%	Recovery: % difference	-	-	↑20%																							
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Kidneys																																																		
Main Study: % difference	-	↑14%	↑14%																																															
Recovery: % difference	-	-	↑20%																																															
Histopathology Adequate battery:	Yes In females with mortality at 300/200 mg/kg/day: Findings observed in kidney (subacute/chronic inflammation, tubular mineralization, and tubular degeneration/necrosis), heart (hemorrhage/inflammation/necrosis and vascular mineralization), and liver (degeneration/necrosis of individual hepatocyte and increased mitotic figures) Surviving animals: See histopathology table below																																																	
T-cell Dependent Antibody Response (TDAR) Evaluation	Anti-KLH IgM: Overall (all time points combined) responses ↓ 41-68% in males and females at all doses compared to controls Anti-KLH IgG: Responses ↓ 36-57% in females at 100 and 300/200 mg/kg/day on Days 57 and 64 compared to controls																																																	

Table 10 Histopathology Changes in Surviving Animals in 26-week Toxicology Study in Rats

Treatment-Related Microscopic Findings			No. of animals affected (main/recovery)							
			Males				Females			
Dose (mg/kg/day)			0	30	100	300/200	0	30	100	300/200
Number of animals examined			16/6	16/6	16/6	16/6	16/6	16/6	16/6	10/6
Organ	Finding									
Eyes	Unilateral degeneration/atrophy of retina	Minimal	-	1/0	1/0	-	-	-	-	-
	Erosion	Minimal	-	-	-	1/0	-	-	-	-
Kidneys	Basophilic tubules	Total	2/1	2/0	2/1	4/1	2/0	3/0	8/1	7/3
		Minimal	2/1	2/0	2/1	4/1	2/0	3/0	6/1	5/1
		Mild	-	-	-	-	-	-	1/0	1/1
		Moderate	-	-	-	-	-	-	1/0	1/1
	Subacute/chronic inflammation	Total	-	-	-	-	-	-	4/0	1/1
		Minimal	-	-	-	-	-	-	3/0	0/1
		Mild	-	-	-	-	-	-	1/0	1/0
	Tubular degeneration/necrosis	Total	-	-	-	-	-	-	3/0	-
		Minimal	-	-	-	-	-	-	2/0	-
		Mild	-	-	-	-	-	-	1/0	-

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Treatment-Related Microscopic Findings			No. of animals affected (main/recovery)							
			Males				Females			
Dose (mg/kg/day)			0	30	100	300/200	0	30	100	300/200
Number of animals examined			16/6	16/6	16/6	16/6	16/6	16/6	16/6	10/6
Organ	Finding									
Liver	Increased mitotic figures	Minimal	-	-	-	-	-	-	-	2/0
	Individual hepatocyte degeneration/necrosis	Total	-	-	-	2/0	-	-	4/0	4/0
		Minimal	-	-	-	-	-	-	2/0	4/0
		Mild	-	-	-	2/0	-	-	2/0	-
Lung	Vacuolated macrophages	Minimal	-	2/0	1/0	2/0	-	1/0	1/0	1/0
Mesenteric lymph node	Erythrocytosis/erythrophagocytosis, sinus	Total	0/1	3/0	5/0	6/0	1/0	5/0	5/0	4/2
		Minimal	-	2/0	4/0	6/0	1/0	5/0	5/0	2/1
		Mild	-	1/0	-	-	-	-	-	1/1
		Moderate	0/1	-	1/0	-	-	-	-	1/0
Pancreas	Acinar atrophy	Total	0/1	8/2	6/1	9/0	1/0	1/0	-	1/0
		Minimal	0/1	8/2	5/1	6/0	1/0	1/0	-	1/0
		Mild	-	-	1/0	3/0	-	-	-	-
	Hemorrhage/pigment/inflammation/fibrosis of islets	Total	1/0	12/0	12/0	12/0	-	-	-	-
		Minimal	1/0	7/0	7/0	5/0	-	-	-	-
		Mild	-	3/0	5/0	6/0	-	-	-	-
		Moderate	-	2/0	-	1/0	-	-	-	-
	Fibrosis	Minimal	-	0/1	0/2	0/2	-	-	-	-
		Total	-	6/0	6/0	5/0	-	-	1/0	1/0
		Minimal	-	5/0	6/0	5/0	-	-	1/0	1/0
		Mild	-	1/0	-	-	-	-	-	-
	Mononuclear cell infiltration	Minimal	-	0/1	-	-	-	-	-	-
	Pigmented macrophages	Minimal	-	0/3	0/5	0/3	-	-	-	-

- = no test-article related changes

Study title/ number: ACP-196: A 91-Day Oral Capsule Toxicity Study in Dogs with a 28-Day Recovery Period/ 2219-030

Key Study Findings

- At the highest dose of 30 mg/kg/day, one female had increases in clinical chemistry parameters (ALT, alkaline phosphatase, urea nitrogen, and creatinine) and clinical signs that led to a 1-week dosing interruption of acalabrutinib (Days 46-52) in this animal. Dosing was resumed at 30 mg/kg/day and the animal finished the study.
- Organs of toxicity of acalabrutinib included the gut-associated lymphoid tissue (GALT), kidney, liver, mandibular and mesenteric lymph nodes, spleen, and thyroid/parathyroid.

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

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Dose and frequency of dosing: 0, 5, 10, or 30 mg/kg/day once daily for 91 days;
28-day recovery period

Due to veterinary observations, one female at 30 mg/kg/day (Animal # 149) was not dosed for a 1 week period on Days 46-52.

Route of administration:

Oral capsules

Formulation/Vehicle:

(b) (4) gelatin capsules; empty capsules
used as control

Species/Strain:

Dog/Beagle

Number/Sex/Group:

Main Study: 5/sex/group

Recovery: 3/sex/group

Age:

5-6 months at receipt

Satellite groups/ unique design:

None

Deviation from study protocol

No

affecting interpretation of results:

Table 11 Observations and Results: changes from control

Parameters	Major findings																																																																																							
Mortality	None																																																																																							
Clinical Signs	Female at 30 mg/kg/day with dose interruption: Clinical signs included excessive shedding (Weeks 5-7), hair sparse (entire body and/or face; Weeks 5-7), hunched posture (Weeks 9-13), thin (Weeks 5-13), and unkempt appearance (Weeks 5-13); veterinary observations (details not provided) lead to the dose interruption																																																																																							
Body Weights	Females at all doses: ↓ mean body weight compared to controls beginning ~Day 42; body weight ↓ 7%, 16%, and 10% at 5, 10, and 30 mg/kg/day, respectively, on Day 91																																																																																							
Food Consumption	Females at all doses: ↓ mean food consumption starting ~Week 3; food consumption ↓ 14%, 14%, and 19% at 5, 10, and 30 mg/kg/day, respectively, at Week 13																																																																																							
Ophthalmoscopy	Unremarkable																																																																																							
ECG	Unremarkable																																																																																							
Hematology	<table><tr><th colspan="8">% Mean differences vs. concurrent controls</th></tr><tr><th rowspan="3">Parameter</th><th rowspan="3">Time point</th><th colspan="3">Males</th><th colspan="3">Females</th></tr><tr><th colspan="3">Dose level (mg/kg/day)</th><th colspan="3">Dose level (mg/kg/day)</th></tr><tr><th>5</th><th>10</th><th>30</th><th>5</th><th>10</th><th>30</th></tr><tr><td rowspan="3">Erythrocytes</td><td>Day 58</td><td>-</td><td>↓7%</td><td>↓10%</td><td>-</td><td>-</td><td>↓10 %</td></tr><tr><td>Terminal</td><td>-</td><td>↓8%</td><td>↓15%</td><td>-</td><td>↓9%</td><td>↓12 %</td></tr><tr><td>Recovery</td><td>-</td><td>-</td><td>↓7%</td><td>-</td><td>↓11%</td><td>↓12 %</td></tr><tr><td rowspan="3">Hemoglobin</td><td>Day 58</td><td>-</td><td>↓7%</td><td>↓8%</td><td>-</td><td>-</td><td>↓7%</td></tr><tr><td>Terminal</td><td>-</td><td>↓8%</td><td>↓12%</td><td>-</td><td>↓6%</td><td>↓6%</td></tr><tr><td>Recovery</td><td>-</td><td>-</td><td>↓5%</td><td>-</td><td>↓8%</td><td>↓8%</td></tr><tr><td rowspan="2">Hematocrit</td><td>Day 58</td><td>-</td><td>↓6%</td><td>↓5%</td><td>-</td><td>-</td><td>↓5%</td></tr><tr><td>Terminal</td><td>-</td><td>↓8%</td><td>↓9%</td><td>-</td><td>↓6%</td><td>↓5%</td></tr></table>	% Mean differences vs. concurrent controls								Parameter	Time point	Males			Females			Dose level (mg/kg/day)			Dose level (mg/kg/day)			5	10	30	5	10	30	Erythrocytes	Day 58	-	↓7%	↓10%	-	-	↓10 %	Terminal	-	↓8%	↓15%	-	↓9%	↓12 %	Recovery	-	-	↓7%	-	↓11%	↓12 %	Hemoglobin	Day 58	-	↓7%	↓8%	-	-	↓7%	Terminal	-	↓8%	↓12%	-	↓6%	↓6%	Recovery	-	-	↓5%	-	↓8%	↓8%	Hematocrit	Day 58	-	↓6%	↓5%	-	-	↓5%	Terminal	-	↓8%	↓9%	-	↓6%	↓5%
% Mean differences vs. concurrent controls																																																																																								
Parameter	Time point	Males			Females																																																																																			
		Dose level (mg/kg/day)			Dose level (mg/kg/day)																																																																																			
		5	10	30	5	10	30																																																																																	
Erythrocytes	Day 58	-	↓7%	↓10%	-	-	↓10 %																																																																																	
	Terminal	-	↓8%	↓15%	-	↓9%	↓12 %																																																																																	
	Recovery	-	-	↓7%	-	↓11%	↓12 %																																																																																	
Hemoglobin	Day 58	-	↓7%	↓8%	-	-	↓7%																																																																																	
	Terminal	-	↓8%	↓12%	-	↓6%	↓6%																																																																																	
	Recovery	-	-	↓5%	-	↓8%	↓8%																																																																																	
Hematocrit	Day 58	-	↓6%	↓5%	-	-	↓5%																																																																																	
	Terminal	-	↓8%	↓9%	-	↓6%	↓5%																																																																																	

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		Recovery	-	-	↓4%	-	↓8%	↓8%																																		
	MCV	Day 58	-	-	↑6%	-	↑4%	↑6%																																		
		Terminal	-	-	↑7%	-	↑4%	↑8%																																		
	Reticulocyte s (absolute)	Terminal	-	-	↑84%	-	-	↑22 %																																		
		Day 58	-	-	↑60%	-	↑20%	↑16 %																																		
Clinical Chemistry	Individual females at 30 mg/kg/day: On Day 29, ↑ ALT observed in 2 females (Animal # 149: ↑ 8.6-fold compared to baseline; Animal # 152: ↑ 4.4-fold compared to baseline). Animal #149 developed clinical signs and special collections were conducted on Days 43, 48, and 52. On Day 43, increases in ALT (↑ 13-fold), cholesterol (↑2-fold), alkaline phosphatase (↑ 3.5-fold), urea nitrogen (↑7-fold), and creatinine (↑5-fold) were observed compared to baseline. Findings were resolved by Days 52 and 58 following the dosing holiday (Days 46-52) and supportive care.																																									
Urinalysis	Unremarkable																																									
Gross Pathology	Unremarkable																																									
Organ Weights	<table><tr><th colspan="5">% Mean difference vs. concurrent controls</th></tr><tr><th rowspan="3">Organ</th><th rowspan="3">Weight</th><th colspan="3">Males</th></tr><tr><th colspan="3">Dose level (mg/kg/day)</th></tr><tr><th>5</th><th>10</th><th>30</th></tr><tr><td rowspan="2">Spleen (% difference)</td><td>Absolute</td><td>-</td><td>-</td><td>↓29%</td></tr><tr><td>Relative: body weight</td><td>-</td><td>-</td><td>↓29%</td></tr><tr><td rowspan="2">Thyroid/ parathyroid (% difference)</td><td>Absolute</td><td>↑25%</td><td>↑36%</td><td>↑26%</td></tr><tr><td>Relative: body weight</td><td>↑27%</td><td>↑24%</td><td>↑24%</td></tr></table>								% Mean difference vs. concurrent controls					Organ	Weight	Males			Dose level (mg/kg/day)			5	10	30	Spleen (% difference)	Absolute	-	-	↓29%	Relative: body weight	-	-	↓29%	Thyroid/ parathyroid (% difference)	Absolute	↑25%	↑36%	↑26%	Relative: body weight	↑27%	↑24%	↑24%
% Mean difference vs. concurrent controls																																										
Organ	Weight	Males																																								
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	Relative: body weight	-	-	↓29%																																						
Thyroid/ parathyroid (% difference)	Absolute	↑25%	↑36%	↑26%																																						
	Relative: body weight	↑27%	↑24%	↑24%																																						
Histopathology Adequate battery:	Yes Microscopic findings were observed in GALT, kidneys, mandibular lymph node, mesenteric lymph node, and spleen. See histopathology table below for details.																																									
Platelet Aggregation	Unremarkable																																									

Table 12 Histopathology Changes in 3-month (91-day) Toxicology Study in Dogs

Treatment-Related Microscopic Findings			No. of animals affected (main/recovery)							
			Males				Females			
Dose (mg/kg/day)			0	5	10	30	0	5	10	30
Number of animals examined			5/3	5/3	5/3	5/3	5/3	5/3	5/3	5/3
Organ	Finding									
GALT	Lymphoid depletion, follicular	Total	-	1/0	4/0	5/0	-	1/0	1/0	2/0
		Minimal	-	1/0	4/0	2/0	-	1/0	1/0	2/0
		Mild	-	-	-	3/0	-	-	-	-
Kidneys	Pigment, tubular, bilateral	Minimal	-	-	-	2/0	-	-	-	-
	Tubular vacuolation (bilateral or unilateral)	Minimal	-	0/1	-	0/2	0/2	0/2	-	0/1

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Treatment-Related Microscopic Findings			No. of animals affected (main/recovery)							
			Males				Females			
Dose (mg/kg/day)			0	5	10	30	0	5	10	30
Number of animals examined			5/3	5/3	5/3	5/3	5/3	5/3	5/3	5/3
Organ	Finding									
Liver	Tubular regeneration	Minimal	0/1	0/2	0/2	2/0	-	-	-	2/0
	Subacute/chronic inflammation	Minimal	-	-	-	-	-	1/0	-	1/0
	Mononuclear cell infiltration	Minimal	-	-	-	-	-	-	-	3/0
Mandibular lymph node	Lymphoid depletion, follicular	Total	-	-	2/0	3/2	-	-	-	-
		Minimal	-	-	2/0	3/1	-	-	-	-
		Mild	-	-	-	0/1	-	-	-	-
	Erythrocytosis/erythrophagocytosis, sinus	Minimal	-	3/0	3/2	1/1	-	3/0	2/0	2/0
	Pigment	Minimal	-	0/2	-	3/0	0/1	1/1	1/1	1/1
Mesenteric lymph node	Lymphoid depletion, follicular	Total	-	-	1/0	4/1	-	-	-	-
		Minimal	-	-	1/0	1/1	-	-	-	-
		Mild	-	-	-	3/0	-	-	-	-
	Erythrocytosis/erythrophagocytosis, sinus	Total	0/2	5/2	4/2	5/3	1/2	3/1	4/0	3/0
		Minimal	0/2	5/2	3/2	5/3	1/2	3/1	4/0	3/0
		Mild	-	-	1/0	-	-	-	-	-
Spleen	Lymphoid depletion, follicular	Minimal	-	-	2/0	3/0	-	1/0	3/0	2/0

- = no test-article related changes

General toxicology; additional studies

Study title/ number: 28-day Oral Gavage Toxicity Study with ACP-196 Followed by a 4-Week Recovery Period in Male and Female Sprague Dawley Rats / 502513

Acalabrutinib was administered by oral gavage at doses of 30, 100, or 300 mg/kg/day once daily for at least 28 days in Sprague Dawley rats. Mortality was observed in 3 males and 3 females at 300 mg/kg/day, and these unscheduled deaths were associated with hepatic, myocardial, and renal necrosis. Pancreatic inflammation was also observed in the males. Target organs of toxicity in the surviving rats were the liver, kidney, pancreas, and adrenals. Adverse findings in rats treated with 100 mg/kg/day included clinical signs (hunched posture, salivation, piloerection, and chromodacryorrhea), changes in hematology (↑ reticulocytes, ↑ neutrophils, and ↓ B-cells), organ weights (↓ thymus, ↓ spleen, and ↑ adrenal gland), and microscopic findings in the pancreas and kidneys.

Study title/ number: ACP-196: A 91-Day Oral Toxicity Study in Rats with a 28-Day Recovery Period/ 2219-029

Acalabrutinib was administered by oral gavage at doses of 10, 30, or 100 mg/kg/day once daily for 91 days in Sprague Dawley rats. No acalabrutinib-related mortality was observed in this study and toxicity was primarily limited to macroscopic and microscopic findings in the pancreas observed at all doses. Findings included small pancreas,

hemorrhage/pigment/inflammation/fibrosis of the islets, and subacute/chronic inflammation of the exocrine pancreas. Following the 28-day recovery period, the macroscopic findings and subacute/chronic inflammation were resolved; however, the incidences of hemorrhage/pigment/inflammation/fibrosis of the islets were similar to the incidences observed at the main study necropsy with slightly decreased severity.

Study title/ number: 28-day Oral Gavage Toxicity Study with ACP-196 in Male and Female Beagle Dogs Followed by a 4-Week Recovery Period/ 502515

Acalabrutinib was administered by oral gavage at doses of 3, 10, or 30 mg/kg/day once daily for at least 28 days in Beagle dogs. Hematology changes included decreases in B-cell counts in males at all doses (21-44%) and in females at 30 mg/kg/day (17-20%) compared to controls. Organ weights were decreased in multiple organs at 30 mg/kg/day compared to controls including the spleen (↓ 13%), thymus (↓ 23%), prostate (↓ 30%), epididymides (↓ 14%), testes (↓ 12%), and ovaries (↓ 16%). Microscopic findings included lymphoid depletion in the spleen and congestion/erythrophagocytosis in the mesenteric lymph node that corresponded to a macroscopic finding of dark red discoloration observed at all doses of acalabrutinib. Increased incidences of findings in the kidney including tubular basophilia, papilla mineralization, and hyaline casts were observed in dogs treated with acalabrutinib.

Study title/ number: ACP-196: A 39-Week Oral Capsule Toxicity Study in Dogs with a 4-Week Recovery Period/ 2219-098

Acalabrutinib was administered orally via gelatin capsules at doses of 10 or 30 mg/kg/day once daily for 39 weeks in Beagle dogs. Toxicities were limited to changes in clinical pathology starting by Weeks 4 or 13 and observed throughout the dosing period. Hematology changes consisted of reversible effects on red blood cell parameters including increases in mean cell volume (MCV; ↑ up to 10%) and mean cell hemoglobin (MCH; ↑ up to 6%) and decreases in mean cell hemoglobin concentration (MCHC; ↓ up to 5%) and red cell distribution width (RDW; ↓ up to 10%) in both males and females at 30 mg/kg/day compared to controls. Additionally, decreases in red cell mass (erythrocytes, hemoglobin, or hematocrit; ↓ up to 14%) were observed in females at 30 mg/kg/day compared to controls. Clinical chemistry changes included decreases in albumin in females at 30 mg/kg/day and in a single female at 10 mg/kg/day.

5.5.2. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Evaluation of the Mutagenic Activity of ACP-196 in the *Salmonella Typhimurium* Reverse Mutation Assay and the *Escherichia Coli* Reverse Mutation Assay/ 503223

Key Study Findings:

- Acalabrutinib did not increase in the number of revertant colonies in tester strains TA100, TA1535, TA 1537, and WP2 uvrA with or without metabolic activation. Tester

strain TA98 increased the number of revertant colonies above the historical control data range both with and without metabolic activation in two separate experiments, but increases were less than 2-fold the concurrent control.

- Acalabrutinib was negative for mutagenicity in the reverse mutation assay.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537; *Escherichia coli* tester strain WP2 uvrA; tested at concentrations up to 5000 ug/plate; +/- S9 activation
Study is valid: Yes

In tester strain TA98, acalabrutinib induced increases in the number of revertant colonies compared to the solvent control at dose levels of 3330 and 5000 ug/plate without S9-activation (up to 1.9-fold) and at 3330 ug/plate with S9-activation (up to 1.8-fold). These increases were below the criterion for a positive result for the TA98 strain of 3-fold the concurrent control used in this study. To verify these results, an additional experiment with concentrations up to 5000 ug/plate was conducted with the TA98 strain and similar results at 1000 (without S9 only) and 3330 ug/plate were observed in the second experiment. Although the increases in the number of revertant colonies were above the historical control data range in two separate experiments, since they were less than 3-fold the concurrent control they were considered to not be biologically relevant by the Applicant. CDER pharmacology/toxicology uses a criterion of 2-fold the concurrent control for a positive result for the TA98 strain. Since the results are below 2-fold the concurrent control, the Agency concurs that acalabrutinib was negative for mutagenicity in this assay.

In Vitro Assays in Mammalian Cells

Study title/ number: Evaluation of the Ability of ACP-196 to Induce Chromosome Aberrations in Cultured Peripheral Human Lymphocytes (with Repeat Experiment)/ 503225

Key Study Findings:

- Acalabrutinib did not induce chromosome aberrations in human peripheral blood lymphocytes with or without metabolic activation; therefore, acalabrutinib was negative for clastogenicity in the in vitro chromosome aberrations assay.

GLP compliance: Yes

Test system: Human peripheral blood lymphocytes; +/- S9 activation; exposure to acalabrutinib of 3, 24, or 48 hours without S9 activation and 3 hours with S9 activation; 24-48 hours fixation time; for cytogenetic assays, concentrations of up to 400 ug/mL for 3 hour exposure, 100 ug/mL for 24 hour exposure, and 150 ug/mL for 48 hour exposure
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: In Vivo Micronucleus Assay in Rats/ AD92XN.125M012ICH.BTL

Key Study Findings:

- Acalabrutinib did not induce an increase in the incidence of micronucleated polychromatic erythrocytes; therefore, acalabrutinib was negative for micronucleus induction and in vivo clastogenicity.

GLP compliance: Yes

Test system: Sprague-Dawley rats; males and females in dose range finding assay, males only in definitive assay; single oral dose of 0, 500, 1000, or 2000 mg/kg acalabrutinib; 24 hour (all doses) or 48 hour (0 and 2000 mg/kg only) bone marrow collection

Study is valid: Yes

5.5.3. Carcinogenicity

Not conducted at this time per ICH S9.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Embryo-Fetal Development

Study title/ number: ACP-196: A Combination Study of Fertility and Embryo Fetal Developmental Toxicity in Rats with a Toxicokinetic Evaluation/ 2219-088

Key Study Findings

- Acalabrutinib caused mortality related to kidney toxicity in males at 300 mg/kg/day.
- No effects on fertility or embryo-fetal development were observed at any dose level; therefore, the NOAEL for male fertility was 300 mg/kg/day and the NOAEL for female fertility and embryo-fetal toxicity was 200 mg/kg/day in rats. Exposures at these doses were approximately 18 times and 16 times, respectively, the human clinical exposure based on AUC at the recommended human dose.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing:

Males: 0, 30, 100, or 300 mg/kg/day; once daily dosing starting 28 days prior to pairing through mating and postmating period (77-79 days total)

Females: 0, 30, 100, or 200 mg/kg/day
Once daily dosing starting 14 days prior to pairing through Gestation Day (GD) 17

Route of administration:

Oral gavage

Formulation/Vehicle:

(b) (4) % (b) (4) (w:v) and (b) (4) % (b) (4); w:v) in NANOPure Diamond Ultrapure water

Species/Strain:

Rat/Crl:CD(SD)

Number/Sex/Group:

25/sex/group

Satellite groups:

Toxicokinetics: 9 males at 300 mg/kg/day administered 28 days prior to pairing through Day 28; 3 females at 0 mg/kg/day and 9 females/group at 30, 200, and 300 mg/kg/day

Study design: administered from GD 6 through GD 17;
females were received time-mated
Females were paired with males from the same
treatment level until evidence of mating;
maximum pairing period of 21 days (14 days
with first male and 7 days with second
successful male); day on which positive
evidence of copulation was observed was
considered GD 0; necropsy/cesarean section
for females conducted on GD 20

Deviation from study protocol
affecting interpretation of results: No

Table 13 Observations and Results

Parameters	Major findings
Mortality	200 mg/kg/day: One female euthanized <i>in extremis</i> on GD 19; at necropsy, 5 late resorptions were found lodged in the vaginal canal and death was considered related to dystocia; since the finding was only in one animal, the Applicant considered it to not be test article-related 300 mg/kg/day: Two males found dead on Day 33 and one male found dead on Day 78; necropsy findings in kidneys (enlarged, white foci, or red discoloration) and pancreas (gelatinous edema)
Clinical Signs	↑ incidences of salivation at all doses
Body Weights	↓ body weight change during some intervals of the study at 100 and 300 mg/kg/day in males: Days 1-4 (↓28%, 300 mg/kg/day), Days 18-22 (↓31-46%), Days 50-53 (↓35-45%), Days 60-64 (↓80-82%)
Fertility	Unremarkable
Necropsy findings Cesarean Section Data	Unremarkable
Necropsy findings Offspring	Unremarkable

Study title/ number: ACP-196: A Study for Effects on Embryo Fetal Development in Rabbits with a Toxicokinetic Evaluation/ 2219-075

Key Study Findings

- Acalabrutinib caused maternal toxicity at 100 and 200 mg/kg/day characterized by decreased food consumption, body weight gain, and body weight leading to mortality. Mortality was observed in all the animals in the 200 mg/kg/day group; therefore, developmental toxicity could not be assessed at this dose.
- Fetal toxicity characterized by decreased fetal body weights and delayed fetal skeletal ossification was observed at the maternally toxic dose of 100 mg/kg/day. Maternal exposures at the 100 mg/kg/day dose were approximately 4 times the human clinical exposure based on AUC at the recommended human dose.
- The NOAEL for maternal and developmental toxicity was 50 mg/kg/day in rabbits.

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Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 50, 100, or 200 mg/kg/day; once daily GD 6-18

Route of administration: Oral gavage

Formulation/Vehicle: (b) (4) % (b) (4) (w:v) and (b) (4) % (b) (4); w:v) in NANOPure

Diamond Ultrapure water

Species/Strain: Rabbit/New Zealand White Hra:(NZW)SPF

Number/Sex/Group: 23 females/group

Satellite groups: Toxicokinetics: 4 females/group

Study design: Pregnant rabbits were administered acalabrutinib once daily on GD 6-18, scheduled necropsy/cesarean section conducted on GD 29

Due to deteriorating health, all surviving females at 200 mg/kg/day were terminated early on GD 21-23; uterine examinations and maternal necropsy were conducted but fetal evaluations were not conducted, therefore, developmental toxicity could not be assessed at 200 mg/kg/day.

Deviation from study protocol affecting interpretation of results: No

Table 14 Observations and Results

Parameters	Major findings
Mortality	100 mg/kg/day: One female found dead on GD 19. 200 mg/kg/day: Total of 7 main study females found dead (1 on GD 18, 2 on GD 19, 2 on GD 20, and 2 on GD 22). All surviving females at 200 mg/kg/day were terminated early on GD 21 to 23 due to deteriorating health. One TK female was also found dead on GD 19. Necropsy finding of red foci in stomach observed in female at 100 mg/kg/day and 5/8 females at 200 mg/kg/day. Discoloration of kidney (red or tan) observed in 4 females at 200 mg/kg/day.
Clinical Signs	100 and 200 mg/kg/day: Decreased activity, thin body condition, severely decreased food consumption, abnormal feces (small, clumped, watery, soft, or few/absent), skin cold to touch, and skin discolored blue/gray Food consumption: For entire dosing period (GD 6-19), ↓23% at 100 mg/kg/day and ↓79% at 200 mg/kg/day compared to controls

Body Weights	100 mg/kg/day: Body weight significantly lower (↓6%) than control on GD 19 and adjusted final body weight was ↓4%; mean overall body weight gain (GD 0-29) was ↓22% compared to controls and the adjusted body weight change was -0.050 kg compared to 0.058 kg in controls 200 mg/kg/day: Body weight significantly lower than controls starting on GD 10 (↓ up to 24%); actual weight loss of 14% on GD 21 compared to GD 0 value
Necropsy findings Cesarean Section Data	50 and 100 mg/kg/day: Unremarkable 200 mg/kg/day: Due to mortality, no main study females had a cesarean section on GD 29. One TK female had a litter consisting of all resorbed fetuses.
Necropsy findings Offspring	100 mg/kg/day: Live fetal body weights ↓14% for males and 10% for females; delayed skeletal ossification findings of hyoid body not ossified (7 fetuses in 4 litters) and talus not ossified (4 fetuses in 2 litters) 200 mg/kg/day: No litters were available for evaluation on GD 29.

Prenatal and Postnatal Development
Not conducted at this time per ICH S9.

5.5.5. Other Toxicology Studies

Studies with Impurities

Studies included a 14-day toxicology study in rats to qualify the process impurity (b) (4) and in vitro genetic toxicology studies of impurities.

Study title/ number: ACP-196 Lot 2584-75-1: A 14-Day Oral Toxicity Study in Wistar Han Rats/ 2219-063

To qualify the process impurity (b) (4) this study evaluated the toxicity of acalabrutinib containing (b) (4) (5 or 25 mg/kg/day; Lot # 2584-75-1) compared to acalabrutinib without the impurity (25 mg/kg/day) or a vehicle control administered by oral gavage for 14 days in Wistar Han rats. Assessment of toxicity included mortality, clinical observations, body weight, food consumption, ophthalmoscopic examinations, clinical and anatomic pathology, and toxicokinetics.

Note: Report is an audited draft and is not signed.

Key study findings:

- There were few toxicity findings observed in this study and no test-article microscopic lesions were observed in animals treated with the acalabrutinib containing (b) (4) (Lot # 2584-75-1). One animal treated with acalabrutinib alone at 25 mg/kg had findings in the islets of the pancreas consisting of degeneration of islet cells, hemorrhage, fibrosis, mixed cell inflammation, and pigmented macrophages.

- Overall, the toxicology profile of acalabrutinib containing (b) (4) and acalabrutinib without (b) (4) were similar at a dose of 25 mg/kg/day for 14 days.

Genetic Toxicology Studies with Impurities

Multiple in vitro bacterial reverse mutation assays and an in vitro chromosomal aberrations assay were conducted to assess the potential for the impurities to induce genotoxicity. These studies, key methods, and the results are listed in the table below. All studies were valid. The impurity (b) (4) was positive for mutagenicity in a bacterial reverse mutation assay.

Table 15 Results of Genetic Toxicology Studies Conducted with Impurities present in Acalabrutinib

Study #	Impurity tested	Assay	Strains/cells tested	Other test system details	Results
AE24KN.5021CH.BTL (2219-065)	Acalabrutinib batch containing (b) (4)	Bacterial reverse mutation assay	<i>Salmonella typhimurium</i> and <i>Escherichia coli</i> ¹	+/- S9 activation; concentrations up to 5000 µg per plate	Negative
AE24KN.3411CH.BTL (2219-066)	Acalabrutinib batch containing (b) (4)	Chromosomal aberration	Human peripheral blood lymphocytes	+/- S9 activation; exposures of 4 and 20 hr (- S9) and 4 hr (+ S9); harvest at 20 hrs; concentrations up to 450 µg/mL for 4 hr exposures and up to 150 µg/mL for 20 hr exposure	Negative
AE25YJ.502005ICH.BTL (2219-070)	(b) (4)	Bacterial reverse mutation assay	<i>Salmonella typhimurium</i> and <i>Escherichia coli</i> ¹	+/- S9 activation; concentrations up to 5000 µg per plate	Negative
AE28XD.502005ICH.BTL (2219-077)	(b) (4)	Bacterial reverse mutation assay	<i>Salmonella typhimurium</i> and <i>Escherichia coli</i> ¹	+/- S9 activation; concentrations up to 5000 µg per plate	Negative
AE38BU.502008ICH.BTL (2219-095)	Acalabrutinib batch with 10% weight (b) (4)	Bacterial reverse mutation assay in 6-well plates	<i>Salmonella typhimurium</i> and <i>Escherichia coli</i> ²	+/- S9 activation; 6-well modified plate incorporation method; up to 1000 µg per well	Negative

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Study #	Impurity tested	Assay	Strains/cells tested	Other test system details	Results
AE44YR.502005ICH.BTL	(b) (4)	Bacterial reverse mutation assay	<i>Salmonella typhimurium</i> and <i>Escherichia coli</i> ¹	+/- S9 activation; concentrations up to 5000 µg per plate	Positive; maximum increases in revertant colonies of 5.4-fold (+ S9) and 8.8-fold (- S9) with strain TA1537

¹ *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 *uvrA*

² *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA97a and *Escherichia coli* strain WP2 *uvrA*

Impurity Qualification

The proposed specifications for impurities (b) (4) in the drug substance and for impurities (b) (4) in the drug product require qualification. In the table below, the dose of each impurity based on BSA (mg/m²) at the proposed specification for the maximum daily dose of 200 mg acalabrutinib is compared to the dose of the impurity (in mg/m²) administered to the animals in the toxicology study.

Table 16 Impurity Qualification with Doses Based on BSA (mg/m²) for Drug Substance

Impurity	Proposed Specification		Levels/Doses in Animal Toxicology Study			Qualification Determination
	%	Dose (mg/m ²)	Study/Lot	%	Dose (mg/m ²)	
(b) (4)	(b) (4)	(b) (4)	2219-063 (14-day special toxicology study) Lot 2584-75-1	(b) (4)	(b) (4)	Qualified
			2219-029 (3-month rat study) Lot CS13-083Am-1403			Qualified
			2219-029 (3-month rat study) Lot CS13-083Am-1403			Qualified
			2219-029 (3-month rat study) Lot CS13-083Am-1403			Qualified
			2219-098 (9-month dog study) Lot 4312.B.15.1 TR18289			Qualified
			2219-084 (6-month rat study) Lot 4312.B.15.1 (4312.BP-002)			Not Qualified (proposed specification to be lowered)

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Impurity	Proposed Specification		Levels/Doses in Animal Toxicology Study			Qualification Determination
	%	Dose (mg/m ²)	Study/Lot	%	Dose (mg/m ²)	
		(b) (4)	2219-063 (14-day special toxicology study) Lot 2584-75-1		(b) (4)	Qualified

Table 17 Impurity Qualification with Doses Based on BSA (mg/m²) for Drug Product

Impurity	Proposed Specification		Levels/Doses in Animal Toxicology Study			Qualification Determination
	%	Dose (mg/m ²)	Study/Lot	%	Dose (mg/m ²)	
		(b) (4)	2219-029 (3-month rat study) Lot CS13-083Am-1403		(b) (4)	Not Qualified (proposed specification to be lowered)
			2219-029 (3-month rat study) Lot CS13-083Am-1403			Qualified

Based on these calculations and comparisons, two of the specifications must be lowered:

- 1) The specification of (b) (4) % for (b) (4) in the drug substance; based on the toxicology batches the data support a specification up to (b) (4) % which equates to an impurity dose of (b) (4) mg/m² (b) (4). This impurity is (b) (4) and is a potential toxicological concern; therefore, Pharmacology/Toxicology recommends that the impurity be lowered. Recent clinical batches have contained up to (b) (4) % (b) (4); however, it is unclear whether these batches have been administered to patients. Based on the proposed indication of mantle cell lymphoma and the known toxicities of acalabrutinib, a specification of (b) (4) % is acceptable from a Pharmacology/Toxicology perspective.
- 2) The specification of (b) (4) % for (b) (4) in the drug product; based on the toxicology batches the data support a specification up to (b) (4) % which equates to an impurity dose of (b) (4) mg/m² (b) (4). Pharmacology/Toxicology recommends that the impurity be lowered to (b) (4) %.

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Brenda J Gehrke, PhD
Primary Reviewer

Christopher M Sheth, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant is seeking the approval of acalabrutinib for the treatment of patients with mantle cell lymphoma (MCL) who have received ≥ 1 prior therapy. Acalabrutinib is an inhibitor of Bruton Tyrosine Kinase (BTK). The proposed dosing regimen is 100 mg twice daily (BID) to be taken with water and without regard to food. The primary evidence of efficacy supporting the proposed dosing regimen is overall response rate (complete response + partial response) that was demonstrated in a phase 2, open-label, single-arm study (**ACE-LY-004**) in patients with relapsed or refractory MCL with ≥ 1 (but not >5) prior therapies (N=124). The overall response rate was 80%. Acalabrutinib was shown to be tolerable, with low rates of adverse events (AEs) leading to dose reduction (2%) or drug discontinuation (6%). AEs leading to dose interruption/delay were reported in approximately 30% of patients.

The Clinical Pharmacology Review evaluated the acceptability of the proposed dosing regimen as well as the food effect, drug-drug interaction potential, organ impairment, population PK and exposure-response analyses for safety and efficacy.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA 210259. This NDA is approvable from a Clinical Pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

REVIEW ISSUE	RECOMMENDATIONS/COMMENTS
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal Study ACE-LY-004 in the target population. The overall response rate was 80% demonstrated in 124 patients with relapsed or refractory MCL.
General dosing instructions	The proposed dosing regimen is 100 mg BID to be taken with water (without regard to food). No clinically relevant food effect was observed following co-administration of acalabrutinib with a standard high-fat, high-calorie meal.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dose modifications are recommended: ▪ Proton pump inhibitors: Avoid concomitant use. ▪ H2-receptor antagonists: Take acalabrutinib 2 h before taking a H2-receptor antagonist. ▪ Antacids: Separate dosing by ≥ 2 h. ▪ Strong CYP3A inducers: Avoid concomitant use. If strong CYP3A inducers cannot be avoided, increase acalabrutinib dose to 200 mg BID. ▪ Strong CYP3A inhibitors: Avoid concomitant use. If strong CYP3A inhibitors will be used short-term, interrupt acalabrutinib treatment. ▪ Moderate CYP3A inhibitors: Reduce dose to 100 mg QD.

Labeling	Generally acceptable.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed capsule formulation was used in the pivotal Study ACE-LY-004 and in most of the clinical pharmacology studies. A (b) (4) capsule formulation was used in early clinical studies; the (b) (4) capsule formulation showed similar acalabrutinib pharmacokinetics as the to-be-marketed capsule formulation in healthy subjects and patients (see Appendix Error! Reference source not found.).

Post-Marketing Requirement (PMR) or Commitment (PMC)

The following issue should be addressed as a PMR:

1. Evaluate the safety and PK of acalabrutinib in subjects with severe hepatic impairment.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Acalabrutinib is an inhibitor of BTK. The following is a summary of the clinical pharmacokinetics of acalabrutinib:

Absorption: Following oral administration, the geometric mean absolute bioavailability of acalabrutinib was 25%. Median time to peak acalabrutinib plasma concentration was 0.75 h. A high-fat meal did not significantly affect the AUC of acalabrutinib.

Distribution: Acalabrutinib is approximately 98% bound to human plasma proteins and the blood-to-plasma ratio was 0.7-0.8. The mean steady-state volume of distribution was 34 L.

Metabolism: Acalabrutinib is primarily metabolized by CYP3A enzymes, and to a lesser extent by glutathione conjugation and amide hydrolysis. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean AUC that is approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 has approximately 50% less potency for BTK inhibition than acalabrutinib.

Elimination: Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life ($t_{1/2}$) of acalabrutinib and its active metabolite ACP-5862 were 1-2 h and 7 h, respectively. Acalabrutinib mean apparent oral clearance (CL/F) was 159 L/h, with similar PK observed between patients and healthy subjects based on population PK analysis. Following multiple-dosing, there was no accumulation of acalabrutinib or ACP-5862. In the mass balance study, 84% of the dose was received in the feces and 12% of the dose was recovered in the urine, with less than 1% of the dose excreted as unchanged acalabrutinib in urine.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The recommended dosing regimen is 100 mg BID to be taken with water (without regard to food) in patients with MCL who have received ≥ 1 prior therapy until disease progression or unacceptable toxicity.

Therapeutic Individualization

In regards to drug-drug interactions (DDI), the following dose modifications are recommended:

- **Proton pump inhibitors:** Avoid concomitant use.
- **H2-receptor antagonist:** Take acalabrutinib 2 h before taking a H2-receptor antagonist
- **Antacids:** Separate dosing by ≥ 2 h.
- **Strong CYP3A inducers:** Avoid concomitant use. If strong CYP3A inducers cannot be avoided, increase acalabrutinib dose to 200 mg BID.
- **Strong CYP3A inhibitors:** Avoid concomitant use. If strong CYP3A inhibitors will be used short-term, interrupt acalabrutinib treatment.
- **Moderate CYP3A inhibitors:** Reduce dose to 100 mg QD.

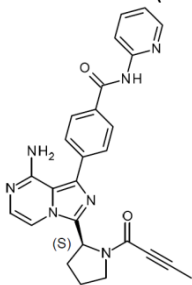
Outstanding Issues

We have issued one PMR, as presented in the PMR/PMC Section above. There are no other outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Table 18 General Pharmacology and Pharmacokinetic Characteristics

PHYSICOCHEMICAL PROPERTIES	
Chemical structure and molecular weight	Acalabrutinib (465.51 g/mol): 
Aqueous solubility	Acalabrutinib has pH-dependent solubility (BCS Class II compound). Acalabrutinib exposure is decreased by gastric acid reducing agents.
PHARMACOLOGY	
Mechanism of action	Acalabrutinib is a covalent inhibitor of BTK ($IC_{50} = 5.1$ nM).
Active moiety	Acalabrutinib has a major active metabolite: ACP-5862. Compared to acalabrutinib, ACP-5862 exhibits approximately 0.5-fold potency for BTK inhibition ($IC_{50} = 3.0$ nM).

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QT/QTc prolongation	Acalabrutinib did not prolong QTc interval to any clinically relevant extent, based on TQT Study ACE-HV-005 .		
GENERAL INFORMATION			
Bioanalytical assay	Validated bioanalytical assays were developed to measure the concentrations of acalabrutinib and ACP-5862 in the clinical studies included in this NDA (see Appendix).		
Patient PK vs. healthy subject PK	No apparent difference.		
Steady-state exposure at the proposed dosing regimen	Daily acalabrutinib steady-state AUC = 1111 ng·h/mL and C _{MAX} = 323 ng/mL, based on population PK model prediction.		
Minimal effective dose or exposure	Unknown.		
Maximum tolerated dose or exposure	Not reached, based on Phase 2 Study ACE-CL-001 in patients with CLL (maximum dose tested = 400 mg QD).		
Dose proportionality	Generally dose-proportional, with linear PK from 75-250 mg following single and multiple dosing, based on population PK analysis.		
Accumulation	None.		
Variability	Based on pivotal Study ACE-LY-004 , the inter-subject variability (CV%) was 60% and 95% for steady-state AUC and C _{MAX} , respectively.		
ABSORPTION			
Bioavailability	The absolute bioavailability of acalabrutinib is approximately 25% (range 20-30%).		
T _{MAX}	Median T _{MAX} = 0.75 h (acalabrutinib), 1.0-1.9 h (ACP-5862).		
Food effect	AUC _{0-∞} (GMR, 90% CI)	C _{MAX} (GMR, 90% CI)	T _{MAX} (median)
	0.93 (0.79, 1.09)	0.31 (0.23, 0.41)	Fed: 2.5 h Fasted: 0.5 h
	No clinically relevant food effect was observed following co-administration of acalabrutinib with a standard high-fat, high-calorie meal. Additionally, acalabrutinib was administered without regard to food in the pivotal Study ACE-LY-004 . Acalabrutinib may be taken without regard to food.		
DISTRIBUTION			
Volume of distribution	The mean volume of distribution at steady-state was 34 L, following a radiolabeled IV microtracer dose. Acalabrutinib and ACP-5862 are approximately 98% and 99% bound to human plasma proteins, respectively.		
Substrate of transporter systems	Acalabrutinib is a substrate of P-gp and BCRP. Acalabrutinib is not a substrate of OAT1, OAT3, OCT2, OATP1B1, or OATP1B3.		
ELIMINATION			
Terminal elimination half-life and clearance	Following a single oral dose of 100 mg acalabrutinib, the median terminal elimination half-life of acalabrutinib and its active metabolite ACP-5862 were 1-2 h and 7 h, respectively. Acalabrutinib mean apparent oral clearance (CL/F) was 159 L/h. Renal clearance accounts for less than 1% of the total systemic clearance.		
Metabolism	Acalabrutinib is primarily metabolized by CYP3A enzymes, and to a lesser extent by glutathione conjugation and amide hydrolysis. Active metabolite ACP-5862 is formed via CYP3A metabolism of acalabrutinib and is metabolized by CYP3A.		
Excretion	In the mass balance study, 84% of the dose was received in the feces and 12% of the dose was recovered in the urine, with less than 1% of the dose excreted as unchanged acalabrutinib in urine.		

Drug interaction liability	As a victim, acalabrutinib exposure may be affected by CYP3A inhibitors, CYP3A inducers, and gastric acid reducing agents. As a perpetrator, acalabrutinib may increase exposure of orally co-administrated BCRP substrates.
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6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

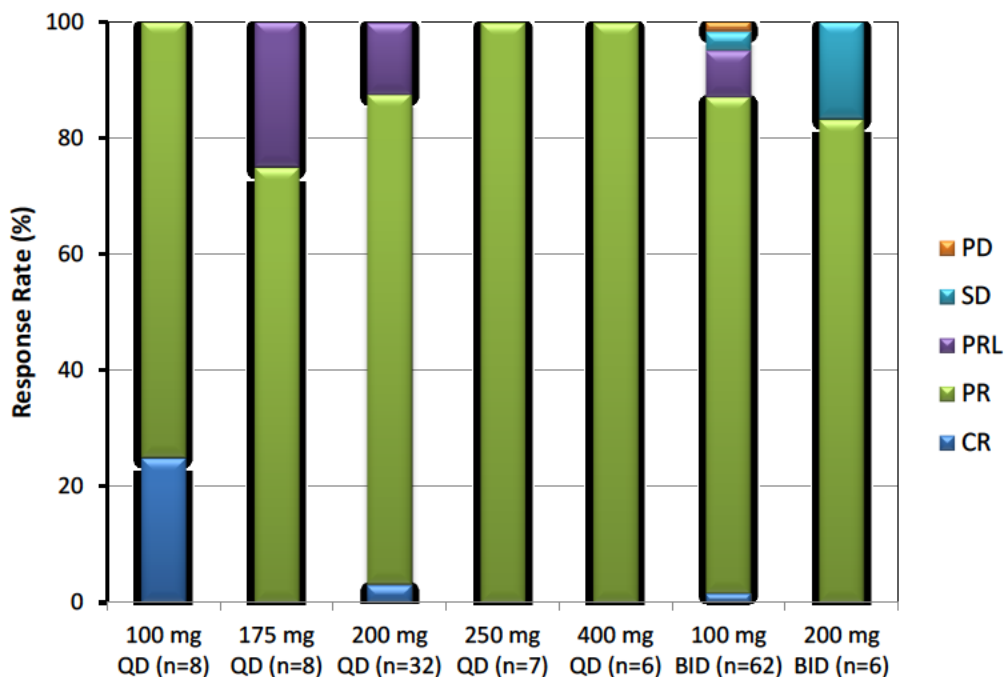
Support for evidence of effectiveness was obtained from pivotal Study **ACE-LY-004**, as detailed in the next section.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Dose Selection (Study ACE-CL-001)

The recommended dosing regimen is 100 mg BID in patients with MCL who have received ≥ 1 prior therapy. Dose selection was based on results of phase 2 dose-finding Study (**ACE-CL-001**), which evaluated acalabrutinib dosing regimens of 100 to 400 mg QD and 100 to 200 mg BID in patients with chronic lymphocytic leukemia (N=134). High response rates ($\geq 75\%$) were observed across all doses, however based on BTK occupancy, 100 mg BID resulted in maximal BTK occupancy with the least inter-patient variability at steady-state trough (**Figure 6**). Increasing the dose higher than 100 mg BID did not appear to further increase BTK occupancy at steady-state trough and may result in off-target effects. MTD was not reached in Study **ACE-CL-001**, and no DLTs were observed during the dose-escalation part of the Study.

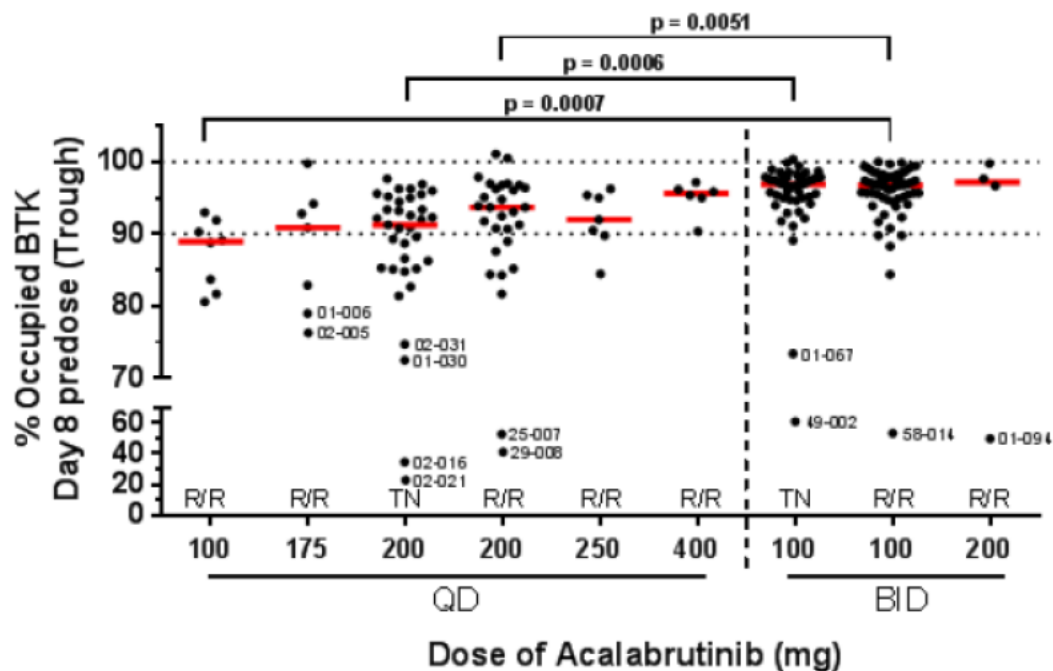
Figure 5 Response rates from Study ACE-CL-001



PD = progressive disease, SD = stable disease, PRL = partial response with lymphocytosis, PR = partial response, CR = complete response

Adapted from Table 11.2.1.1 of Applicant's ACE-CL-001 CSR

Figure 6 BTK occupancy from Study ACE-CL-001



Source: Figure 35 from Applicant's Summary of Clinical Pharmacology Studies

Pivotal Study ACE-LY-004

Based on **Study ACE-CL-001** that identified 100 mg BID as a well-tolerated dosing regimen that provided sustained and near complete BTK occupancy and high response rate in patients with CLL, the Applicant evaluated 100 mg BID in their pivotal phase 2, open-label, single-arm **Study ACE-LY-004** in patients with R/R MCL (n=124). In Study **ACE-LY-004**, treatment with acalabrutinib resulted in a high overall response rate of 80%, half of which were complete responses and the other half were partial responses (**Section 8.1.2**). The safety profile was generally tolerable (**Section 8.2.4**), with low rates of AEs leading to dose reduction (2%) or drug discontinuation (6%). AEs leading to dose interruption/delay were reported in approximately 30% of patients. Common AEs included headache (38%), diarrhea (31%), fatigue (27%), myalgia (21%), and cough (19%). Study **ACE-LY-004** primarily used the to-be-marketed capsule formulation.

Exposure-Response (E-R)

Exposure response relationship for efficacy and safety were conducted using data summarized in table 19. Exposure-efficacy analysis was based on data from 45 patients who took part in the pivotal trial. Exposure-safety analysis was based pooled data from 6 clinical trials (N=292).

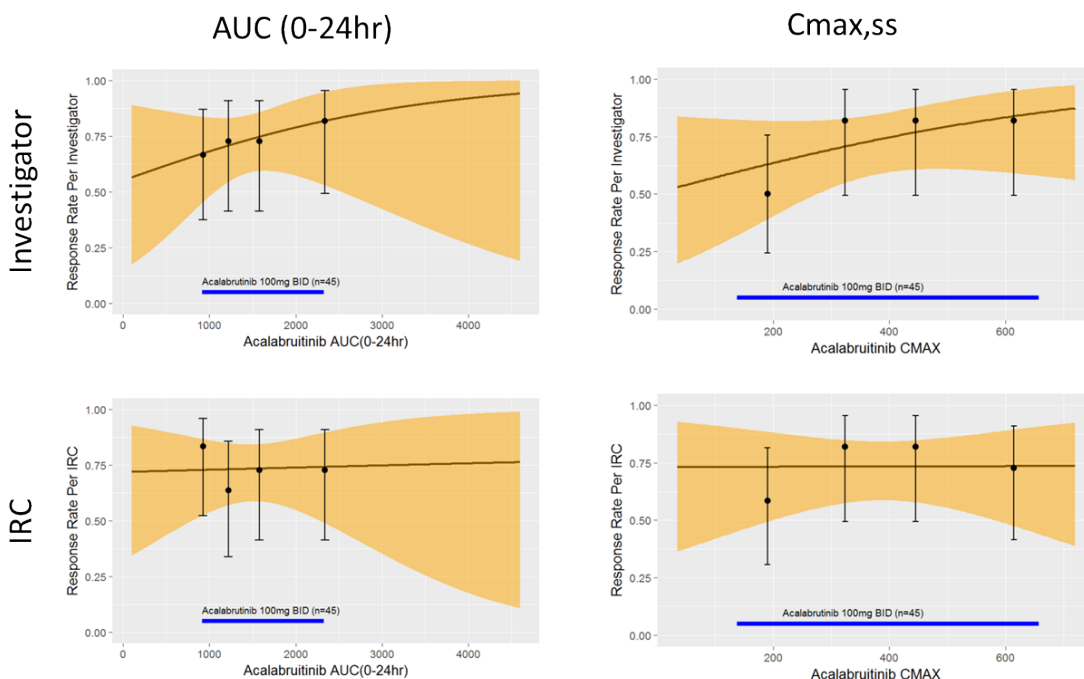
Table 19 Summary of Clinical Studies and Data Used for Exposure-Response Analyses

	Exposure-Efficacy	Exposure Safety
N in ER analysis (all/100 mg bid)	45/45	292/180
Indications	Mantle cell lymphoma (MCL)	B cell malignancy
Dosing Range	100 mg BID	100 mg QD – 200 mg BID
Study involved to conduct the analysis	ACE-LY-004	ACE-CL-001; ACE-LY-004 ;ACE-WM-001; ACE-LY-002; ACE-LY-003; ACE-MY-001

Source: adopted from Sponsor's summary of clinical pharmacology (Table 5).

The PK parameters for acalabrutinib were summarized as cumulative AUC over 24 h (AUC_{0-24h}) in the left panel and C_{max} in the right panel. The efficacy of acalabrutinib, measured as Overall Response Rate (ORR) per investigator and IRC (**Figure 7**). No statistically significant relationship was identified for E-R for efficacy by logistic regression.

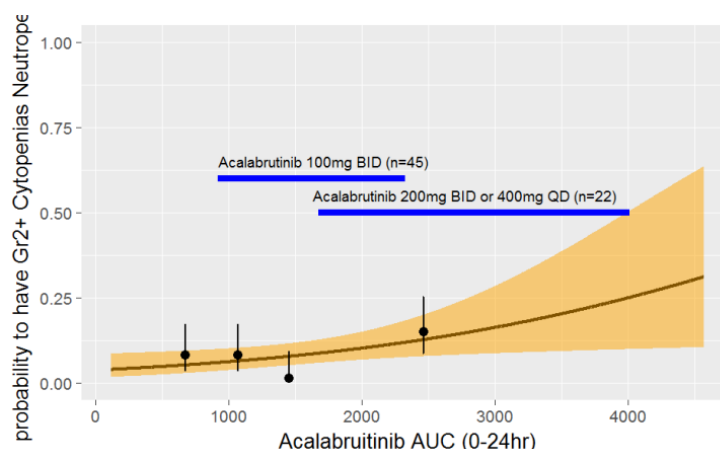
Figure 7 Exposure-response for efficacy by logistic regression



Source: FDA reviewer's analysis. Solid line is the logistic regression of the predicted ORR per investigator (upper panel) or IRC (lower panel). The yellow area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs. the mean concentration. The blue bar is 5% to 95% quantile of acalabrutinib exposure in the pivotal at the recommended dosing regimen of 100mg BID. E-R analyses showed no correlation between PK exposure (maximum plasma concentration [Cmax] or AUC over 2 dosing intervals [AUC_{0-24h}]) and overall response rate (ORR).

Exposure- safety analysis showed a positive relationship between drug exposure (AUC_{0-24h}) and the probability to have Grade 2+ neutropenia (**Figure 8**). With increasing dose from 100 mg BID to 200 mg BID, the probability to have Grade 2+ neutropenia increased from 7.5% (95% CI: 4.9%, 11.2%) to 13 % (95% CI: 7.9%, 20.8%).

Figure 8 Exposure-response relationship for AUC_{0-24h} versus incident rate of neutropenia by logistic regression



Source: FDA's Analysis. Solid line is the logistic regression of the predicted probability of Grade 2+ Cytopenias Neutropenia. The yellow area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration. The blue bar is 5% to 95% quantile of exposure of Acalabrutinib in the pivotal at dosing regimen of 100mg BID (upper) and a subgroup patients in ACE-CL-001 at dosing regimen of 200mg BID or 400mg QD.

There was no evidence of exposure-response relationship for other adverse events of interests including Grade 2+ hemorrhage, cardiac events, anemia, thrombocytopenia, hepatic events, hypertension, infections, diarrhea or headache at the exposure range from 116 ng·h/ml to 4575 ng·h/ml (dose range 100 mg QD to 200mg BID).

Given the strong efficacy results and mild safety profile, the recommended dosing regimen of 100 mg BID is acceptable in the general population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No dose adjustment is proposed in patients with hepatic or renal impairment.

Hepatic Impairment (HI)

Study **ACE-HI-001** was a 2-part, open-label, non-randomized study to evaluate a single-dose of acalabrutinib on acalabrutinib PK in subjects with HI (per Child-Pugh classification) vs. subjects with normal hepatic function (n=18). Part 1 of the study evaluated a single-dose of 50 mg acalabrutinib in subjects with mild or moderate HI vs. subjects with normal hepatic function. Part 2 of the study was intended to evaluate a single-dose of 50 mg acalabrutinib in subjects with severe HI. However, the Applicant stated that following a review of the safety and PK data in Part 1, a decision was made to not conduct Part 2 of the study. As seen in **Table 20**, acalabrutinib AUC was increased by 48-66% and C_{MAX} was increased by up to 83% in subjects

with mild or moderate HI compared to those with normal hepatic function. This study used the (b) (4) capsule formulation.

Table 20 Summary of acalabrutinib PK parameters and LSM analysis in hepatic impairment study

	Geometric Mean (%CV)		GMR (90% CI) vs. Normal hepatic function	
	AUC _{0-∞} (ng·h/mL)	C _{MAX} (ng/mL)	AUC _{0-∞}	C _{MAX}
Mild HI (n=6)	366 (61%)	291 (51%)	1.66 (0.69, 3.98)	1.83 (0.60, 5.59)
Moderate HI (n=6)	326 (178%)	156 (247%)	1.48 (0.62, 3.55)	0.98 (0.32, 2.99)
Normal hepatic function (n=6)	293 (17%)	159 (180%)	N/A	N/A

Source: Reviewer's analysis based on data from Applicant's Study ACE-HI-001 CSR

Population PK analysis showed that there was no impact of hepatic function as measured by NCI criteria on the systemic exposure to acalabrutinib. The exposure in patients with mild or moderate HI is around 1.2-fold compared with patients with normal hepatic function. The population PK analysis was based on 533 subjects with normal hepatic function, 41 patients with mild HI, and 3 patients with moderate HI. No patient with severe HI was included in the studies.

No dose adjustment is needed in patients with mild or moderate HI. A PMR will be issued to determine the PK and safety of acalabrutinib in patients with severe HI.

Renal Impairment (RI)

A dedicated study of acalabrutinib in subjects with renal impairment was not conducted because renal clearance contributes minimally to the overall clearance of acalabrutinib (< 1%) following an IV microtracer dose in healthy subjects. Population PK analysis indicated that mild or moderate RI is not a significant covariate for acalabrutinib PK. **No dose adjustment is needed in patients with RI.**

Covariate Analysis

Population PK model showed that gender, body weight, age, race (white vs. black), ethnicity, or ECOG performance are not significant covariates for clearance. No dose adjustment is needed in these populations.

QT/QTc Prolongation

Study **ACE-HV-005** was a randomized, double-blind, double-dummy, placebo- and positive-controlled (400 mg moxifloxacin), 4-way cross-over study to formally evaluate the effect of a single-dose of acalabrutinib (100 or 400 mg) on the QTc interval in healthy subjects (n=48). The results showed that the upper bounds of the 90% 2-sided CI of the LSM difference in QTcF change baseline for both the therapeutic (100 mg) and supra-therapeutic (400 mg) dose were < 10 ms at all post-dose time-points over 24 h. This study used the to-be-marketed capsule formulation. FDA's QT-IRT review found that based on this study, **administration of a single-**

dose of acalabrutinib that is 4-fold the maximum recommended single-dose did not prolong the QTc interval to any clinically relevant extent.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes, acalabrutinib should be taken with water and without regard to food. In regards to drug-drug interactions (DDI), the following dose modifications are recommended:

- **Proton pump inhibitors:** Avoid concomitant use.
- **H2-receptor antagonist:** Take acalabrutinib 2 h before taking a H2-receptor antagonist
- **Antacids:** Separate dosing by ≥ 2 h.
- **Strong CYP3A inducers:** Avoid concomitant use. If strong CYP3A inducers cannot be avoided, increase acalabrutinib dose to 200 mg BID.
- **Strong CYP3A inhibitors:** Avoid concomitant use. If strong CYP3A inhibitors will be used short-term, interrupt acalabrutinib treatment.
- **Moderate CYP3A inhibitors:** Reduce dose to 100 mg QD.

Food-Drug Studies

Juice Effect

Study **ACE-HV-112** was a 3-part, single-center, open-label study to evaluate the effect of an acalabrutinib acidic formulation and acidic beverages on acalabrutinib exposure in healthy subjects (n=36). Parts 2 and 3 of the study evaluated the effect of orange juice (pH=3.0) and grapefruit juice (pH=3.2; mechanism-based inhibitor of CYP3A) on the exposure of acalabrutinib, with a washout period of 2 days between doses. Subjects were administered 100 mg acalabrutinib taken with 240 mL water, orange juice, or grapefruit juice (note: grapefruit juice was taken 12 h before acalabrutinib dose). As seen in **Table 21**, acalabrutinib AUC was decreased by 38% and 16% when taken with orange juice and grapefruit juice, respectively, compared to when taken with water. This study used the to-be-marketed capsule formulation. Due to the overall exposure decrease, **acalabrutinib should be taken with water.**

Table 21 Summary of acalabrutinib PK parameters and LSM analysis in juice-effect parts of Study ACE-HV-112

	Geometric LSM (%CV)		Geometric LSM Ratio (90% CI)	
	AUC _{0-∞} (ng·h/mL)	C _{MAX} (ng/mL)	AUC _{0-∞}	C _{MAX}
Part 2				
Orange Juice (n=12)	468 (39%)	296 (87%)	0.62 (0.53, 0.72)	0.44 (0.25, 0.75)
Water (n=12)	758 (51%)	680 (55%)		
Part 3				
Grapefruit Juice (n=12)	680 (45%)	519 (52%)	0.84 (0.73, 0.95)	0.65 (0.45, 0.93)
Water (n=12)	814 (40%)	798 (42%)		

Adapted from Tables 11-6 and 11-9 in Applicant's ACE-HV-112 CSR

Food Effect

Study **ACE-HV-001** was a 3-part, single-center, open-label, dose-escalation study to evaluate the safety, PK, PD, food effect, and DDI of acalabrutinib in healthy subjects (n=59). Part 2 of the study evaluated the effect of a standard high-fat/high-calorie meal on the exposure of acalabrutinib. Subjects were administered a single-dose of 75 mg QD acalabrutinib with or without a high-fat/high-calorie breakfast, with a washout period of 7 d between doses. The high-fat/high-calorie breakfast consisted of fried eggs, bacon strip, slice bread, butter pat, hash browned potatoes, and whole milk. As seen in **Table 22**, compared to the fasted condition, while a high-fat/high-calorie meal decreased acalabrutinib C_{MAX} by 69%, the AUC was not changed significantly. Median T_{MAX} increased from 0.5 to 2.5 h under fed condition. This study used the (b) (4) capsule formulation. Additionally, patients in the pivotal Study **ACE-LY-004** were administered acalabrutinib without regard to food. **Acalabrutinib may be administered without regard to food.**

Table 22 Summary of acalabrutinib PK parameters and LSM analysis in food-effect part of Study ACE-HV-001

	Geometric LSM		Geometric LSM Ratio (90% CI)	
	AUC _{0-∞} (ng·h/mL)	C _{MAX} (ng/mL)	AUC _{0-∞}	C _{MAX}
Fed (n=12)	431	112	0.93 (0.79, 1.09)	0.31 (0.23, 0.41)
Fasted (n=12)	464	364		

Adapted from Table 11-3 in Applicant's ACE-HV-001 CSR

Drug-Drug Interaction

Effect of calcium carbonate (an antacid) and omeprazole (a proton pump inhibitor):

Acalabrutinib shows pH-dependent solubility. Study **ACE-HV-004** was a single-center, open-label, fixed-sequence, 2-period, 3-part study to evaluate the 1-way interaction of calcium carbonate, omeprazole, and rifampin on acalabrutinib exposure in healthy subjects (n=72). In Part 1, subjects were administered 100 mg acalabrutinib on Day 1 of Period 1, followed by 1 g calcium carbonate with concomitant 100 mg acalabrutinib on Day 1 of Period 2. In Part 2, subjects were administered 100 mg acalabrutinib on Day 1 of Period 1, followed by 40 mg omeprazole QD for 5 d with concomitant 100 mg acalabrutinib on Day 5 of Period 2. As seen in **Table 23**, concomitant calcium carbonate or omeprazole decreased acalabrutinib exposure significantly. This study used the (b) (4) capsule formulation. **Avoid concomitant use with proton pump inhibitors due to their effect on gastric acid production. Stagger dose with concomitant antacid (separate dosing by ≥ 2 h). For H2-receptor antagonists, take acalabrutinib 2 h before taking a H2-receptor antagonist.**

Table 23 Summary of acalabrutinib PK parameters and LSM analysis in gastric acid reducing agent parts of Study ACE-HV-004

	Geometric LSM		Geometric LSM Ratio (90% CI)	
	AUC _{0-LAST} (ng·h/mL)	C _{MAX} (ng/mL)	AUC _{0-LAST}	C _{MAX}
Part 1				
+Calcium carbonate (n=23)	183	60	0.47 (0.36, 0.62)	0.25 (0.17, 0.38)
-Calcium carbonate (n=24)	386	237		

Part 2				
+Omeprazole (n=23)	222	81	0.43 (0.30, 0.63)	0.21 (0.11, 0.40)
-Omeprazole (n=23)	512	383		

Adapted from Tables 7 and 9 in Applicant's ACE-HV-004 CSR

Effect of rifampin (a strong CYP3A inducer):

Acalabrutinib is metabolized by CYP3A enzymes. Study **ACE-HV-004** was a single-center, open-label, fixed-sequence, 2-period, 3-part study to evaluate the 1-way interaction of calcium carbonate, omeprazole, and rifampin on acalabrutinib exposure in healthy subjects (n=72). In Part 3, subjects were administered 100 mg acalabrutinib on Day 1 of Period 1, followed by 600 mg rifampin QD for 9 d with concomitant 100 mg acalabrutinib on Day 9 of Period 2. As seen in **Table 24**, concomitant rifampin decreased acalabrutinib AUC by almost 80% and C_{MAX} by almost 70%. This study used the (b) (4) capsule formulation. **Avoid concomitant use with concomitant strong CYP3A inducers. If strong CYP3A inducers cannot be avoided, increase acalabrutinib dose to 200 mg BID** (refer to PBPK review in Appendix for details).

Table 24 Summary of acalabrutinib PK parameters and LSM analysis in rifampin DDI part of Study ACE-HV-004

	Geometric LSM		Geometric LSM Ratio (90% CI)	
	AUC _{0-∞} (ng·h/mL)	C _{MAX} (ng/mL)	AUC _{0-∞}	C _{MAX}
Part 3				
+Rifampin (n=24)	154	142	0.21 (0.18, 0.24)	0.32 (0.24, 0.42)
-Rifampin (n=24)	749	450		

Adapted from Tables 7 and 9 in Applicant's ACE-HV-004 CSR

Effect of itraconazole (a strong CYP3A inhibitor and P-gp inhibitor):

Acalabrutinib is metabolized by CYP3A enzymes. Study **ACE-HV-001** was a 3-part, single-center, open-label, dose-escalation study to evaluate the safety, PK, PD, food effect, and DDI of acalabrutinib in healthy subjects (n=59). Part 3 of the study evaluated the effect of concomitant itraconazole on acalabrutinib exposure. Subjects were administered 50 mg acalabrutinib on Day 1 followed by 200 mg itraconazole BID on Days 4 to 8 and once on Day 9 with concomitant 50 mg acalabrutinib. As seen in **Table 25** concomitant itraconazole increased acalabrutinib AUC by 5-fold and C_{MAX} by almost 4-fold. Avoid concomitant use with strong CYP3A inhibitors. If strong CYP3A inhibitors will be used short-term, interrupt acalabrutinib treatment. Analyses conducted by Clinical Reviewers showed that response rates were similar in 31 patients who had interrupted therapy of ≥ 7 d compared to overall population in pivotal Study **ACE-LY-004**.

Table 25 Summary of acalabrutinib PK parameters and LSM analysis in itraconazole DDI part of Study ACE-HV-001

	Geometric LSM		Geometric LSM Ratio (90% CI)	
	AUC _{0-∞} (ng·h/mL)	C _{MAX} (ng/mL)	AUC _{0-∞}	C _{MAX}
+Itraconazole (n=16)	1250	648	5.0 (4.4, 5.6)	3.9 (3.2, 4.8)
-Itraconazole (n=17)	252	166		

Adapted from Table 11-4 in Applicant's ACE-HV-001 CSR

Effect of erythromycin, fluconazole, diltiazem (moderate CYP3A inhibitors):

The Applicant developed a physiologically-based pharmacokinetic (PBPK) model of acalabrutinib and its active metabolite ACP-5862 (refer to PBPK review in Appendix for details). The Applicant used the PBPK model to predict the effect of concomitant erythromycin, fluconazole, or diltiazem (all moderate CYP3A inhibitors) on the exposure of acalabrutinib and ACP-5862. As seen in **Table 26**, under 100 mg BID acalabrutinib, while total activity was similar (i.e., 50-60% higher compared to 100 mg BID acalabrutinib alone), acalabrutinib exposures may be expected to increase up to 3-fold (i.e., 2.3-2.8X higher compared to 100 mg BID acalabrutinib alone). In the context of an exposure-response relationship for neutropenia and the lack of clinical experience above 400 mg QD dosing (highest administered dose), it is recommended that **patients reduce dose to 100 mg QD when taking concomitant moderate CYP3A inhibitors**. As seen in **Table 26**, under 100 mg QD, acalabrutinib exposure increase is reduced to 1.1-1.4X to improve safety profile while efficacy is maintained based on the lack of an exposure-response for efficacy within the exposure range.

Table 26 Predicted effect of moderate CYP3A inhibitors on acalabrutinib exposure

Moderate CYP3A Inhibitor	Acalabrutinib Dosing Regimen	Geometric Mean AUC Ratio (vs. 100 mg BID alone)		
		Acalabrutinib	ACP-5862	Adjusted Free Total Activity ¹
Erythromycin (also P-gp inhibitor)	100 mg BID	2.8	0.70	1.6
	100 mg QD	1.4	0.37	0.79
Fluconazole	100 mg BID	2.4	0.85	1.5
	100 mg QD	1.3	0.42	0.75
Diltiazem also P-gp inhibitor)	100 mg BID	2.3	0.81	1.5
	100 mg QD	1.1	0.42	0.75

¹Total Activity = acalabrutinib activity + ACP-5862 activity (reviewer calculated), adjusted for fraction unbound and BTK inhibition potency of acalabrutinib and ACP-5862

Source: Reviewer's analysis based on data from Applicant's D8220C00003 Study Report and Applicant's Response to Clinical Pharmacology Information Request, dated 08-11-2017

Acalabrutinib as a P-gp substrate and inhibitor:

Acalabrutinib is a substrate of P-gp transporter. The Applicant has conducted a clinical DDI study with concomitant itraconazole (a strong CYP3A inhibitor and P-gp inhibitor) and PBPK modeling with other dual inhibitors of CYP3A and P-gp (clarithromycin, erythromycin, diltiazem). The data indicate that, compared to P-gp, CYP3A metabolic pathway is the rate-limiting process in the overall clearance of acalabrutinib.

Acalabrutinib does not inhibit P-gp transporter at clinically relevant concentrations, per calculations according to FDA Draft Guidance on DDI ($[I]_1/IC_{50} < 0.1$, $[I]_2/IC_{50} < 10$).

Acalabrutinib as a BCRP substrate and inhibitor:

Acalabrutinib is a substrate of BCRP. However, acalabrutinib exposure is not expected to be affected by concomitant BCRP inhibitors, due to its high absorption. Additionally, BCRP genotype (421C>A) did not appear to have a clinically relevant effect on acalabrutinib exposure.

Acalabrutinib is a weak BCRP inhibitor at the intestinal level, per calculations according to FDA Draft Guidance on DDI ($[I]_1/IC_{50} < 0.1$, $[I]_2/IC_{50} = 21$). Acalabrutinib may therefore increase the exposure of concomitant BCRP substrates (e.g., methotrexate) via inhibition of intestinal BCRP.

APPEARS THIS WAY ON ORIGINAL

6.3.3. Physiologically-Based Pharmacokinetic Modeling Review

Objective

The main objective of this review is to evaluate the adequacy of Applicant's acalabrutinib physiologically-based pharmacokinetic (PBPK) model to 1) predict the effect of moderate and weak CYP3A inhibitors/ inducers on the exposure of acalabrutinib and its active metabolite (ACP-5862 or M27); 2) predict the DDI potential of acalabrutinib and ACP-5862 as a perpetrator in various drug-drug interaction (DDI) mechanisms with CYP substrate; 3) provide a dosing recommendation based on the predicted DDI potential.

To support its conclusions, the Applicant provided the following PBPK modeling and simulation reports and updates:

- *Summary of Clinical Pharmacology Studies [1]*
- *A PBPK M&S Evaluation (Using the SIMCYP Population-Based Simulator) of the Potential Drug-Drug Interactions Between Midazolam (a CYP3A4 Substrate), Moderate Inhibitors and Inducers of CYP3A and Oral Doses of ACP-196 (Study R2016001)[2]*
- *Physiologically Based Pharmacokinetic Modeling using SIMCYP(version 14) to Evaluate Potential Drug-Drug Interactions with Acalabrutinib and its Metabolite ACP-5862 (Study D8220C00003)[3]*
- *Response to FDA information request regarding PBPK (Email). [4][5]*

Background

Acalabrutinib (ACP-196) is a selective covalent inhibitor of Bruton's tyrosine kinase (BTK) for the treatment of patients with multiple indications (Mantle cell lymphoma (MCL), (b) (4)

. The proposed dosing regimen is 100 mg taken orally twice daily (bid) using a capsule formulation.

Acalabrutinib was extensively metabolized into more than 3 dozen metabolites by three primary metabolic pathways: amide hydrolysis, glutathione (GSH) conjugation, and CYP3A mediated hydroxylation. Acalabrutinib is mainly metabolized via CYP3A. Clinical studies showed that acalabrutinib pharmacokinetic (PK) was linear over the 75 to 250 mg dose range [1]. No drug accumulation in plasma was observed after repeated bid doses.

The Applicant reported that the active metabolite, ACP-5862, is the only metabolite in plasma that accounted for >10% of total acalabrutinib (¹⁴C) exposure in human plasma. Acalabrutinib and ACP-5862 accounted for 8.63% and 34.7%, respectively, of total acalabrutinib(¹⁴C) exposure in human plasma [1]. ACP-5862 was synthesized by the Applicant and its metabolism, physical chemistry, pharmacological activity and kinase selectivity were extensively characterized. Biochemical profiling showed that the kinase selectivity profile for ACP-5862 was similar to acalabrutinib [1]. In-vitro studies showed that ACP-5862 has approximately half of the BTK inhibitory potency of acalabrutinib [6]. Results of in-vitro studies and in-vivo metabolism profiling showed that the formation and metabolism of ACP-5862 are both mediated by CYP3A (Sec 5.2 of [6]).

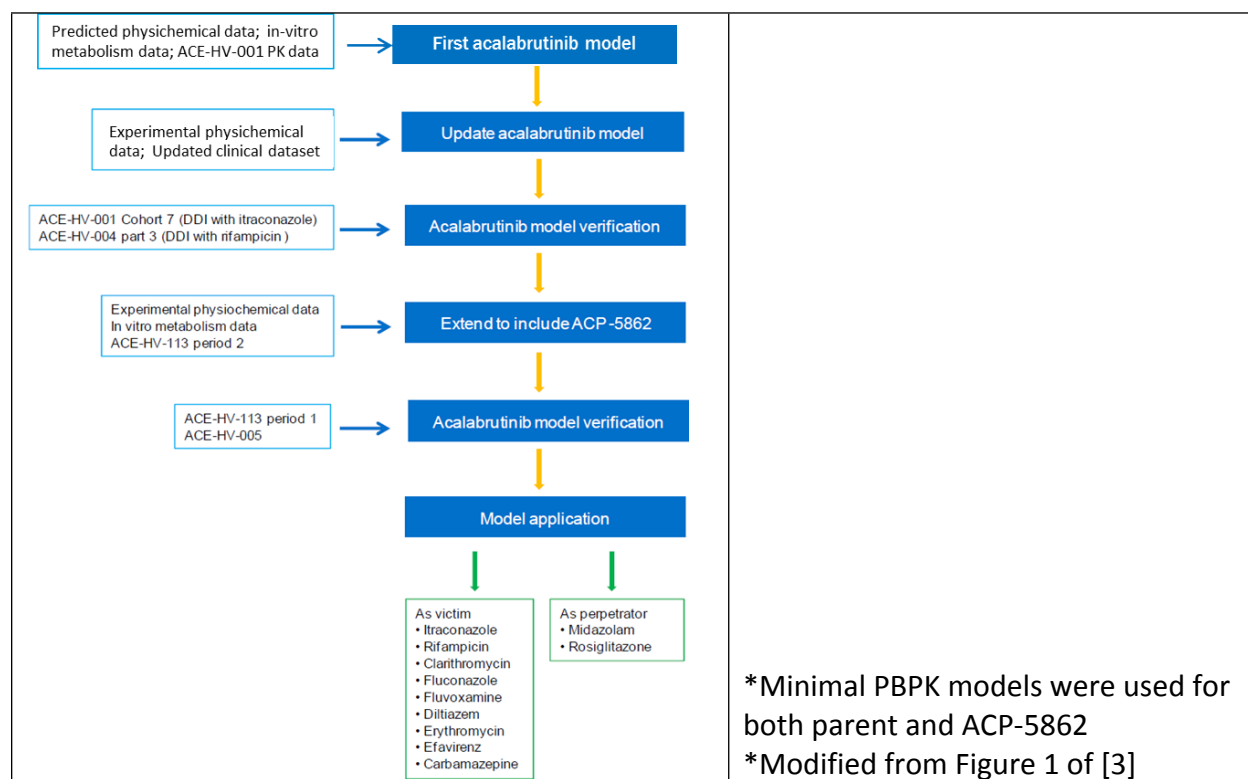
The Applicant conducted two clinical drug-drug interaction (DDI) studies with itraconazole and rifampicin in healthy subjects. Itraconazole increased acalabrutinib AUC by 5-fold and rifampicin reduced acalabrutinib AUC to 20%. In the current submission, the Applicant used PBPK modeling to derive the exposure of the active components (acalabrutinib and ACP-5862) under various DDI scenarios by accounting for the BTK inhibitor potency (IC_{50}) of acalabrutinib and ACP-5862.

Model Development

PBPK models

The Applicant submitted two versions of PBPK models of acalabrutinib using Simcyp software. In the first model [2], a minimal acalabrutinib PBPK model was developed to describe the clinical plasma concentration-time profiles of acalabrutinib in the healthy subjects and to predict DDI potential between acalabrutinib and various CYP modulators. The Applicant stated that experimentally measured values of acalabrutinib LogP and pKa were not available during the development of the first PBPK model. Thus, in-house predicted values of LogP and pKa were used. Similarly, values of fraction unbound in plasma protein (fup) and blood: plasma ratio (B/P) was determined based on preliminary dataset. In the second PBPK model [3], the Applicant updated the input parameters with new experimental data. The updated parent model was then extended to include the active metabolite, ACP-5862. Model parameters used for ACP-5862 were based on physiochemical characteristics, in vitro metabolism data and clinical PK data for ACP-5862. **Figure 9** shows a workflow of the development, verification and application of final PBPK model for acalabrutinib. Unless noted, this review is focused on the development and application of the second acalabrutinib PBPK model [3].

Figure 9 Workflow of development, verification and application of final acalabrutinib PBPK model



Oral clearance, CL_{po} , was 169 L/hr based on the human PK data following escalating single oral doses of acalabrutinib to healthy subjects (ACE-HV-001). Renal clearance, CL_R , is calculated as 1.33 L/hr based on the human mass-balance study (ACE-HV-009). Acalabrutinib PBPK model assumed first order oral absorption. In vitro studies showed that proportional contributions of glutathione and CYP450 mediated metabolic pathways of 21% and 79% respectively [6]. Based on the CYP recombinant data, CYP3A4-mediated metabolism accounts for 90% formation of the CYP metabolites. Based on these in-vitro datasets, the Applicant first assigned a value of 0.7 as the fractional metabolism by CYP3A4 (fm_{CYP3A}). The applicant later updated the value for fm_{CYP3A} to 0.82 to describe the DDI effects observed in a clinical trial with itraconazole (ACE-HV-001 Cohort 7).

The formation and metabolism of ACP-5862 was characterized in human microsome and recombinant CYP3A4 system. In-vitro studies showed that acalabrutinib was converted to ACP-5862 by CYP3A-mediated oxidation. Inhibitor study (XT164096) also showed that ketoconazole abolished 100% of ACP-5862 clearance in human liver microsomes. Therefore, the Applicant assigned CYP3A4 as the only enzyme for the formation and elimination of ACP-5862 in the model. A renal clearance (CL_R) of 0.3 L/h for ACP-5862 reported in ACE-HV-009 was applied in the model. On July 21 2017, a FDA information request was issued to clarify if ACP-5862 is the sole active metabolite of acalabrutinib [4]. The Applicant stated that other circulating metabolites either did not demonstrate BTK activity or were of low abundance [4]. Based on

relative abundance in plasma and chemical structure-activity relationships, the Applicant only characterized ACP-5862 in detail [4]. **Appendix Table 1** listed the PBPK model parameters for acalabrutinib and ACP-5862.

DDI simulations

Perpetrator models (clarithromycin (“clarithromycin.cmp”), fluconazole (“SV-fluconazole.cmp”), erythromycin (“Sim-erythromycin.cmp”), rifampicin (“SV-rifampicin-MD.cmp”), carbamazepine (“SV-Carbamazepine.cmp”) and efavirenz (“SV-Efavirenz.cmp”); and victim models diltiazem (“Sim-Diltiazem.cmp”) and rosiglitazone (“Sim-Rosiglitazone.cmp”) from the Simcyp V14/V15 drug model library were directly used by the Applicant in the PBPK analysis [3].

For fluvoxamine and midazolam, minor modifications were made on the Simcyp default models to improve the recovery of clinical dataset [3].

Applicant also developed PBPK models of itraconazole and its metabolite, hydroxy itraconazole. Itraconazole PBPK model was based on in vitro dataset and clinical plasma concentration profiles for itraconazole and hydroxy itraconazole reported in Barone et al., 1993 [3]. Itraconazole PBPK model was verified by comparing the simulated and observed plasma concentration-time profiles of itraconazole reported in Olkkola et al., 1994. The Applicant’s itraconazole PBPK model also was able to describe the DDI between midazolam and itraconazole reported in Olkkola et al., (1994). Itraconazole PBPK model parameters are presented in **Appendix Table 2**.

The Applicant conducted DDI simulations with midazolam or rosiglitazone to assess the potential for acalabrutinib and ACP-5862 to inhibit CYP3A4 or CYP2C8, respectively. In-vitro reported inhibition parameters of acalabrutinib and ACP-5862 of various CYP enzymes are presented in **Appendix Table 1**.

Model applications

Table 27 summarizes the design of simulations and clinical studies for each interacting drug.
Table 27 Trial designs for key PBPK simulations used in the PK and DDI simulations

	Perpetrator Drug	Dose Regimen	Victim Drug	Dose Regimen	Analysis	Note
1	acalabrutinib	50 mg sd	NA	NA	Pred-vs Obs PK of parent	Model development
2	acalabrutinib	100 mg bid	NA	NA	Pred-vs Obs PK of parent and M27	Model development
3	acalabrutinib	25 mg bid	NA	NA	Pred-vs Obs PK of parent	Model verification
4	acalabrutinib	75 mg bid	NA	NA	Pred-vs Obs PK of parent	Model verification
5	acalabrutinib	100 mg bid	NA	NA	Pred-vs Obs PK of parent and M27	Model verification
6	acalabrutinib	400 mg bid	NA	NA	Pred-vs Obs PK of parent and M27	Model verification

	Perpetrator Drug	Dose Regimen	Victim Drug	Dose Regimen	Analysis	Note
7	itraconazole	200 mg bid	acalabrutinib	50 mg sd	Pred-vs Obs PK of parent	Model development
8	rifampin	600 mg qd	acalabrutinib	100 mg sd	Pred-vs Obs PK of parent	Model verification
9	itraconazole	200 mg bid	acalabrutinib	100 mg bid	Pred only	Model application
10	rifampin	600 mg qd	acalabrutinib	100 mg bid	Pred only	Model application
11	rifampin	600 mg qd	acalabrutinib	200 mg bid	Pred only	Model application
12	clarithromycin	500mg qd	acalabrutinib	100 mg bid	Pred only	Model application
13	fluconazole	200 mg qd	acalabrutinib	100 mg bid	Pred only	Model application
14	fluvoxamine	150 mg qd	acalabrutinib	100 mg bid	Pred only	Model application
15	diltiazem	90 mg tid	acalabrutinib	100 mg bid	Pred only	Model application
16	erythromycin	500 mg tid	acalabrutinib	100 mg bid	Pred only	Model application
17	efavirenz	600 mg qd	acalabrutinib	100 mg bid	Pred only	Model application
18	carbamazepine	400 mg qd	acalabrutinib	100 mg bid	Pred only	Model application
19	acalabrutinib	100 mg bid	midazolam	5 mg sd	Pred only	Model application
20	acalabrutinib	100 mg bid	rosiglitazone	4 mg sd	Pred only	Model application

*Data source: PBPK reports [2, 3]

6.3.4. Results

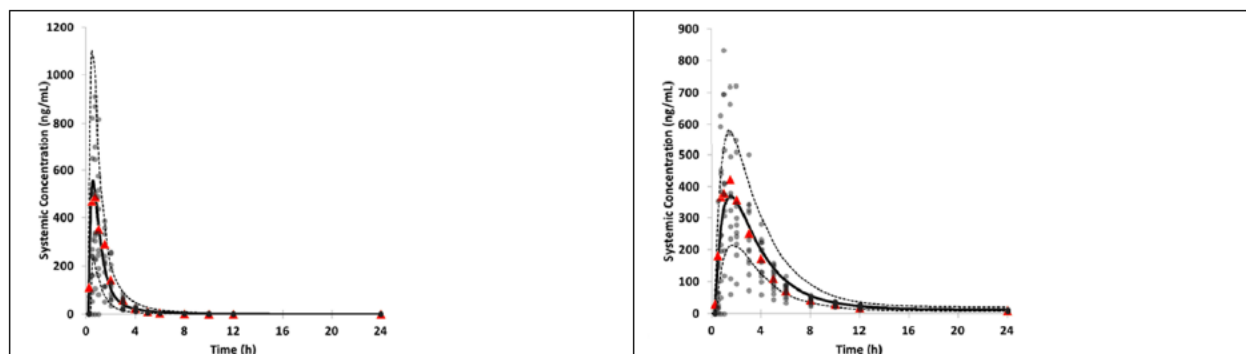
Q1. Can PBPK model reasonably describe the PK of acalabrutinib and ACP-5862 in healthy subjects?

Yes. Simulations using the submitted acalabrutinib PBPK model reasonably described the plasma concentration-time profiles of acalabrutinib following single oral doses of 25, 50, 75 or 100 mg acalabrutinib in healthy subjects. The model also simultaneously described the plasma concentration-time profiles of acalabrutinib and ACP-5862 after a single oral dose of 100 mg acalabrutinib (**Figure 10**).

Figure 10 Observed and simulated PK of acalabrutinib and ACP-5862 after a single oral dosing of 100 mg acalabrutinib in healthy subjects

A. acalabrutinib	B. ACP-5862
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NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}



* Simulated values are displayed as lines, including mean (solid line), 5% and 95% percentile (dashed lines). Observed data from Clinical Study ACE-HV--113 period 2 are displayed as dots, including mean (red triangles) and individual values (grey dots).

*Extracted from Applicant's PBPK report Figure 5 [3]

In addition, the model reasonably described the PK of ACP-5862 following a single oral dose of 400 mg acalabrutinib. However, the model under-predicted the PK of acalabrutinib following a single oral dose of 400 mg acalabrutinib (Table 28). The Applicant did not provide a rationale for the under-prediction of the acalabrutinib exposure after a single dose of 400mg acalabrutinib. Applicant stated a 2-fold difference on the observed and simulated exposure of acalabrutinib is acceptable.

Table 28 Observed and simulated PK of acalabrutinib and ACP-5862 after a single oral dosing of 400 mg acalabrutinib in healthy subjects

	acalabrutinib		ACP5862(M27)	
	Cmax (ng/mL)	AUC (ng/mL.hr)	Cmax (ng/mL)	AUC (ng/mL.hr)
Predicted Geo Mean (n=180)	1650	2509	1350	7011
Predicted Mean (n=180)	1864	2797	1439	7338
Predicted Minimum	174	364	313	1673
Predicted Maximum	5877	8154	3588	15003
Predicted CV (%)	52	48	36	31
Observed Geo Mean (n = 18)	1940	4681	2039	7938
Observed Mean (n=18)	2153	5347	2190	8629
Observed CV (%)	45	45	35	38

*Summarized from Applicant's PBPK report Table 7[3]. Observed data were from Clinical Study ACE-HV-005 treatment 2

Q2. Can acalabrutinib PBPK models provide a reasonable description of the observed DDI effects of acalabrutinib as a victim (with CYP3A moderators)?

The current acalabrutinib PBPK model reasonably described the plasma concentration-time profiles for acalabrutinib with/without itraconazole as shown in Table 29 and Appendix Figure 1.

Table 29 Observed and simulated PK of acalabrutinib and ACP-5862 following repeat dosing of itraconazole 200mg bid

	acalabrutinib 50mg sd		acalabrutinib 50mg sd + itraconazole 200mg bid		Ratio with/without itraconazole	
	Cmax (ng/mL)	AUC (ng/mL.hr)	Cmax (ng/mL)	AUC (ng/mL.hr)	Cmax ratio	AUC ratio
Predicted Geo. Mean	193	297	624	1427	3.23	4.80
Observed Geo. Mean	166	239	649	1242	3.90	5.21

*Summarized from Table 2 of Applicant's PBP model report [3]

Hepatic fm_{CYP3A} value of 0.82 was assigned to allow the best description of observed DDI effect with itraconazole [3]. The Acalabrutinib PBPK model was able to predict the observed DDI effects with rifampin (**Table 30 and Appendix Figure 2**), supporting the estimated value of fm_{CYP3A} . Therefore, acalabrutinib PBPK model is adequate to predict untested clinical DDI scenarios with CYP3A modulators.

Table 30 Observed and simulated PK of acalabrutinib and ACP-5862 following repeat dosing of rifampicin 600mg qd

	acalabrutinib 100mg sd		acalabrutinib 100mg sd + rifampicin 600mg qd		Ratio with/without rifampicin	
	Cmax (ng/mL)	AUC (ng/mL.hr)	Cmax (ng/mL)	AUC (ng/mL.hr)	Cmax ratio	AUC ratio
Predicted Geo. Mean	407	614	96	127	0.24	0.21
Observed Geo. Mean	450	641	142	150	0.32	0.23

*Summarized from Table 3 of Applicant's PBP model report [3]

The Applicant then used the acalabrutinib PBPK model to predict DDIs for acalabrutinib and its metabolite with various CYP3A modulators at steady-state. Given CYP3A is the enzyme responsible for the formation and elimination of ACP-5862 (based on in-vivo metabolite profiling and in vitro studies) [5], the acalabrutinib PBPK model is sufficient to predict the effects of CYP3A modulators on the PK of acalabrutinib and ACP-5862.

Two types of plasma AUC were used by the Applicant to represent the systemic exposure of acalabrutinib and its metabolite: 1) AUC of acalabrutinib only, and 2) total active moiety AUC combined the exposure of acalabrutinib and ACP-5862 based on their molecular weights and potency for BTK inactivation (Equation 1) [3].

$AUC_{\text{total active moiety}} = AUC_{\text{acalabrutinib}} + \frac{MW_{\text{Acalabrutinib}}}{MW_{M27}} \times AUC_{M27} \times 0.5$	Equation 1
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One additional type of plasma AUC was used by the FDA review to further adjust total active moiety with fup and IC₅₀s of BTK inactivation of each active moiety (Equation 2).

$AUC_{\text{adjusted free total active moiety}} = AUC_{\text{acalabrutinib}} \times fup_{\text{acalabrutinib}} \times IC_{50_{\text{acalabrutinib}}} + \frac{MW_{\text{Acalabrutinib}}}{MW_{M27}} \times AUC_{M27} \times fup_{M27} \times IC_{50_{M27}}$	Equation 2
---	------------

*IC_{50-acalabrutinib}: 5μM; IC_{50-M27}: 3μM [5]

Table 31 shows the simulated plasma AUC for acalabrutinib and ACP-5862, and ratios of three type of AUC with/without co-administration with CYP3A modulators.

Table 31 Simulated geometric mean AUC values of acalabrutinib and ACP-5862 in the absence and presence of different CYP3A4 inhibitors/inducers

	acalabrutinib dosing (mg)	acalabrutinib AUC ng/mL.hr		ACP5862(M27) AUC ng/mL.hr		acalabrutinib AUC ratio	total moiety AUC ratio	adjusted free total moiety AUC ratio
		Drug	Drug +inh	Drug	Drug +inh			
ITZ	100bid	1209	5550	6072	927	4.59	1.45	1.96
RIF	100bid	1252	214	7578	3888	0.17	0.43	0.39
RIF	200bid	1252	433	7578	7776	0.35	0.85	0.78
CLR	100bid	1267	4233	6115	3142	3.34	1.36*	1.69
FLC	100bid	1266	3082	7024	5958	2.43	1.28	1.46
FLU	100bid	1262	1731	6564	6324	1.37	1.08	1.13
DTZ	100bid	1243	2831	5042	4060	2.28	1.30	1.48
ERY	100bid	1267	3499	6115	4266	2.76	1.32	1.56
EFV	100bid	1267	497	6115	5037	0.39	0.69	0.64
CBZ	100bid	1239	484	6457	5626	0.39	0.73	0.68

*1.47 was misprinted in Table 34 of Applicant's PBPK report [3]

‡ ITZ- Itraconazole, RIF- Rifampicin, CLR- Clarithromycin, FLC- Fluconazole, FLU- Fluvoxamine, DTZ – Diltiazem, ERY-Erythromycin, EFV- Efavirenz, CBZ -Carbamazepine

As shown in **Table 31**, PBPK simulations predicted an approximate 5-fold increase in the acalabrutinib AUC and 5-fold decrease in ACP-5862 AUC following concomitant use of itraconazole. However, the magnitudes of changes in exposure of total active moiety and adjusted free total moiety AUC were much lower. The model predicted less than 2-fold increase in the AUC of adjusted free total moiety following concomitant use of acalabrutinib 100mg bid with strong or moderate CYP3A inhibitors. The simulation results showed that concomitant use of acalabrutinib with rifampin would result in approximate 80% decrease in acalabrutinib AUC and less than 20% decrease in ACP-5862 AUC. The model predicted a 30%-50% reduction in the

AUC of adjusted free total moiety following concomitant use of acalabrutinib 100mg bid with strong or moderate CYP3A inducers. The FDA reviewer views the exposure of adjusted free total active moiety as the preferred exposure marker for efficacy of acalabrutinib, given it was determined based on free concentration and potency for BTK inactivation for individual moiety. However, there is limited information available to characterize the exposure-relationship between individual active moiety and the clinical adverse response such as neutropenia.

On August 10 2017, a FDA information request was issued to simulate 100 mg acalabrutinib once daily with concomitant moderate CYP3A inhibitors (fluconazole, diltiazem, erythromycin) [5]. **Table 32** summarizes the simulated exposure of acalabrutinib and its metabolite under different DDI scenarios, using 100 mg acalabrutinib bid as reference.

Table 32 Predicted effect of moderate CYP3A inhibitors on acalabrutinib exposure

Moderate CYP3A Inhibitor	Acalabrutinib Dosing Regimen	Geometric Mean AUC Ratio (vs. 100 mg bid alone)		
		acalabrutinib AUC ratio	total moiety AUC ratio	adjusted free total moiety AUC ratio
Erythromycin	100 mg bid	2.76	1.32	1.56
	100 mg qd	1.37	0.67	0.79
Fluconazole	100 mg bid	2.43	1.28	1.46
	100 mg qd	1.27	0.65	0.75
Diltiazem	100 mg bid	2.28	1.30	1.48
	100 mg qd	1.13	0.66	0.75

Source: calculated based on Table 34 of Applicant's PBPK report [3] and Applicant's Response to Clinical Pharmacology Information Request, dated 08-11-2017

Q3. Can acalabrutinib PBPK models provide a reasonable prediction of the DDI effects of acalabrutinib as a perpetrator (on probe CYP3A and CYP2C8 substrates)?

Yes, the current PBPK models are adequate to predict effects of acalabrutinib on the PK of sensitive probe CYP3A and CYP2C8 substrates.

In vitro studies have shown that both acalabrutinib and ACP-5862 can inhibit CYP2C8 and CYP3A via reversible and/or non-reversible mechanisms [1]. The Applicant included in-vitro derived inhibition parameters in the PBPK model to evaluate the effect of acalabrutinib and ACP-5862 on the PK of midazolam (CYP3A substrate) and rosiglitazone (CYP2C8 substrate). The model predicted no interactions with CYP3A4 or CYP2C8 substrates after repeated doses of acalabrutinib 100-mg bid (**Table 33 and Table 34**). Additional simulations were conducted by FDA reviewer to represent worst-case scenarios. By assigning the values of K_i that is one-tenth of the in-vitro value, the model predicted minimal changes in the PK of midazolam and rosiglitazone as shown in **Table 33 and Table 34**.

Table 33 Simulated effects of acalabrutinib on PK of midazolam

CYP3A4/5	acalabrutinib K_i = 23.9 μ M ; K_I = 10.1 μ M (original in-vitro/PBPK inputs)	acalabrutinib K_i = 2.4 μ M ; K_I = 1 μ M
	Predicted GM (5-95% percentile)	Predicted GM (5-95% percentile)
Midazolam Cmax Ratio	1.02 (1.02-1.02)	1.21 (1.20-1.23)
Midazolam AUC Ratio	1.03 (1.03-1.04)	1.36 (1.33-1.39)

*see **Table 27** for simulation protocol; K_i , time-dependent inhibition constant; K_I , reversible inhibition constant

Table 34 Simulated effects of acalabrutinib on PK of rosiglitazone

CYP2C8	acalabrutinib K_i = 20.6 μ M; ACP5862(M27) K_I = 4 μ M (original in- vitro/PBPK inputs)	acalabrutinib K_i = 2 μ M; ACP5862(M27) K_I = 0.4 μ M
	Predicted GM (5-95% percentile)	Predicted GM (5-95% percentile)
Rosiglitazone Cmax Ratio	1 (1.0-1.0)	1.02 (1.02-1.02)
Rosiglitazone AUC Ratio	1.02 (1.02-1.02)	1.16 (1.14-1.18)

*see **Table 27** for simulation protocol; K_i , time-dependent inhibition constant; K_I , reversible inhibition constant

Conclusion

The acalabrutinib PBPK model is sufficient to predict the PK of acalabrutinib and active metabolite, ACP-5862, co-administered with various CYP3A modulators. The model predicted a less than 2-fold increase in the AUC of free total active moiety following concomitant use of acalabrutinib 100mg bid with strong or moderate CYP3A inhibitors. When co-administrated with strong or moderate CYP3A inducers, the model predicted a 30%-60% reduction in the AUC of free total active moiety following acalabrutinib 100mg bid. Of note, the dosing recommendation for DDI scenarios such as strong inhibitors, where the increase in acalabrutinib AUC exceeded those observed in acalabrutinib 400 mg qd dosing (highest administered dose), should be determined in conjunction of the exposure-safety analyses of parent compound.

The Applicant's acalabrutinib PBPK model is also adequate to predict DDIs between acalabrutinib and sensitive probe CYP3A and/or CYP2C8 substrates. Simulation results indicated there are minimal effects of acalabrutinib on PK of midazolam (CYP3A substrate) and rosiglitazone (CYP2C8 substrate) after repeated doses of acalabrutinib 100-mg bid.

Abbreviations

bid., twice daily dosing; B/P, blood to plasma ratio; AUC, area under the concentration-time profile; AUC ratio, the ratio of the area under the curve of the substrate drug in the presence

and absence of the perpetrator; B/P, blood to plasma ratio; C_{max}, maximal concentration in plasma; C_{max} ratio, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; DDI, drug-drug interaction; F, bioavailability; F_a, fraction absorbed; f_{mCYP3A}, fraction of clearance mediated; f_{up}, fraction unbound in plasma; K_i, time-dependent inhibition constant; K_i, reversible inhibition constant; K_m, Michaelis-Menten Constant; k_{inact}, maximal inactivation rate constant; logP, logarithm of the octanol-water partition coefficient; NA, not applicable; P_{eff,man}, effective passive permeability in man; PBPK: Physiological-based Pharmacokinetic; qd, once daily dosing; sd, single dosing

6.3.5. Population Pharmacokinetics and Exposure-Response Analyses

Pharmacometric review

Summary of Findings

Key Review Questions

The purpose of this review is to address the following key questions.

Do E-R relationships for efficacy and safety support a 100 mg BID dose regimen of acalabrutinib in patients with Mantle Cell Lymphoma (MCL) who have received at least 1 prior therapy?

Yes.

No significant ER relationship for efficacy was identified. A positive relationship with the incident rate of Grade 2+ neutropenia versus acalabrutinib AUC was identified. No evident relationship for other adverse events of interest including Grade 2+ Hemorrhage, Cardiac events, Cytopenias Anemia, Cytopenias Thrombocytopenia, Hepatic events, Hypertension, Infections, Diarrhoea or Headache was observed. Given the strong efficacy results and mild safety profile, the dosing regimen of 100-mg BID is acceptable in general population.

Is dose adjustment needed for specific population?

No.

Population PK analysis suggested that the following factors, i.e. gender, age, body weight, race (white vs. black), ethnicity, acid reducing agents or ECOG performance, have no clinically meaningful effect on the clearance of acalabrutinib. Therefore, the conclusion that no dose adjustment is needed in specific population is acceptable. The relative change in exposure from use of ARA estimated in this study was smaller than observed in controlled healthy volunteer DDI studies. However, data on concomitant ARA use, such as time of administration during PK assessment periods, were less detailed in the patient studies.

Is dose adjustment needed for renal impairment or hepatic impairment patients?

No.

Renal clearance contributes minimally to the overall clearance of acalabrutinib (< 1%) following an IV microtracer dose in healthy subjects. Population PK analysis indicated that mild or moderate RI is not a significant covariate for acalabrutinib PK. No dose adjustment is needed in patients with renal impairment.

Population PK analysis showed there was no impact of mild/moderate hepatic impairment as measured by NCI criteria on acalabrutinib exposure. The acalabrutinib exposure in patients with mild/moderate hepatic impairment is around 1.24 fold higher than that in patients with normal hepatic function. The population PK study was based on 533 subjects with normal hepatic function, 41 patients with mild hepatic impairment, and 3 patients with moderate hepatic impairment. No patient with severe hepatic impairment was included in the studies. Therefore, no dose adjustment is needed in patients with mild or moderate hepatic impairment.

6.3.6. Recommendations

The sponsor's proposed dosing regimen is acceptable.

6.3.7. Results of Sponsor's Analysis

Population Pharmacokinetics

Plasma concentrations of acalabrutinib and relevant covariate data from 12 clinical trials were included in the analysis: 6 Phase I trials in healthy volunteers and 6 Phase I/II trials in patients with CLL, MCL, FL, DLBCL, MY or WM. The pooled analysis dataset comprised 11196 acalabrutinib plasma concentrations and relevant covariates from 285 healthy volunteers and 292 patients. The bulk of the concentration records are from the 15, 25, 100 and 200mg dose groups. Acalabrutinib metabolite concentrations were not included in the analysis.

Data were analyzed using a nonlinear mixed effects modelling approach in NONMEM. Body weight was added in the base model according to allometric principles to account for the impact of body weight on structural parameters. A full covariate model approach was conducted. Covariates added to Vc/F and/or CL/F included: (i) acid reducing agents, (ii) race, (iii) sex, (iv) health group, (v) estimated glomerular filtration rate (eGFR), (vi) hepatic impairment (NCI criteria), and (vii) dose.

A 2-compartment structural model with sequential zero- and first order absorption and a lag time best described the acalabrutinib concentration-time data. The model was parameterized in terms of lag time (ALAG1), duration of zero order input (D1), first order absorption constant (Ka), apparent clearance (CL/F), apparent volume of central compartment (Vc/F), inter-compartment clearance (Q/F) and apparent volume of peripheral compartment (V2/F). Between subject variability (BSV) was estimated for CL/F and Vc/F. The correlation between the two random effects was considered.

The estimated population means of ALAG1, D1, Ka, CL/F, Vc/F, Q/F and Vp/F are: 0.161 (h), 0.361 (h), 0.941 (h⁻¹), 159 (L/h), 33.9 (L), 14.6 (L/h), and 213 (L), respectively. BSV in CL/F and Vc/F were 46.8 (%CV) and 178 (%CV), respectively. The developed PK model for acalabrutinib was adequate for deriving exposure estimates to be used in subsequent PK/PD analyses relating exposure of acalabrutinib to clinical outcomes.

The model predicted area under the plasma concentration-time curve and maximum concentration at steady state (AUC_{24h,ss}, C_{max,ss}) for the reference subject were 1111 [457-2840] ng/mL *h and 323 [47.7-934] ng/mL, respectively (point estimate and range representing between subject variability obtained by Monte Carlo simulations of the model).

The reference subject was defined as a white, male patient, with a body weight of 80 kg, an eGFR of 90 mL/min/1.73m², normal hepatic function and no concomitant acid reducing agents.

CL/F was found to decrease with dose. The 15mg dose group had a 1.35-fold higher CL/F compared to the 100 mg dose group, while the 400 mg dose group had a 0.80-fold lower CL/F. However, the change in CL/F over the 75 mg–250 mg range was negligible and the PK can generally be considered linear in that range.

Body weight was the only intrinsic covariate included in the full model that caused a mean change in AUC_{24h, ss} of more than 20% (142% and 66% of the value in an 80 kg subject for 50 kg and 140 kg, respectively). However, the relationship between CL/F and body weight was fixed based on allometric principles and not estimated from this data. Further exploration of the AUC_{24h, ss}-body weight relationship indicated that there is no clinically relevant impact.

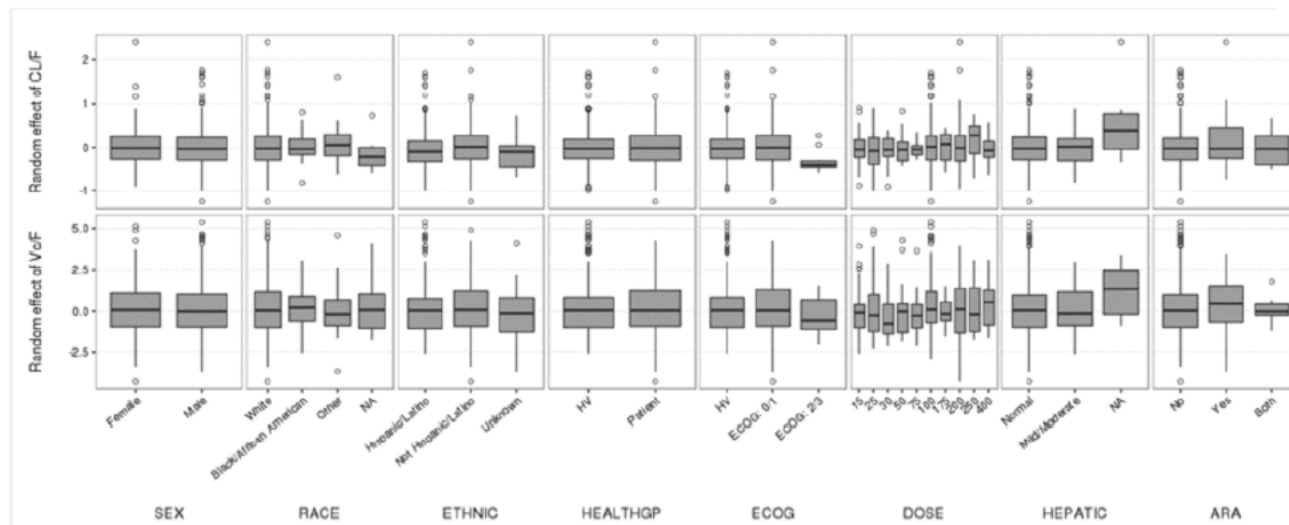
Acid reducing agents (ARA; H₂RA and/or PPI) had an impact on Vc/F, causing a 0.68-fold lower C_{max,ss} (68% of the value in an untreated subject). The impact on AUC_{24h,ss} was smaller (83% of the value in an untreated subject). The relative change in exposure from use of ARA estimated in this study was smaller than observed in controlled healthy volunteer DDI studies (68% and 83% compared to 25% and 47% in ACE-HV-004, 28% and 64% in ACE-HV112 for C_{max} and AUC, respectively). However, data on concomitant ARA use, such as time of administration during PK assessment periods, were less detailed in the patient studies.

AUC_{0-last} of acalabrutinib increased less than 2-fold in subjects with mild or moderate hepatic impairment compared to subjects with normal liver function. Patients with severe hepatic impairment were not studied. Based on this study and the population PK analysis, no dose adjustment is necessary in mild or moderate hepatic impairment.

To illustrate the impact of covariates on exposure, individual predictions of AUC_{24hr, ss} and C_{max,ss} for a 100 mg BID acalabrutinib regimen (therapeutic dose) were calculated and data were plotted versus relevant covariates. The full model and additional graphics show that none of the covariate-PK parameter relationships revealed any clinical meaningful changes in acalabrutinib exposure (Figure 11). Therefore, there is no need for dose adjustment due to age,

body weight, sex, ethnicity, race (white vs. black), mild or moderate renal impairment status, mild hepatic impairment status and/or ECOG performance status (0 vs. 1).

Figure 11: Boxplots of random Effects of CL/F(top row) and Vc/F (bottom row) vs Categorical Covariates (columns)



Source: Table 11 of population –PKPD report

Table 35: Summary of AUC_{24h,ss} and C_{max,ss} from 100 mg BID regimen by categorical covariate category

Characteristic	Category	N	AUC _{24h,ss} ^a	C _{max,ss} ^a
Sex	Female	200	1268 [542.8-2470]	364 [63.62-766.2]
	Male	397	1069 [382-2412]	299.5 [38.24-709]
Renal Impairment	Normal	226	1116 [353.6-2146]	322.4 [28.67-667.4]
	Mild	282	1117 [479.6-2549]	309.6 [64.07-775.3]
	Moderate	86	1255 [457.4-2108]	359.9 [39.89-634]
	Severe	1 ^b	1208	235.1
	Missing	2 ^b	123, 856.6	24.65, 283.2
Hepatic Impairment (NCI)	Normal	539	1120 [401.8-2395]	321.7 [38.64-728.8]
	Mild/Moderate	51	1145 [507.6-2655]	300.7 [114.6-820.2]
	Missing	7	875.9 [190.6-1595]	212.2 [28.19-517.7]
Race	White	505	1127 [400.8-2441]	316.9 [38.72-740.9]
	Black/African American	48	1118 [597.7-1917]	336.3 [110-619.3]
	Other	29	1066 [468.4-2258]	297.6 [50.36-720.4]
	Missing	15	1355 [709.4-2283]	354.2 [71.32-603.4]
Ethnicity	Hispanic/Latino	186	1152 [310-2253]	339.2 [23.59-667.9]
	Not Hispanic/Latino	389	1090 [464.2-2469]	301.4 [47.95-745.4]
	Unknown	22	1270 [577.4-2236]	372 [87.97-657.2]
ARA	No	514	1132 [438.7-2436]	330.4 [39.19-748.2]
	Yes	83	1077 [340.3-2368]	236 [38.33-556.4]
ECOG Performance status	HV	285	1077 [384-2126]	322.5 [33.41-639.6]
	0	112	1112 [462.9-2213]	306.1 [47.53-748.6]
	1	187	1168 [463.3-2524]	301.4 [40.38-786.1]
	2	11	1649 [862.3-2078]	409.9 [165.9-548.5]
	3	2 ^b	1676, 2358	423.5, 526.8

Source: Table 12 of population –PKPD report

Reviewer's Comments: Overall the sponsor's pop-PK model is acceptable, which could describe the concentration time curve pretty well. Gender, renal Impairment, hepatic impairment (mild or moderate), race, ethnicity, ARA or ECOG performance are not significant covariates for clearance. There is no information for patients with severe renal impairment. The conclusion that no dose adjustment is needed in specific population is acceptable.

The relative change in exposure from use of ARA estimated in this study was smaller than observed in controlled healthy volunteer DDI studies. However, data on concomitant ARA use, such as time of administration during PK assessment periods, were less detailed in the patient studies.

For further information, please refer to Section 0 in FDA reviewer's analysis.

Exposure Response Analysis

Exposure-safety and exposure-efficacy relationships were evaluated in patients with B-cell malignancies receiving acalabrutinib monotherapy in clinical studies. A total of 6 studies were included for exposure-safety and exposure-efficacy exploratory analyses, see Table 36.

Exposure-safety analyses were performed using pooled data from the 6 studies listed in Table 36. A total of 292 patients were included in the exposure-safety analyses; exposure data (AUC₀₋₂₄ and C_{max}) derived from the population PK analysis (Study D8220C00002) were used in the analysis. Analyses were performed using data from all patients who had at least one set of the estimated PK parameters. Individual PK parameters (AUC and C_{max}) from the 6 studies were merged with the corresponding safety data collected in the same studies. In the studies, acalabrutinib was administered orally as bid and qd regimens (100, 175, 200, 250, and 400 mg qd or 100 mg and 200 mg bid). A total of 180 patients received acalabrutinib 100-mg bid as a starting dose.

Exposure-efficacy analyses were performed using data from Study ACE-LY-004 alone. A total of 45 patients with MCL were included in the exposure-efficacy analyses.

Table 36: Studies included in exposure-response analyses

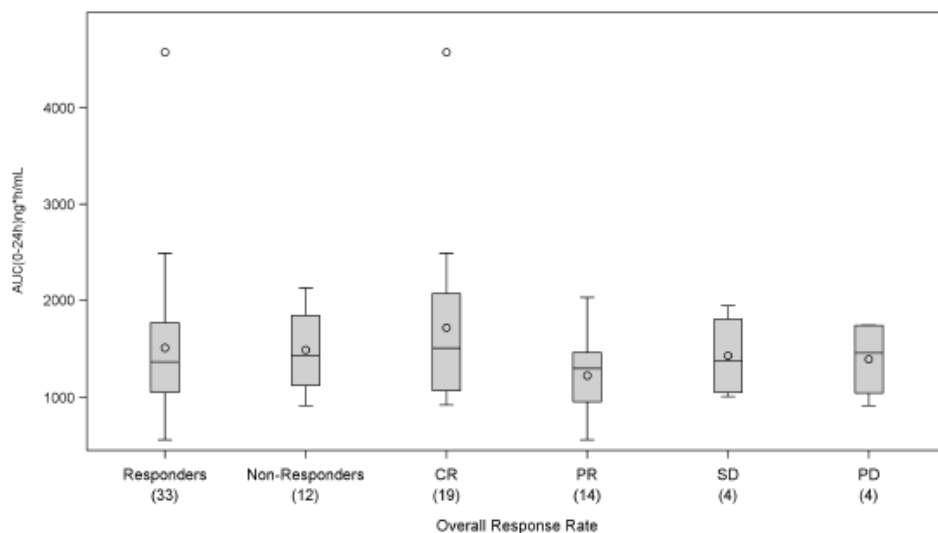
Study	Study Description	PK sample collection	N with PK data (all/100 mg bid)
ACE-CL-001	Phase 1/2 study in patients with CLL, Richter's Syndrome or PLL	Cycle 1: Days 1, 8, 15, 22 and 28	160/54
ACE-LY-004	Phase 2 study in patients with MCL	Cycle 1: Days 1, 8, 15, 22 and 28	45/45
ACE-WM-001	Phase 1/2 in patients with WM	Cycle 1: Days 1, 8, 15, 22 and 28	50/44
ACE-LY-002	Phase 1b study in patients with R/R de novo activated B-cell subtype of DLBCL	Cycle 1: Days 1, 8, 15, 22 Cycle 2: Day 1	15/15
ACE-LY-003	Phase 1b study of acalabrutinib alone or in combination with rituximab in patients with FL	Cycle 1: Days 1, 8, 15, 22 and 28	9/9
ACE-MY-001	Phase 1b study of acalabrutinib or in combination with dexamethasone in patients with MM	Cycle 1: Days 1, 8, 15, 22 and 28	13/13
Total			292/180

Source: Table 9 of summary of clinical pharm report

Only data from the ongoing Study ACE-LY-004 in patients with MCL (n=45) were included in the exposure-response analysis of efficacy outcomes. In this study, patients received oral doses of acalabrutinib 100-mg bid. The PK exposure for acalabrutinib was summarized as cumulative AUC over 24 h (AUC₀₋₂₄) and C_{max}. The efficacy of acalabrutinib, measured as Overall Response Rate (ORR), ie, responder, or nonresponder versus PK exposure was investigated. The responder group was further divided into complete response (CR) or partial response (PR), and the nonresponder group was divided into patients with stable disease, and progressive disease. Investigator and IRC assessments per Lugano classification (2014) were provided.

Figure 12 depicts box plots of the relationship between AUC0-24 and ORR, and the figure is also stratified by categories of response. The left-hand side of the figure depicts AUC0-24 by overall response (responder [CR or PR] or nonresponder). Per protocol, any patient missing response information was categorized as a nonresponder for ORR. The right-hand side of the figure depicts AUC0-24 by best overall response in patients for which response information is available. Per protocol, any patient missing ORR information was categorized as a nonresponder. Corresponding exposures (AUC0-24) are summarized in table 37.

Figure 12: Box plot of acalabrutinib AUC0-24 by overall response rate as assessed by IRC per Lugano Classification (n=45; ACE-LY-004)



Source: Figure 38 of summary of clinical pharm report

As depicted in Figure 12, there were no trends between AUC0-24 and ORR (responders and non-responders) and median acalabrutinib AUC0-24 was similar between responders and nonresponders, as well as across the 4 response categories. Similar results were observed when ORR, including the 4 response categories, was evaluated against Cmax. The results based on investigator assessments are consistent with those based on IRC assessments. No further investigations of effects of covariates on efficacy were undertaken due to small sample size.

Table 37: Summary of AUC0-24 by efficacy response as assessed by IRC per Lugano classification (ACE-LY-004; n=45)

Response	n	AUC ₀₋₂₄ (ng•h/mL)			
		Mean (SD)	Median	Minimum	Maximum
Responder	33	1508.7 (725.13)	1366.0	564.4	4575.0
Nonresponder ^a	12	1487.9 (445.80)	1424.5	914.3	2127.0
Responders:					
Complete response (CR)	19	1716.5 (847.21)	1505.0	924.1	4575.0
Partial response (PR)	14	1226.7 (389.45)	1299.9	564.4	2028.0
Nonresponders:					
Stable disease	4	1428.9 (452.12)	1381.9	1007.6	1944.0
Progressive disease	4	1393.8 (415.19)	1459.5	914.3	1742.0

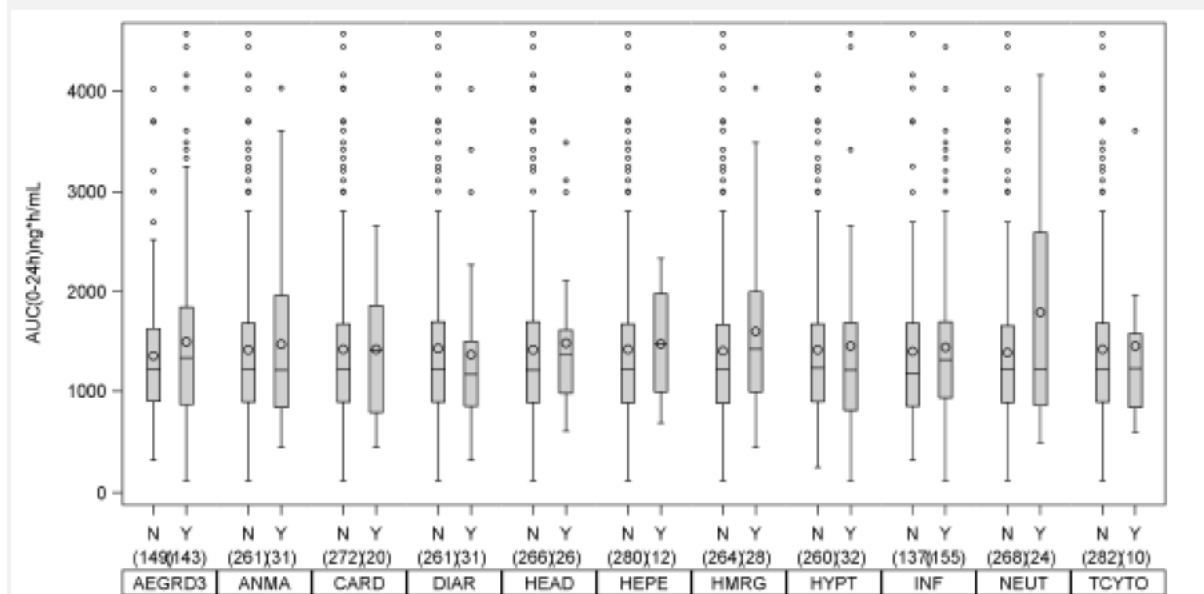
Source: Table 10 of summary of clinical pharm

Exposure-safety analyses were performed on data from patients with B-cell malignancies who received acalabrutinib as monotherapy (n=292) in the 6 clinical studies. Safety parameters included the occurrence of adverse events (AEs) grade ≥ 3 , headache, diarrhea, as well as AEs of clinical interest. The AEs of clinical interest investigated in the exposure-safety analysis included anemia, cardiac events, hepatic events, hemorrhage, hypertension, infections, neutropenia, and thrombocytopenia.

Figure 13 depicts box plots of AUC0-24 by AEs. The first boxes (Y/N) on the left-hand side depict the number of patients that experienced a grade ≥ 3 AE (Y) and those who did not (N). The other boxes depict the number of patients with headache, diarrhea, as well as individual events of clinical interest.

The AUC0-24 by AEs depicted in Figure 13. There were no trends between of PK exposure (AUC0-24) and AEs. Similar results were observed when AEs were evaluated against C_{max} (Exposure-response analysis. Exposure-safety relationships were further evaluated for patients receiving 100-mg bid treatment of acalabrutinib (n=180). Acalabrutinib AUC0-24 was comparable whether AEs that are grade 3 and above, anemia, cardiac events, hepatic events, hemorrhage, hypertension, infections, neutropenia, and thrombocytopenia are present or absent. Similar results were observed when AEs were evaluated against C_{max}.

Figure 13: Box plot of acalabrutinib AUC0-24 by AEs in patients with B-cell malignancies (==292)



Source: Figure 39 of summary of clinical pharm

Reviewer's Comments: Please refer to FDA reviewer's analysis in Section 0 and Section 0. Briefly logistic regressions for exposure efficacy and exposure safety relationships were conducted. No significant ER relationship for efficacy was identified. A positive relationship with the incident rate of Grade 2+ neutropenia versus acalabrutinib AUC was identified. No evident relationship for other interested events like Grade 2+ Hemorrhage, Cardiac events, Cytopenias Anemia, Cytopenias Thrombocytopenia, Hepatic events, Hypertension, Infections, Diarrhea or Headache was identified.

6.3.8. Reviewer's Analysis

Objectives

The reviewer's analysis is to answer the following question:

- Is the proposed dosing appropriate in patients with hepatic or renal impairment?
- Is dose adjustment needed for specific population?
- Do E-R relationships for efficacy and safety support a 100 mg BID dose regimen of acalabrutinib in patients with Mantle Cell Lymphoma (MCL) who have received at least 1 prior therapy?

Data Sets

- acalabrutinib_Comb_20161118.csv
- ADSL.csv
- CMAXAUC.csv

Software

- NONMEN (Version 7.2, ICON Development Solutions)
- R (3.4.0. Insightful Inc.)
- Pirana 2.9.0 (Pirana Software & Consulting BV 2014)

6.3.9. Results

Population Pharmacometrics

Population pharmacometrics models (Pop-PK models) were evaluated by removing certain covariates on clearance (run100e – run112 in Table 38). All the models minimized successfully. Sponsor's final model (model ID: run100d) was set as reference model. Clearance in sponsor's final model was demonstrated as follows:

$$CL = TVCL * \left(\frac{BWT}{70}\right)^{0.75} * \left(\frac{DOSE}{100}\right)^{Dose_CL} * \left(\frac{BEGFR}{75.3}\right)^{EGFR_CL} * (1+ARA_CL) \\ *(1+SEX_CL)*(1+RACE_CL)*(1+HEP_CL)*(1+ECOG_CL)*EXP(ETA(3))$$

Results are shown in Table 38. The results showed that by removing acid reducing agents (ARA; H2RA and/or PPI), hepatic impairment status, renal impairment status, gender, ECOG performance status (0 vs. 1), race or body weight on clearance, pop-PK model does not show a significant higher OFV compared with reference model run100d. These results indicated incorporation of these covariates in clearance will not help better explaining the source of variability in clearance. In run112, pop-PK model showed a lower OFV by removing the body weight's effect on clearance following the allometric principles indicating an over prediction of the body weight's effect on clearance by allometric principles. Dose was the only significant covariate on clearance as stated by sponsor. A parameter comparison between reference model run100d and FDA's lowest OFV model run110 was listed in Table 43.

Population PK analysis showed there was no impact of mild/moderate hepatic impairment as measured by NCI criteria on the exposure to acalabrutinib. The exposure in patients with mild/moderate hepatic impairment is around 1.24 fold higher than that in patients with normal hepatic function. The population PK study was based on 533 subjects with normal hepatic function, 41 patients with mild hepatic impairment, and 3 patients with moderate hepatic impairment. No patient with severe hepatic impairment was included in the studies (

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Figure 14).Based on the result showed in Table 38 and post hoc comparison showed in Figure 11, no dose adjustment is needed for the following factors: age, body weight, sex, ethnicity, race (white vs. black), mild or moderate renal impairment status, mild hepatic impairment status and/or ECOG performance status (0 vs. 1).

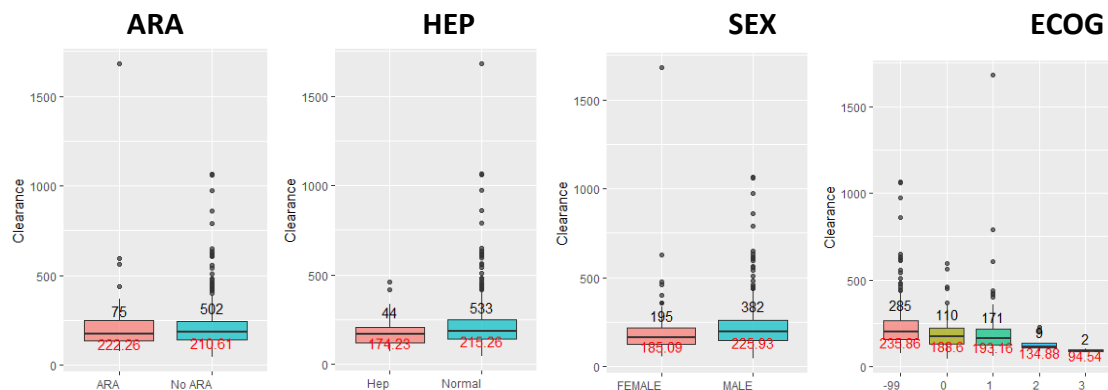
Table 38: Pop-PK model comparison by removing certain covariate on clearance

Notes		Model ID	Reference Model	OFV	dOFV
Sponsor	Base model Final model	run067b run100d		8071.6 7929.9	
FDA	Remove ARA ~ CL	run100e	run100d	7930.9	1.021
	Remove ARA & Hepetic ~CL	run105		7930.9	1.026
	Remove ARA & Hepetic & eGFR~CL	run106		7933.1	3.256
	Remove Sex~CL	run107		7929.9	0
	Remove Ecog~CL	run108		7927	-2.884
	Remove Race ~ CL	run109		7930.5	0.651
	Remove Body Weight~CL*	run110		7909.2 (*)	-20.725
	Remove Dose~CL	run112		7980.7	50.851

* = lowest OFV

Source: FDA's analysis

Figure 14: Boxplots of random Effects of CL/F vs Categorical Covariates



FDA reviewer's analysis: Black numbers in the figure indicate the N number in each group; Red numbers in the figures are median clearance (L/h). For hepatic impairment analysis, the population PK analysis included 533 subjects with normal hepatic function, 41 patients with mild hepatic impairment, and 3 patients with moderate hepatic impairment; no subjects with severe hepatic impairment were included in the studies.

Table 39: Parameter comparison between sponsor's final Pop-PK model and FDA's final Pop-PK model

Model		Sponsor's Final	FDA's Final
Parameter	Description	run100d	run110
OFV	Objective function value	7929.889	7909.164
dOFV	OFV diff with run100d	0	-20.725
	Parameter	Units	
TH 1	1_Ka	h ⁻¹	0.938
TH 2	2_F1	1*	1*
TH 3	3_CL/F	L/h	157
TH 4	4_V2/F	L	34
TH 5	5_Q	L/h	17
TH 6	6_V3	L	336
TH 7	7_ALAG1	h	0.161
TH 8	8_D1	h	0.362
TH 9	9_ARA_CL/F	0.209	0.16
TH 10	10_ARA_V/F	1.65	1.73
TH 11	11_SEX: Female~CL/F	-0.0734	-0.19
TH 12	12_SEX: Female~V2/F	-0.198	-0.204
TH 13	13_RACE: Black~CL/F	-0.0597	-0.0106
TH 14	14_RACE: Black~V2/F	-0.445	-0.448
TH 15	15_RACE: Other~CL/F	-0.0273	-0.0498
TH 16	16_RACE: Other~V2/F	-0.0438	-0.0522
TH 17	17_HEP: Mild+Moderate ~ CL/F	-0.00552	-0.00215
TH 18	18_ECOG: HV~CL/F	0.127	0.104
TH 19	19_ECOG: HV~V2/F	-0.056	-0.0562
TH 20	20_eGFR~CL/F	0.135	0.09
TH 21	21_DOSE~CL/F	-0.164	-0.161
TH 22	22_RSVadd	ng/mL	0.835
TH 23	23_RSVprop	0.179	0.184
OM 1	1_BSV_Ka	0%*	0%*
OM 2	2_BSV_F1	0%*	0%*
OM 3	3_BSV_CL_V	49.70%	49%
OM 4	5_BSV_Q	482.60%	495.30%
OM 5	6_BSV_V3	0%*	0%*
OM 6	7_BSV_ALAG1	0%*	0%*
OM 7	8_BSV_D1	0%*	0%*
OM 8		0%	0%

Source: FDA's analysis

Exposure-Response Relationship for Efficacy

We have conducted exposure response analysis for efficacy and safety for acalabrutinib. Forty-five patients with mantle cell lymphoma (MCL) from the pivotal study ACE-LY-004 were included in the exposure-response analysis of efficacy outcomes. Only 45 patients in the American site were included due to the availability of PK data. To prove these 45 patients are representative of the total 122 patients in study ACE-LY-004, objective response rate per investigator and IRC were assessed and the overall response rate is consistent with the overall result (Table 40). All patients involved in exposure-efficacy analysis received oral doses of acalabrutinib at a dosing regimen of 100-mg bid.

Table 40: Overall response rate based on investigator and IRC assessment

	Investigator Assessment N=45	IRC Assessment N=45
ORR (CR+PR)	33 (73%)	33 (73%)
CR	19 (42%)	19 (42%)
PR	14 (31%)	14 (31%)

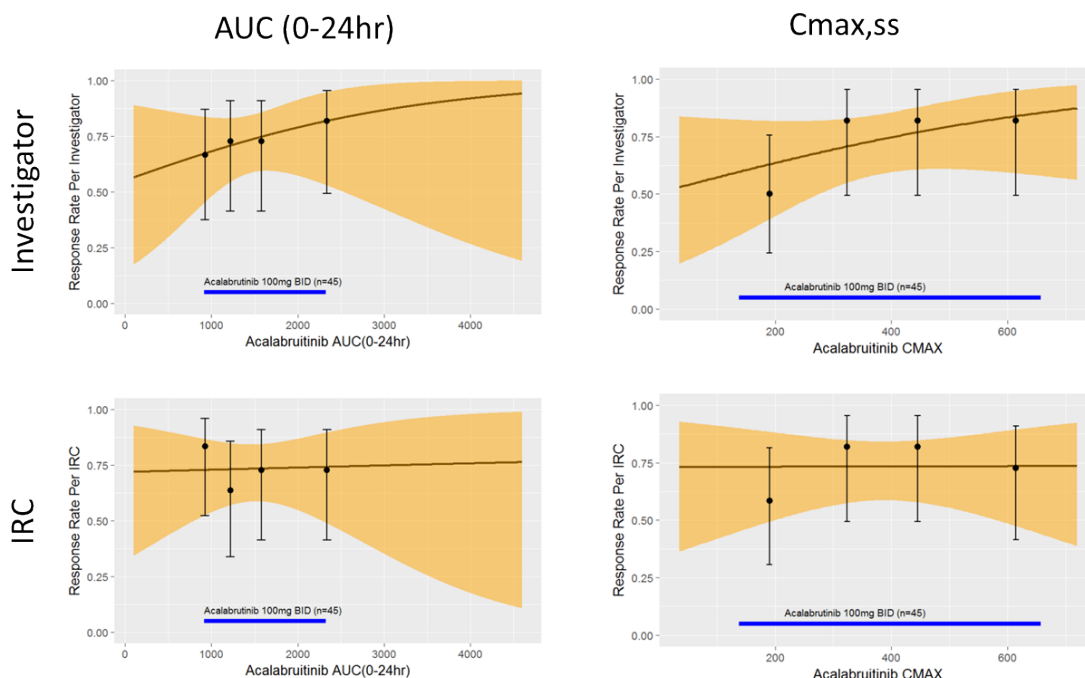
Source: FDA reviewer's analysis

The PK exposure for acalabrutinib was summarized as cumulative AUC over 24 h (AUC₀₋₂₄) in the left panel and C_{max} in the right panel. The efficacy of acalabrutinib, measured as Overall Response Rate (ORR) per investigator and IRC (

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Figure 15). No statistic significant relationship was identified for exposure response for efficacy by logistic regression (Table 41).

Figure 15: Exposure response for efficacy by logistic regression



Source: FDA reviewer's analysis. Solid line is the logistic regression of the predicted ORR per investigator (upper panel) or IRC (lower panel). The yellow area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration. The blue bar is 5% to 95% quantile of exposure of Acalabrutinib in the pivotal at dosing regimen of 100mg BID. Exposure-response analyses showed no correlation between PK exposure (maximum plasma concentration [Cmax] or AUC over 2 dosing intervals [AUC0-24]) and overall response rate (ORR).

Table 41: Estimated Parameters in logistic regression for ER relationship for efficacy

		Estimate	Std. Error	P value
Investigator ~ AUC	Intercept	0.206	0.99	0.834
	Exposure Slope	0.0005	0.00067	0.402
IRC ~ AUC	Intercept	0.93	0.85	0.275
	Exposure Slope	5.028e-05	5.284e-04	0.924
Investigator ~ Cmax	Intercept	0.029	0.84	0.972
	Exposure Slope	0.003	0.002	0.222
IRC ~ Cmax	Intercept	1.000	0.85	0.245

Exposure Slope	2.982e-05	2.035e-03	0.988
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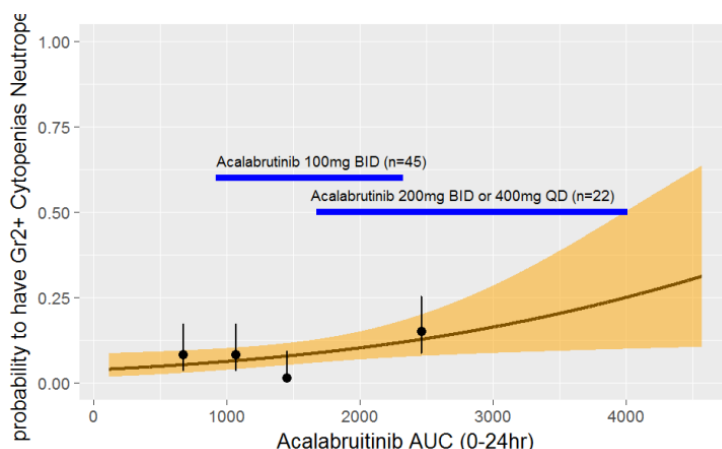
Source: FDA's analysis

Exposure-Response Relationship for Safety

The exposure safety analysis included 292 patients with B cell malignancy from 6 studies. Patients received oral doses of acalabrutinib from 100mg QD to 200mg BID. Among the 292 patients, 180 patients received the therapeutic 100mg BID dose.

Exposure-response relationship was conducted and a positive relationship was identified with drug exposure (AUC 0-24hr) versus the probability of Grade 2+ neutropenia (Figure 16). With dose increasing from 100mg BID to 200mg BID, the probability of Grade 2+ neutropenia increased from 7.5% (95% Confidence Interval: 4.9%, 11.2%) to 13 % (95% Confidence Interval: 7.9%, 20.8%; Table 42).

Figure 16: Exposure response relationship for AUC(0-24hr) versus incident rate of neutropenia by logistic regression



Source: FDA's Analysis. Solid line is the logistic regression of the predicted probability of Grade 2+ Cytopenias Neutropenia. The yellow area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration. The blue bar is 5% to 95% quantile of exposure of Acalabrutinib in the pivotal at dosing regimen of 100mg BID (upper) and a subgroup patients in ACE-CL-001 at dosing regimen of 200mg BID or 400mg QD.

Table 42: Incident rate of neutropenia prediction by logistic regression

	Median AUC(0-24hr)	Probability (95% CI)
100mg BID	1366	7.5% (4.9%, 11.2%)
200mg BID or 400ng QD	2522.5	13 % (7.9%, 20.8%)

Source: FDA's Analysis.

No evident relationship for other AEs of interest including Grade 2+ Hemorrhage, Cardiac events, Cytopenias Anemia, Cytopenias Thrombocytopenia, Hepatic events, Hypertension, Infections, Diarrhoea or Headache was identified at the exposure range from 115.74ng*h/ml to 4575.00 ng*h/ml (Dose range 100mg QD up to 200mg BID; Table 43).

Given the strong efficacy results and mild safety profile, the dosing regimen of 100-mg BID is acceptable in general population.

Table 43: Parameters estimated for ER-Safety logistic regression

AE of Interest	AUC(0-24hr) Slope	Std. Error	P Value
Cardiac events	0.00000	0.00030	0.993010
Cytopenias Anemia	0.00009	0.00024	0.699918
Cytopenias Neutropenia	0.00054	0.00023	0.018596
Cytopenias Thrombocytopenia	0.00005	0.00041	0.895929
Hemorrhage	0.00029	0.00023	0.202671
Hepatic events	0.00009	0.00037	0.805749
Hypertension	0.00006	0.00024	0.806564
Infections	0.00006	0.00015	0.675955
Diarrhoea	-0.00011	0.00026	0.675490
Headache	0.00011	0.00026	0.679702

Source: FDA's Analysis

Table 44 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
acalabrutinib_Comb_20161118.csv	Pop-PK dataset	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Acalabrutinib_NDA210259_YX\Acalabrutinib_PPK\Acalabrutinib PPK
run110.mod	Pop-PK FDA final program	
run110.lst	Pop-PK FDA final program output	
run100d.mod	Pop-PK sponsor final program	
run100d.lst	Pop-PK sponsor final program output	
Acalabrutinib_ER.R	Exposure response program	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Acalabrutinib_NDA210259_YX\Acalabrutinib_ER\FDA ER
ADSL.csv	Exposure response dataset	
CMAXAUC.csv	Exposure response dataset	

X

X

Vicky Hsu, Ph.D.

Gene Williams, Ph.D.

Primary Reviewer

Team Leader

7 Sources of Clinical Data and Review Strategy

Data was submitted for a total of 7 studies. Six of these studies evaluated acalabrutinib in patients with hematologic malignancies with one study performed in healthy volunteers.

7.1. Table of Clinical Studies

Table 45: Listing of Clinical Studies Relevant to this NDA

Study Identity	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Pivotal Study							
ACE-LY-004	Phase 2, multicenter, single arm, open label study	100mg PO twice daily until disease progression or unacceptable toxicity	Overall Response Rate (ORR) as defined by investigator assessed CR or PR per Lugano (2014) criteria	Until PD, relapse or unacceptable toxicity	124	Patients with MCL who had received between 1 and 5 prior therapies	40 centers 9 countries
Additional Studies to Support Safety							
ACE-CL-001	Phase 1/2, multicenter, open-label dose escalation study	Escalating doses starting with 100 mg through 400mg PO daily	MTD, safety, PD/PD	Until PD, relapse or unacceptable toxicity	305	Patients with CLL/SLL including Richter Syndrome and ibrutinib intolerant	12 centers 3 countries
ACE-WM-001	Phase 2, open label study	100mg PO twice daily and 200mg PO daily	Response, safety	Until PD, relapse or unacceptable toxicity	106	Waldenström's macroglobulinemia previously treated with a small cohort of untreated	27 centers 6 countries
15-H-0016	Phase 2, open label 2-arm study	200mg PO daily 100mg PO twice daily	Response, safety	Until PD, relapse or unacceptable toxicity	33	Patients with CLL or small lymphocytic lymphoma (SLL)	1 center (NIH) 1 country (US)

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}

Study Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
ACE-LY-002	Phase 1b open-label	100mg PO twice daily	Response, safety, PK/PD	Until PD, relapse or unacceptable toxicity	21	ABC, Diffuse Large B- Cell Lymphoma	7 Centers 2 countries
ACE-LY-003	Phase 1b, open-label parallel groups (monotherapy and combination therapy)	100mg PO twice daily 100mg PO twice daily plus Rituximab	Response	Until PD, relapse or unacceptable toxicity	40	Follicular Lymphoma	10 Centers 1 country (US)
ACE-MY-001	Phase 1b, open-label, parallel group	100mg PO twice daily 100mg PO twice daily plus Dexamethasone 40mg	Response, Safety, PK/PD	Until PD, relapse or unacceptable toxicity	27	Multiple Myeloma	11 centers 2 countries

Source: Applicant Provided CSR and SCS

7.2. Review Strategy

Study ACE-LY-004 was used for the primary analysis of efficacy and safety. The Applicant submitted the complete data set for this study using a data cut date of February 28, 2017. An updated safety data set was also submitted with a data cut-off date of May 29, 2017.

The evaluation of safety was based primarily on the pivotal study population. In addition, two larger populations that included patients with a variety of hematological malignancies were evaluated for safety. The three separate safety populations included: 124 patients from the pivotal study ACE-LY-004, 442 patients with hematologic malignancies from six additional studies who received 100mg twice daily as monotherapy, 610 patients with hematologic malignancies who received acalabrutinib at any dose. A 90-day safety update was also provided by the Applicant which increased the total safety population to 612 patients (two additional patients).

All major efficacy and safety analysis were reproduced or audited. Summaries of data by the clinical reviewer were performed using JMP 13.0(SAS institute, Cary, NC). Further safety analysis was performed using MedDRA Adverse Events Diagnostic 1.3 (MAED) (FDA, Silver Spring, MD).

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Data Sources

The key materials used for the review of efficacy and safety included:

- NDA 210259
- Relevant published literature
- Relevant information in the public domain

Analysis datasets, SDTM tabulations, and software codes are located at:

<\\CDSESUB1\evsprod\NDA210259\0000\m5\datasets>

Data and Analysis Quality

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The data in this submission are in electronic Common Technical Document (eCTD) format, in accordance with FDA guidance on electronic submission. The data sets are well documented and include definition files. The data sets, clinical study reports, summary of clinical safety, and summary of clinical efficacy are located in Modules 5 and 2 of the eCTD.

<\\CDSESUB1\evsprod\NDA210259>

The reviewers were able to:

- Reproduce the applicant's analysis and analysis results
- Evaluate documentation of data quality control/assurance procedures
- Conduct FDA sensitivity analyses

The efficacy endpoints such as overall response rate (ORR) and time-to-event endpoints were derived and saved in analysis datasets "ADEF". Demographic and disease characteristics were derived and saved in analysis datasets "ADSL". The statistical reviewer is able to reproduce the derived ORR, DoR (Duration of Response), PFS (Progression-free Survival) and OS (Overall Survival) datasets from the NDA tabulation datasets.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study ACE-LY-004: An Open Label, Phase 2 Study of ACP-196 in Subjects with Mantle Cell Lymphoma

Trial Design

Clinical Trial ACE-LY-004 was a phase 2, single arm, global, multicenter trial that enrolled 124 patients with mantle cell lymphoma. Patients received between one and 5 prior therapies. Acalabrutinib was administered as 100mg orally daily until disease progression or unacceptable toxicity.

The primary objective of the study was to determine the activity of acalabrutinib in patients with relapsed and refractory MCL as measured by response rate, duration of response (DOR), progression free survival (PFS) and overall survival (OS).

The primary endpoint was investigator assessed overall response rate (ORR) per the Lugano (2014) classification for NHL. Responses were also assessed by an independent review committee.

Patients were assessed for disease response by imaging at baseline and then after cycles 2, 4 and 6 by Computed tomography (CT) and Positron-emission topography (PET). After cycle 6 patients only required imaging for confirmation of complete response or if clinically indicated.

Secondary objectives of the study were to characterize the safety profile of acalabrutinib, characterize the pharmacokinetic (PK) profile of acalabrutinib, and pharmacodynamics (PD) effects of acalabrutinib.

Key Inclusion Criteria (summarized from protocol)

- Pathologically confirmed mantle cell lymphoma with documentation of monoclonal B cells that had a chromosomal translocation (t(11,14) and/or overexpression of cyclin D1
- Age $\geq$ 18 years
- Relapsed or refractory to at least 1 prior therapy and required further treatment
- Documented failure to achieve at least partial response (PR) with or documented disease progression after, the most recent treatment regimen
- Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (presence of $\geq$ 1 lesion that measured $\geq$ 2cm in the longest dimension and $\geq$ 1cm in the longest perpendicular dimension as assessed by computed tomography (CT) scan.
- At least 1 but no more than 5 prior treatment regimens for MCL
- ECOG performance status of $\leq$ 2

Key Exclusion Criteria (summarized from protocol)

- Significant cardiovascular disease including uncontrolled or symptomatic arrhythmias, CHF, or myocardial infarction within 6 months of screening
- Malabsorption syndrome, IBD
- Immunotherapy within 4 weeks of first dose of study treatment
- Prior exposure to BCR inhibitor (BTK, phosphoinositide-3 kinase (PI3K), or spleen tyrosine kinase (SYK), or B cell lymphoma (BCL)-2 inhibitor

- Ongoing immunosuppressive therapy (including systemic steroids >10mg day of Prednisone equivalent)
- Known history of bleeding diathesis
- History of stroke or intracranial hemorrhage
- Required or received anticoagulation with warfarin or equivalent vitamin K antagonist within 7 days of study treatment
- Required treatment with proton pump inhibitors
- ANC < $0.75 \times 10^9/L$ or platelet counts < $50 \times 10^9/L$ for patients with bone marrow Involvement ANC < $0.5 \times 10^9/L$ and platelet < 30
- Creatinine > 2.5 X institutional upper limit of normal (ULN)
- Total Bilirubin >2.5 x ULN
- AST or ALT > 3 X ULN
- Known CNS or leptomeningeal disease
- Required treatment of a strong cytochrome P450 (CYP)3A inhibitor/inducer
- Presence of a GI ulcer diagnosed by endoscopy within 3 months of screening

Primary Efficacy Endpoints

The primary endpoint of the study was ORR (Overall Response Rate) as assessed by investigator. Overall response rate was defined at either a complete response (CR) or Partial Response (PR) per Lugano (Cheson 2014) criteria.

Reviewer comment: The acalabrutinib NDA represents the first regulatory application based on the Lugano 2014 response criteria for a mantle cell lymphoma indication. The approvals for lenalidomide and bortezomib for MCL indications were based on response rates that were assessed using the 1999 Response criteria. The accelerated approval for Ibrutinib was based on ORR was assessed using the 2007 Response Criteria. The primary differences between older response criteria and the 2014 Lugano criteria is that the Lugano criteria relies on a more objective point scale for PET avid assessment when assessing response and allows for one new PET avid lymph node to be considered progressive disease. The use of the 2014 Lugano criteria did not substantially impact the efficacy analysis and are the preferred current criteria for assessing lymphoma response.

Statistical Analysis Plan

Sample Size Determination

The sample size was calculated based on a one-sample Chi-square test with a 0.025 1-sided significance level to have more than 99% power to test the null hypothesis that overall response rate (ORR) will be $\leq 20\%$ versus the alternative hypothesis that ORR of $\geq 40\%$.

The primary efficacy endpoint was the ORR, defined as the proportion of subjects achieving either a partial response (PR) or complete response (CR) per the Lugano classification for non-Hodgkin lymphoma (NHL) by the investigators. ORR by IRC (Investigational Review Committee) was also conducted for labeling purposes.

The secondary endpoints were:

- DOR per Lugano classification as assessed by investigators
- PFS per Lugano classification as assessed by investigators
- OS
- IRC-assessed ORR, DOR, and PFS per Lugano classification

The safety endpoints were:

- Frequency and severity of AEs/SAEs
- Frequency of AEs requiring discontinuation of study drug or dose reductions
- Effect of acalabrutinib on peripheral T/B/natural killer (NK) cell counts
- Effect of acalabrutinib on serum immunoglobulin levels

The final analysis of primary and secondary efficacy endpoints occurred approximately 14 months after the last subject has been enrolled.

Efficacy Evaluation

The All-treated Population was defined as all enrolled subjects who receive ≥ 1 dose of study drug.

The primary efficacy endpoint was the ORR, defined as the proportion of subjects achieving either a partial response (PR) or complete response (CR) per the Lugano classification for non-Hodgkin lymphoma (NHL).

The proportion was estimated by dividing the number of subjects within each category of response by the total number of subjects in the analysis population. Each subject was counted within only one response group, with the best response during the study as the classification group.

The primary analysis of ORR was conducted on the All-treated Population. ORR and the corresponding 95% two-sided CI calculated using the exact binomial distribution were presented.

DOR was defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of objective MCL disease progression or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date were censored.

The analysis of DOR was conducted on the subset of the All-treated Population who achieve CR or PR as their best overall response.

PFS was defined as the interval from the start of study treatment to the first documentation of objective MCL disease progression per investigator assessment or death from any cause. Subjects not meeting the criteria and alive by the analysis data cutoff date were censored.

A sensitivity analysis of PFS was performed where all subjects who progressed or died (including those after the start of subsequent therapy) were considered as events.

The analysis of DOR, PFS, and OS were estimated using the Kaplan-Meier (KM) method.

Protocol Amendments

There were 7 protocol amendments to the pivotal study ACE-LY-004. The table below summarizes relevant changes to the protocol.

Table 46: Summary of Major Protocol Changes to Pivotal Study ACE-LY-004

Document	Date	Summary of Major Protocol Changes in Amendments
Original Protocol	July 2014	• Original Protocol submitted
Amendment 1	November 20, 2014	• Study design was revised to follow a Simon two-stage design with 2 cohorts (Bortezomib naïve and Bortezomib exposed) with a total of 117 patients planned. • Secondary endpoint time to next treatment was replaced with overall survival
Amendment 2	March 16, 2015	• Excluded patients with known bleeding disorder • Narrowed ECG criteria to exclude QTc >480 msec. • Final analysis endpoint extended from 6 months from last therapy to 9 months to allow for meaningful assessment of response.
Amendment 3	July 17, 2015	• Updated therapeutic options for MCL section. • Frequency of PET/CT scans was reduced – clarified that patients with confirmed CR

Document	Date	Summary of Major Protocol Changes in Amendments
		were not required to undergo further PT/CT unless clinical suspicion of PD. Text added to ensure that disease progression identified by PET/CT alone is confirmed by a more specific modality (diagnostic CT or biopsy).
Amendment 4	November 14, 2015	• Simplified response rates by removal of separate cohorts of bortezomib naïve and bortezomib exposed cohorts based on similar ORR in the two groups. • Revision of the protocol to allow use of PPI with acalabrutinib if PPI therapy was determined to be necessary while on study
Amendment 5	January 5, 2016	• Reduction in PT/CT scan requirement during the treatment phase of the trial after 6 months. PET/CT scans will be performed at the end of cycle 2 and cycle 6 and are required to confirm CR or as clinically indicated. • HBV Virus reactivation added as a precaution with recommendations to monitor monthly PCRs for patient with a history of Hepatitis B PCR and discontinued if rising titers noted
Amendment 6	July 19, 2016	• The final analysis was changed to occur approximately 14 months after the last subject was enrolled, based on feedback from the Agency requesting duration of response data for 12 months for responders • Changes to secondary study endpoints: • IRC assessed ORR, DOR and PFS per Lugano classification were added • Exploratory endpoints added: ○ Health related quality of life ○ Time to Response (TTR) as assessed by Investigators and IRC ○ Time to initial response ○ Time to best response ○ Time to complete response

Document	Date	Summary of Major Protocol Changes in Amendments
		○ IRC-assessed ORR, DOR, TTR and PFS per Revised Response Criteria for Malignant Lymphoma Cheson 2007)

Prior to Protocol Amendment 4.0, dated November 14, 2015, the protocol consisted of 2 parallel cohorts (bortezomib-naïve and the bortezomib-exposed) each based on a Simon's 2 stage design.

An interim analysis for futility based on response rate was performed in September 2015 per Protocol Amendment 3 (dated July 17, 2015). In this interim analysis, within the first 28 patients enrolled to bortezomib-naïve cohort, the required response rate for continuation ($\geq 8/28$ responders) was exceeded. Within the first 12 subjects enrolled to the bortezomib-exposed cohort, the required response rate for continuation ($\geq 3/12$ responders) was also exceeded. Based on this interim analysis, enrollment to both study cohorts continued without interruption.

The protocol was amended in November 2015 (Protocol Amendment 4.0) based on emerging data that support the merging of the two cohorts by prior bortezomib exposure.

8.1.2. Study Results ACE-LY-004

Compliance with Good Clinical Practices

The Applicant provided attestation that the protocol, protocol amendments, and patient informed consent forms for Study ACE-LY-004 were reviewed and approved by the Institutional Review Boards (IRBs) or Independent Ethics Committees (IECs) of the participating study centers. The Applicant also provided a list of IRBs and IECs for the participating study center.

The Applicant provided a statement that Study ACE-LY-004 was conducted in accordance with the International Council for Harmonization guideline for Good Clinical Practice, the principles of the Declaration of Helsinki, and the US Code of Regulations, Title 21, Parts 50, 56, and 312 providing the protection of the rights and welfare of human patients participating in biomedical research. All patients or their legal representatives voluntarily consented prior to trial enrollment.

Financial Disclosure

The Applicant submitted financial disclosure information from 52 investigators and 170 sub investigators from two studies (ACE-LY-004 and ACE-CL-001) indicating that none of the investigators had disclosable financial interests or arrangements. For details, refer to the Clinical Investigator Financial Disclosure Review Template in Section 14.2. None of the

disclosures submitted revealed a potential conflict of interest.

Patient Disposition

A total of 124 patients were enrolled onto study ACE-LY-004 and all patients received study treatment. As of the data cutoff date (28 February 2017), 70 subjects (56.5%) were continuing study treatment and 54 subjects (44%) had discontinued study treatment. The primary reason for discontinuing study treatment was PD (39 subjects, 31.5%). Seven subjects (5.6%) discontinued study treatment due to AEs. The median time on study was 15.2 months (range 0.3 to 23.7 months). The following table summarizes patient disposition for study ACE-LY-004.

Table 47: Summary of Patient Disposition on Study ACE-LY-004 (All Treated)(N=124)

	Primary Analysis n(%)	90 day Safety Update n (%)
Treated	124 (100)	124 (100)
Continuing on acalabrutinib	70 (56.5)	60 (48.4)
Continuing on Study	92 (74.2)	89 (71.8)
Discontinued acalabrutinib	54 (43.5)	64 (48.4)
Disease progression	39 (31.5)	46 (37.1)
Adverse Event	7 (5.6)	8 (6.5)
Subject started subsequent anticancer therapy	5 (4.0)	6 (4.8)
Lost to follow up	1 (0.8)	1 (0.8)
Withdrawal of consent	32 (26)	4 (3.2)
Other ^a	1 (0.8)	1 (0.8)
Discontinued Study		
Died	27 (21.8)	30 (24.2)
Withdraw of consent	4 (3.2)	4 (3.2)
Lost to follow up	1 (0.8)	1 (0.8)
Time on study (months)		
Mean (SD)	14.5 (4.97)	16.6 (5.97)
Median	15.2	18
Min, Max	(0.3, 23.7)	(0.26, 26.6)

^asubject decision to stop treatment

Source: Study ACE-LY-004 clinical report, page 52, Table 7 and Confirmed by Statistical Reviewer

At the time of the 90-day safety update, 48% of patients were still on acalabrutinib therapy. Ten additional patients had discontinued therapy due to progressive disease and one additional patient had discontinued therapy due to an adverse event (non-small cell lung cancer).

Reviewer comment: Changes in patient disposition with longer follow up were predominantly due to progressive disease. No new safety signals were identified with 90-day safety-follow-up.

Protocol Violations/Deviations

Major protocol deviations described by the Applicant were confirmed by the clinical and statistical reviewer. Those subjects were not considered to have major impact on evaluation of overall efficacy and safety and were included in the evaluation.

Nine subjects on study had important protocol deviations. The breakdown for these deviations is displayed in the table below. These deviations involved SAE reporting, eligibility criteria, and study drug lot dispensing.

- Five subjects did not have an SAE reported within 24 hours as required in the protocol. All SAEs were reported and are included in the safety analysis.
- One subject had a squamous cell carcinoma surgically removed several days after starting study treatment. This was in violation of the exclusion criteria: prior malignancy except for adequately treated basal cell or squamous cell skin cancer. This patient remained on therapy, was reported to have a CR and was still on therapy at time of data cut off
- Three patients received acalabrutinib from a different lot than intended, although the dose of 100mg was the intended dose.

Table 48: Important Protocol Deviations in Study ACE-LY-004

Important Protocol Deviations	N = 124 n(%)
Subjects with at least 1 important protocol deviation	9 (7.3)
Subjects with assessments or procedures deviations; SAEs (Serious Adverse Events) not reported within 24 hours	5 (4.0)
Subjects with eligibility deviation	1 (0.8)
Subjects with study medication compliance deviation	3 (2.4)

Source: Study ACE-LY-004 clinical report, page 53, Table 8 and Confirmed by Statistical Reviewer

Reviewer Comment: The protocol deviations described above did not impact the results of the study. Despite study medication compliance violations, patients with this deviation received the intended dose of acalabrutinib. Review of the SAEs reported > 24 hours did not significantly impact safety conclusions or study conduct. The one patient with a protocol eligibility violation had a second malignancy (skin) that would have made him ineligible for study but would not have changed conclusions regarding the efficacy of acalabrutinib.

Table of Demographic Characteristics

This multicenter study was conducted at 40 study sites that enrolled subjects in 9 countries. A total of 124 subjects were enrolled into the study and all received study treatment. Baseline demographics characteristics were summarized in the table below.

Table 49: Baseline Demographic Characteristics of Patients Enrolled on ACE-LY-004

Demographic Parameters	N=124 n(%)
Sex n(%)	
Male	99 (80)
Female	25 (20)
Age	
Mean years (SD)	67
Median (years)	68
Min, max (years)	42,90
Age Group n(%)	
< 65 years	44 (36)
≥ 65 years	80 (65)
< 75 years	92 (74)
≥ 75 years	32 (26)
Race n(%)	
Black or African American	3 (2.4)
White	92 (74)
Not Reported ¹	29 (23)
Ethnicity n(%)	
Hispanic or Latino	4 (3.2)
Not Hispanic or Latino	90 (73)
Missing	30 (24)
Region n(%)	
United States	45 (36)
Ex- United States	79 (64)

¹ Data on race and/or ethnicity were not collected in XX country because of local regulations.

Source: Study ACE-LY-004 clinical report, page 54, Table 10 and Confirmed by Statistical Reviewer

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 50: Additional Disease - Related Baseline Characteristics of Patients on ACE-LY-004

Demographic Parameters	N=124 n(%)
Tumor Bulk	
< 5 cm	78 (62.9)
≥ 5 and < 10 cm	36 (29.0)
≥ 10 cm	10 (8.1)
Demographic Parameters N = 124	Total n(%)
Ann Arbor staging for lymphoma	
I	2 (1.6)
II	7 (5.6)
III	22 (17.7)
IV	93 (75.0)
Simplified MIPI score¹	
Low risk (0-3)	48 (38.7)
Intermediate risk (4-5)	54 (43.5)
High risk (6-11)	21 (16.9)
Missing	1 (0.8)
Refractory disease at baseline	
Yes	30 (24.2)
No	94 (75.8)
LDH > Upper limit of normal (ULN)	
Yes	33 (26.6)
No	90 (72.6)
Bone marrow aspiration and biopsy result	
Involved	62 (50.0)
Not Involved	60 (48.4)
Indeterminate	1 (0.8)
Other*	1 (0.8)
Number of Subjects with extranodal disease	90 (72.6)
Bone Marrow	63 (50.8)
Gastrointestinal	13 (10.5)
Pulmonary/Lung	12 (9.7)
Skin/dermis	8 (6.5)
Pleura	7 (5.6)
Soft tissue	7 (5.6)
Osseous/bone	6 (4.8)
Hepatic/liver	2 (1.6)
Unknown	2 (1.6)

¹Simplified MIPI was derived using age, ECOG score, LDH, and WBC (White Blood Cell) Count at baseline. Low = 0-3, intermediate = 4 or 5, high-risk

Source: Study ACE-LY-004 clinical report, page 55-56, Table 10 and Confirmed by Statistical Reviewer

Prior therapies

The median number of prior therapies for patients on ACE-LY-004 was 2 (range 1-5). Almost all (95.2%) of patients had received rituximab as a single agent or as part of a regimen. A breakdown of prior therapies is provided in the table below.

Table 51: Select Prior Therapy Regimens for Patients on ACE-LY-004

	All Subjects N=124 n(%)
Number of prior therapies for MCL	
Mean (SD)	1.9 (1.1)
Median	2
Min, Max	1,5
1	59 (47.6)
2	37 (29.8)
≥ 3	28 (22.6)
Select Prior Therapies	
Rituximab as single agent or part of a regimen	118 (95.2)
CHOP based regimen	64 (51.6)
Cyclophosphamide,/doxorubicin/vincristine/prednisone	
ARA-C (Cytarabine) based regimen	42 (33.9)
Bendamustine and rituximab based regimen	27 (21.8)
Hyper-CVAD	26 (21.0)
Rituximab/cyclophosphamide/vincristine/doxorubicin/dexamethasone	
Alternating with high dose methotrexate and cytarabine	
Bortezomib/carfilzomib	24 (19.4)
DHAP	24 (19.4)
Dexamethasone/high dose ARA-C/cisplatin	
Stem Cell Transplant	22 (17.7)

[Source: Study ACE-LY-004 clinical report, page 58, Table 11 and Confirmed by Statistical Reviewer]

Additional, less frequent prior therapies included BEAM (Carmustine/etoposide/cytarabine/melphalan) (7.3%), Lenalidomide (7.3%), Fludarabine and cyclophosphamide (FC), mTOR (mammalian target of rapamycin) inhibitor (4.8%).

Reviewer comment: The population studied in ACE-LY-004 was characteristic of the demographics expected for patients with relapsed and refractory Mantle cell lymphoma. This population represented a heavily pretreated population of patients who received standard accepted chemotherapy regimens. The majority of patients had disseminated disease which is characteristic of mantle cell lymphoma. Results from this study would be expected to be

experienced by patients with relapsed and refractory lymphoma in the post marketing setting.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Most subjects (97.6%) received concomitant medications after study entry. The therapeutic classes of concomitant medications received by $\geq 20\%$ of subjects included antibacterials for systemic use (58.9%), analgesics (50.8%), antithrombotic agents (41.9%), lipid-modifying agents (33.1%), antivirals for systemic use (32.3%), agents acting on the renin-angiotensin system and drugs for acid-related disorders (each 30.6%), beta-blocking agents (29.8%), anti-gout preparations (25.8%), antihistamines for systemic use and blood substitutes and perfusion solutions (each 21.8%), psycholeptics (21.8%), urological agents and vitamins (each 20.2%).

Reviewer comment: The types of concomitant medications used in this trial would not have been expected to affect efficacy as they would have no activity against mantle cell lymphoma. There were a low number of patients who received moderate CYP3A4 inducers that could have influenced exposure. The relatively high incidence of anti-thrombotic agents (41.9%) might be expected to have an influence on bleeding related AEs and an increased the risk of major hemorrhage, however this complication was low (0.8%) in this population.

Efficacy Results – Primary Endpoint

ORR was defined as the proportion of subjects achieving either PR or CR as best overall response according to the Lugano classification as assessed by investigators. The order of overall response category was: CR > PR > SD > PD. The primary endpoint was ORR based on investigator-assessed. IRC-assessed ORR was also evaluated. For those patients with not evaluable, i.e. NE, it was considered as non-responders.

The results are summarized in the table below.

Table 52: Overall response rate and best overall response by investigator assessment and Independent Review Committee according to Lugano classification (all treated subjects)

	Investigator Assessment		IRC assessment	
	n(%)	95% CI ^a	n(%)	95% CI ^a
ORR (CR = PR)	100 (80.6)	(72.6%, 87.2%)	99 (79.8)	(71.7%-86.5%)
Best Response				
CR	49 (39.5)	(30.9,48.7)	49 (39.5)	(30.9,48.7)
PR	51 (41.1)	(32.4,50.3)	50 (40.3)	(31.6, 49.5)
SD	11 (8.9)	(4.5,15.3)	9 (7.3)	(3.4, 13.3)
PD	10 (8.1)	(3.9, 14.3)	11 (8.9)	(4.5, 15.3)
NE ^b	3 (2.4)	(0.5, 6.9)	5 (4.0)	(1.3, 9.2)

^a 95% exact binomial CI

^b Included subjects without any adequate post baseline disease assessment

[Source: Study ACE-LY-004 clinical report, page 60, Table 12 and Confirmed by Statistical

Reviewer]

Efficacy Results – Secondary and other relevant endpoints

At the time of data cutoff (28 February 2017), all responders who had not progressed and remained on study had been followed for a minimum of 12 months, except for 2 subjects (10.4 and 11.8 months).

Secondary endpoints were evaluated for DoR, PFS and OS. Kaplan-Meier estimates were provided. The results were summarized in table 53 for investigator-assessed and Table 54 for IRC-assessed values. Median had not been reached for all endpoints yet.

Table 53: Secondary Endpoints Results (Progression based on Investigator assessment)

Secondary Endpoints	Median Estimates (Range)	N
DoR	NE (0.59, 20.27+)	100
PFS	NE (0.03+, 22.08+)	124
OS	NE (0.26, 22.28+)	124

[Source: Statistical Reviewer's Analysis]

Table 54: Secondary endpoint result - IRC-assessed

Secondary Endpoints	Median Estimates (Range)	N
DoR	NE (0.03+, 20.27+)	99
PFS	16.6 (0.03+, 22.08+)	124

[Source: Statistical Reviewer's Analysis]

The concordance of ORR and CR by IRC and investigator-assessed was compared in Table 55. The concordance was about 91% for ORR and 93.5% for CR.

Table 55: Concordance between investigator and IRC-assessed responses according to 2014 Lugano classification (all treated subjects)

Responder (CR or PR by IRC)	Responder (CR or PR) by Investigator		
	Yes	No	Total
	n(%)	n(%)	n(%)
Yes	94 (75.8)	5 (4.0)	99 (79.8)
No	6 (4.8)	19 (15.3)	25 (20.2)
Total	100 (80.6)	24 (19.4)	124 (100.0)
Overall concordance rate	91.1%		
Complete Response by Investigator			

Responder (CR or PR by IRC)	Responder (CR or PR) by Investigator		
	Yes n(%)	No n(%)	Total n(%)
Complete response by IRC	Yes n(%)	No n(%)	Total n(%)
Yes	45 (36.3)	4 (3.2)	49 (39.5)
No	4 (3.2)	71 (57.3)	75 (60.5)
Total	49 (39.5)	75 (60.5)	124 (100)
Overall concordance rate	93.5%		

Source: Study ACE-LY-004 clinical report, page 87, Table 18 and Confirmed by Statistical Reviewer

Additional Analyses Conducted on the Individual Trial

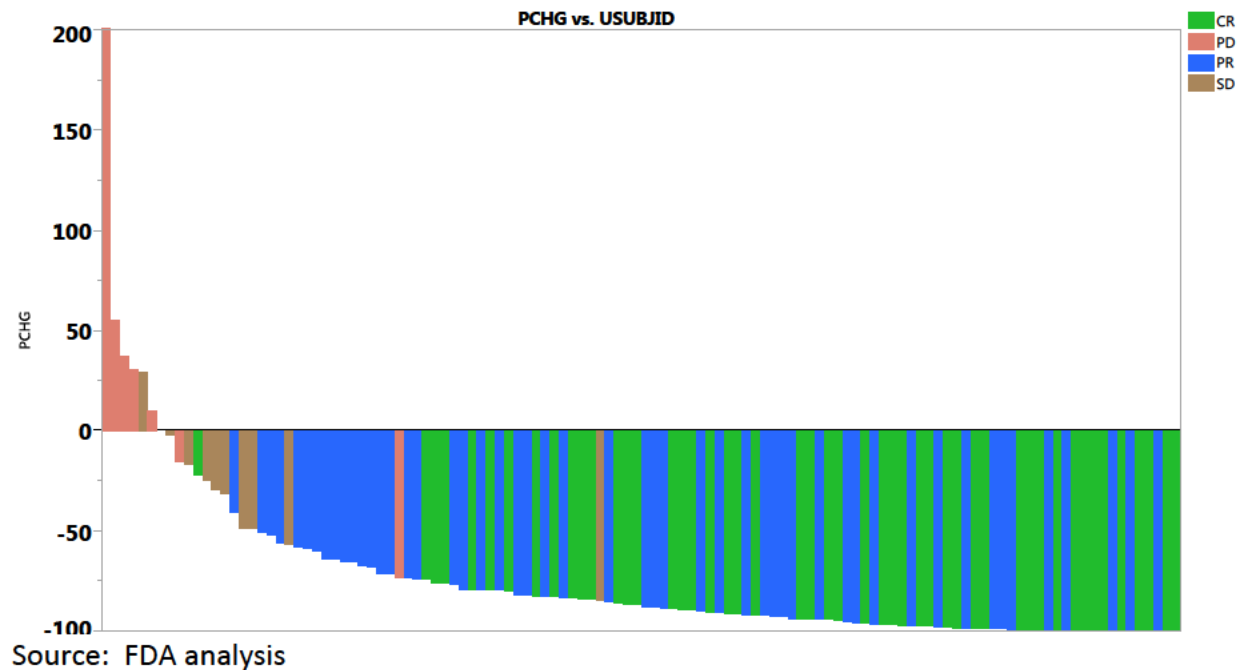
Tumor Shrinkage

A reduction in tumor size was demonstrated in 90% of the patients taking acalabrutinib, including some patients with a best response of SD.

Reviewer Comment: This further supports clinical benefit since in general patients who experience a reduction in tumor size in mantle cell lymphoma would likely experience clinical benefit due to symptom reduction due to mass effect.

The waterfall plot below demonstrates tumor shrinkage in patients on ACE-LY-004.

Figure 17: Waterfall plot of tumor shrinkage and response to treatment for individual patients on ACE-LY-004



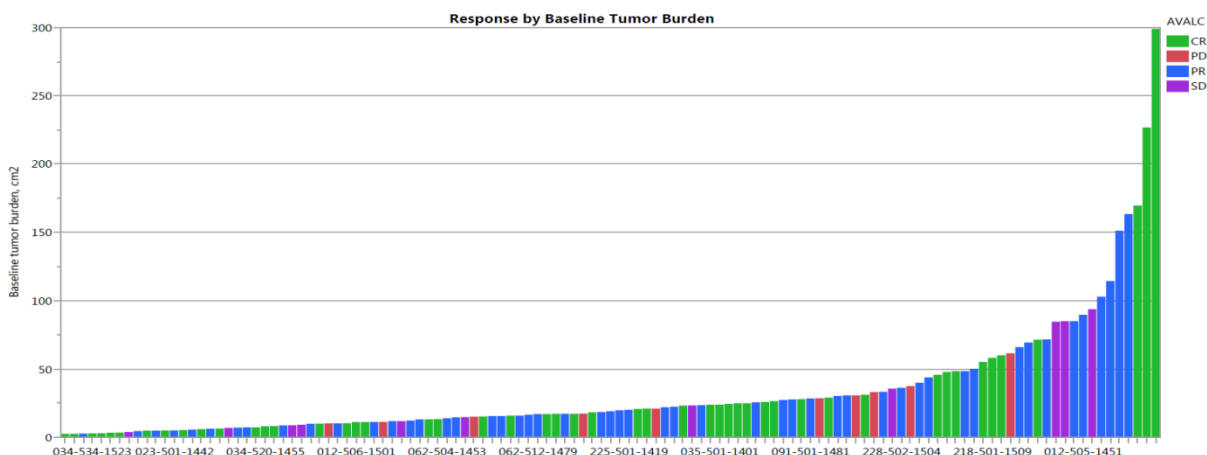
Reviewer Comment: Due to incorporation of standardized PET-CT responses into the 2014 Lugano Response Criteria, not all patients will have a 100% reduction in tumor shrinkage who have CR. Some patients while in CR, may have residual mass that is not PET-avid or have residual mass on CT scan that is < 1.5 cm.

Tumor volume and correlation with response:

A response to acalabrutinib was demonstrated in patient with both high and low tumor burden as demonstrated in the figure below. This provides supportive evidence of acalabrutinib's activity in this disease across high and low disease burden patient populations.

Figure 18: Best response and baseline tumor volume

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}



Source: FDA analysis

Impact of dose Interruption on efficacy of acalabrutinib

Thirty-one patients on study ACE-LY-004 were identified to have a dose interruption of at least 7 days. The most common reason for dose interruption was procedure (52%).

The table below displays best response data for patients with a dose interruption of > 7 days.

Table 56 Best Response for Patients with Dose Interruption of > 7 days

Best response	N=124 n(%)
CR	14 (45.2)
PR	14 (45.2)
PD	2 (6.4)

Source: FDA Analysis

The response rates for patients with dose interruption of greater than 7 days had an ORR 90.4%, not decreased from the overall study population.

Reviewer comment: Although these numbers are small and this analysis is exploratory, the data provides support that temporary dose interruptions do not impact efficacy. This information was taken into consideration for labeling recommendations for dose interruptions prior to surgical procedures and for acalabrutinib therapy interruption with the need for temporary strong CYP3A4 inhibitors (i.e. antifungal therapies).

Subgroup Analysis

Response to acalabrutinib therapy was reported to be greater than 50% across pre-specified subgroups (age, sex, race, prior therapy, ECOG score, and extranodal disease.

Reviewer comment: The subgroup analyses are considered exploratory; nevertheless, these findings provide supportive evidence of the effectiveness of acalabrutinib across the subpopulations. However, given the exploratory nature of findings, we recommend not including the subgroup analysis in the USPI.

Table 57: Response rates(percentage) in Patients with Extranodal Disease

Extranodal Disease	Best Response		
	CR	PR	ORR
Total(n=90)	27%	50%	78%
Bone Marrow (n=63)	12%	65%	78%
Gastrointestinal (n=13)	31%	46%	77%
Lung (n=11)	36%	18%	54%

Source: Reviewer's table

Response data in extranodal disease sites was requested by the Agency and provided by the Applicant with the NDA submission. Analysis of the data is limited due to the lack of standard assessments and time of assessments for extranodal disease. Patients with extranodal disease were not required to undergo standard assessments at the sites of extranodal disease. In the majority of cases, patients with extranodal disease did not have histologic verification (i.e. bone marrow examination or colonoscopy) to verify response or confirm the presence of extranodal disease. Patients with bone marrow involvement were reported to have lower rates of CR (12%) than the overall population although similar rates of ORR (78%).

Reviewer comment: The decreased rates of CR reported in patients with bone marrow disease may reflect the persistence of disease in the bone marrow or may reflect the requirement of documentation of negative bone marrow for patient with initial bone marrow involvement in order to meet the criteria of CR.

8.1.3. Assessment of Efficacy Across Trials

One study, ACE-LY-004, was submitted to support the efficacy of acalabrutinib monotherapy for patients with relapsed and refractory mantle cell lymphoma. The efficacy of acalabrutinib was demonstrated by a high rate of overall response (81%) by investigator assessment per Lugano response criteria in 124 patients with mantle cell lymphoma who had received at least one prior therapy. The median duration of response had not been reached with 15.2 months of follow-up.

8.1.4. Integrated Assessment of Effectiveness

One study, ACE-LY-004, was submitted to support the efficacy of acalabrutinib monotherapy for relapsed and refractory mantle cell lymphoma. The efficacy of acalabrutinib was demonstrated by a high rate of overall response (81%) by investigator assessment per Lugano response criteria in 124 patients with mantle cell lymphoma who had received at least one prior therapy. The duration of response was not reached with median follow-up of 15.2 months. In addition, the complete response rate of 40% provides additional supportive evidence for the efficacy of acalabrutinib in patients with relapsed or refractory mantle cell lymphoma. The use of acalabrutinib as monotherapy with no radiation or immunotherapy permitted on study allows for any clinical efficacy noted on study to be attributed to acalabrutinib.

The use of overall response rate in mantle cell lymphoma is considered a surrogate endpoint and is clinically meaningful with supporting evidence from duration of response. Overall response rate with verified durable response as an endpoint has been the basis for accelerated approval and regular approval in past reviews. Approvals based demonstration of an improvement on ORR for mantle cell lymphoma and other non-Hodgkin lymphomas have historically required confirmation of benefit based on an accepted clinical meaningful endpoint such as PFS or OS in a randomized trial to support regular approval.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety analysis provided by the Applicant was reviewed for the 124 subjects enrolled and treated with acalabrutinib 100mg orally twice daily on study ACE-LY-004. The primary focus of the safety review was the patient population for study ACE-LY-004. The Applicant provided two additional safety populations: 1) patients with hematologic malignancies who had received acalabrutinib at 100mg orally twice daily as monotherapy (ISS-100, N= 442) and 2) all patients with hematologic malignancies who had received acalabrutinib monotherapy at any dose (ISS-All, N=610). These populations provided supportive safety data.

Safety analysis was conducted on the complete dataset provided by the Applicant for study ACE-LY-004 with a cut-off date of February 28, 2017. In addition, the Applicant submitted a 90-day safety update with a safety cut-off date of May 29, 2017. The 90-day safety updated included 2 additional patients to the ISS ALL(N=612).

Case report forms were provided and reviewed for all serious AEs and deaths that occurred in the primary safety population within 30 days of taking acalabrutinib. Particular attention was placed on the treatment emergent adverse events (TEAE) of hemorrhage and cardiac arrhythmia, potential class effect TEAEs. The reviewer performed additional analyses for

lymphocytosis, hemorrhage and infections.

The clinical review of safety was based upon:

- CSR for study ACE-LY-004
- Protocol and Statistical Analysis Plan for ACE-LY-004
- Integrated data sets for the three populations described above
- Summary of Clinical Safety
- Integrated Summary of Safety
- Proposed labeling for acalabrutinib

8.2.2. Review of the Safety Database

The safety data provided by the Applicant were derived from seven open-label safety and efficacy studies in patients with mantle cell lymphoma, chronic lymphocytic leukemia (CLL), Waldenström's Macroglobulinemia (WM), Diffuse Large B-cell Lymphoma (DLBL), Multiple Myeloma, and Follicular Lymphoma (FL). The primary safety analysis was performed on the dataset for Study ACE-LY-004. Two additional patient safety data sets were reviewed and provided supportive safety data. ISS-100 consisted of 442 patients who had received 100mg of acalabrutinib orally, twice daily, as monotherapy for hematologic malignancies and ISS-ALL was comprised of 610 patients who received acalabrutinib as monotherapy at any dose.

Overall Exposure

The median duration of exposure to acalabrutinib at a dose of 100mg orally twice daily was 13.8 months with a maximum exposure of 22 months. Over half (59.7%) of patients were exposed to acalabrutinib for greater than 12 months. The median relative dose intensity calculated as the ratio of the actual cumulative dose to the planned cumulative dose through the treatment exposure period was 98.7%. A summary of exposure to acalabrutinib for the pivotal study population is provided in the table below.

Table 58: Duration of Exposure in the Primary Safety Population

	≤ 3 Months n(%)	>3 to ≤6 Months n(%)	>6 to ≤12 Months n(%)	>12 Months n(%)
Primary Safety Pool (N=124)	16(12.9)	17(13.7)	17(13.7)	74 (59.7)
ISS-100 (N = 442)	55 (12)	43 (10)	57 (13)	287 (65)
ISS-ALL (N = 610)	86 (14)	52(9)	69 (11)	403 (66)

Source: FDA analysis of ADEX data set

Relevant characteristics of the safety population:

The demographic information for the patients evaluated for safety is summarized in the table below.

Table 59: Demographics of the Safety Population

	Primary Safety Pool		
	ISS-LY-004 N = 124	ISS-100 N = 442	ISS-All N = 610
Sex n(%)			
Male	99 (79.8)	310 (70.1)	419 (68.7)
Female	25 (20.2)	132 (30)	191 (31)
Age (years)			
Mean	67	66	66
Median	68	67	66
Min, Max	42, 90	32, 90	32, 90
≥ 65 n(%)	80 (64.5)	266 (60.2)	348 (57.0)
ECOG Status n(%)			
0	51 (57.3)	200 (45.2)	251 (41.1)
1	44 (35.5)	222 (50.2)	238 (53.8)
2	8 (6.5)	19 (4.3)	29 (4.8)
3	1 (0.8)	1 (0.8)	2 (0.8)
White	92 (74)	372(84)	523 (86)
Black	3 (2.4)	19 (4.3)	26 (4.3)
Asian	0(0)	4 (<1)	1 (<1)
American Indian	0(0)	1 (<1)	15 (2.5)
Other	0(0)	7 (1.2)	15 (2.5)
Not Reported	29 (23)	39 (9%)	39 (6)
Ethnicity n(%)			
Hispanic or Latino	4 (3)	10(2)	14 (2.3)
Not Hispanic or Latino	90 (73)	392 (89)	548 (90)
Not Provided	0(0)	10 (2)	12 (2)
Unknown	30 (24)	30 (7)	36 (6)
Trial Site n(%)			
United States	45 (36)	247 (56)	391 (64)
Ex-US	79 (64)	195 (44)	219 (36)
Number of Prior systemic regimens			
Median (range)	2 (1,5)	2 (0,13)	1 (0,13)

Adequacy of the safety database

The size of the database for the primary safety pool is adequate to provide an analysis of adverse reactions associated with acalabrutinib in a pretreated population with mantle cell lymphoma. The database from the pooled population (N=610) includes patients with other

hematologic malignancies (CLL, NHL, WM) and provides supportive safety. The demographic characteristics of the primary safety population which are predominately elderly, Caucasian males are representative of the demographics of patients with relapsed and refractory mantle cell lymphoma in the United States. Females, non-whites and Hispanic patients are under-represented.

The safety database does not provide adequate length of follow up to fully characterize the safety profile of acalabrutinib with extended or chronic use. This is important, because patients who have a disease response will likely continue acalabrutinib for an indefinite time. Safety data from a longer follow-up period will be informative to fully characterize the safety of acalabrutinib.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

This submission was of adequate quality for clinical review. Overall, the submission was well-organized with appropriate analyses and detailed reports and summaries. There are no concerns regarding the integrity of the submission.

Adequate narratives were provided for patients who died within 30 days of the final dose of acalabrutinib (N=5) as well as for patients who experienced an SAE (n = 48), or an AE leading to discontinuation of treatment (N=7). A subset of the safety data was traced back to the primary source (individual case report forms) and no discrepancies were identified.

Additional information was requested from the sponsor for details related to the death of one patient, USUBJID 091-503-1502. This data was provided and was adequate for review.

A 90-day safety update was provided with a cut of date of May 29, 2017, for the pivotal study and June 1, 2017, for five other studies in the safety pool. One remaining study in the safety pool had a cut-off date of April 3, 2017.

Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 and reported down to the investigator's verbatim term. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 4.03). Treatment emergent adverse events were defined as those events that occurred or worsened on or after the first dose of study treatment through 30 days following the last dose of study treatment.

Routine Clinical Tests

Laboratory assessments were carried out as specified in the protocol (ACE-LY-004) and included Complete Blood Count (CBC) and serum chemistries assessments weekly during cycle 1, days 1 and 15 of cycle 2, and monthly for subsequent cycles. Laboratory abnormalities to be reported as AEs were defined in the protocol as any clinically significant laboratory values. Clinically significant was defined as requiring treatment, discontinuation from the study or dose modification.

8.2.4. Safety Results

Deaths

The Applicant assessed all deaths in the pivotal and the pooled safety population, to include the follow-up period, deaths within 30 days after last dose, and Grade 5 TEAEs. The table below provides a summary of death categorizations.

Table 60: Summary of Deaths

	ISS-LY-004 N =124 n(%)	ISS-100 N = 443 n(%)	ISS-All N = 610 n(%)
All Deaths	27 (21.8)	48 (10.9)	70 (11.5)
Disease Progression	22 (17.7)	30 (6.8)	43 (7.0)
Adverse Event	1 (0.8)	13 (2.9)	22 (3.6)
Other	2 (1.6)	3 (0.7)	3 (0.5)
Unknown	2 (1.6)	2 (0.5)	2 (0.3)
Within 30 days of Last Dose	5 (4.0)	15 (3.4)	34 (5.6)
Disease Progression	5 (4.0)	8 (1.8)	19 (3.1)
Adverse Event	0(0.0)	7 (1.6)	15 (2.5)

Source: FDA Analysis

There was an increase in the percentage of deaths in Study LY-004 compared to the ISS-100 and ISS-ALL. The Applicant's rationale for the greater percentage of deaths in ISS-LY004 is due to the aggressive nature of mantle cell lymphoma compared to more indolent diseases in the larger safety populations. This rationale is supported by the most common cause of deaths in the ISS-LY004 population as due to disease progression.

Narratives were reviewed for all deaths due to TEAEs and deaths assessed by the investigator as progressive disease. There were no deaths attributed by the Applicant or investigator as PD that were assessed by the Agency to be due to other causes.

The table below summarizes patients who died within 30 days of last dose of acalabrutinib, died due to an AE regardless of timing from last acalabrutinib dose, or who died from causes listed as "unknown" or "other" regardless of timing from acalabrutinib therapy. The total

number of patients fitting these categories is 10. Brief summaries for each patient are provided below the table.

Table 61: Selected Summaries of Deaths within 30 days of study drug, death due to an AE or death due to “other” or “unknown” in Ace-LY-004

USUBJID	Study Day of Death	Days from last dose Acalabrutinib	Applicant provided Cause of Death	Agency assessed cause of death
202-501-1450	8	5	Disease Progression	● Disease Progression
091-503-1502	32	7	Disease Progression	● Tumor Lysis in the setting of PD as a cause of death Possible TEAE
055-501-1421	28	6	Disease Progression	● Disease progression and associated lymphocytosis and leukostasis syndrome
062-511-1472	112	16	Disease Progression	● Disease Progression
062-503-1462	451	12	Disease Progression	● Disease Progression
034-506-1401	175	58	Worsening Aortic Stenosis TEAE	● Worsening Aortic Stenosis TEAE
034-518-1447	240	109	unknown	● Disease progression and MDS this may have begun on treatment as patient discontinued treatment due to thrombocytopenia
034-509-1412	226	344	unknown	● Unknown (Pt had PD)
225-501-1419	463	277	Other – secondary AML	● Secondary AML
062-508-1460	246	63	Other - Complications after removal of colorectal tumor	● Complications after removal of colorectal tumor

Source: FDA Analysis

Select Patient Death Summaries

- **Patient 202-501-1450** was a 77-year-old male with relapsed and refractory MCL who had received two prior therapies. Per reports he died on study day 8 after discontinuing

therapy on study day 3 due to disease progression as assessed by clinical exam and physician assessment that he was “too unwell to continue.”

Reviewer comment: This patient appears to have developed clinical deterioration prior to beginning study. The ECOG performance status worsened from a 1 on study day -11 to 2 on study day 1. This reviewer agrees with the Applicants assessment based on the information provided and the timing of the death.

- **Patient 091-503-1502** was a 75-year-old male with relapsed or refractory MCL and a past medical history of hypertension, diabetes, hyperuricemia and mild renal failure. The patient was reported to have died on study day 32 due to progressive disease. He was also reported to have developed tumor lysis syndrome on day 26.

Reviewer comment: Additional information was requested from the Applicant to clarify the information supporting progressive disease as assessed by the investigator rather than tumor lysis syndrome as the cause of death. The Applicant provided additional information to demonstrate that this patient had evidence of transformation to aggressive lymphoma based on flow cytometry. The patient also had evidence of ureteral obstruction which may have contributed to renal failure. This reviewer agrees with the Applicant's assessment.

- **Patient 055-501-1421** was a 62-year-old female with multiply relapsed MCL who had been treated with five prior chemotherapy regimens and was refractory at the time of enrollment onto the study. Her WBC was $66.6 \times 10^9/L$ and Absolute lymphocyte count was $47.3 \times 10^9/L$ at the time of screening. She had normal vital signs on the day of initiation of treatment. On study day 1 her lymphocyte count had increased to $120 \times 10^9/L$. The patient developed dyspnea and study treatment was discontinued on day 22. She was diagnosed with leukostasis syndrome and anemia and was hospitalized. Her lymphocyte count at the time of hospitalization was $284 \times 10^9/L$. The patient died on study day 28, 6 days following the final dose of treatment. Her death was reported as due to disease progression. The investigator considered dyspnea to be unrelated to study treatment and the leukostasis syndrome to be related to study treatment.

Reviewer comment: This patient had marked lymphocytosis at study entry which worsened after subsequent initiation of study therapy. The patient's underlying progressive disease was likely the primary cause of death but it is impossible to rule out acalabrutinib associated lymphocytosis as contributing to her clinical deterioration.

- **Patient 062-511-1472** was a 74-year-old male with relapsed mantle cell lymphoma who had received three prior regimens and was refractory at the time of study enrollment. The patient had a MCL infiltrating wound of his thigh. He was diagnosed with disease progression per clinical and radiographic criteria and discontinued study therapy. No alternative therapy was pursued and the patient was reported to have died from disease progression on study day 112, 16 days after stopping study therapy. The patient

did have a TEAE of sepsis on study days 72-83; however, this was reported to be resolved at the time of death.

Reviewer comment: This reviewer agrees with the Applicant's cause of death of progressive disease based on the clinical information provided documenting radiographic and clinical progression of MCL.

- **Patient 062-503-1462** was a 51-year-old male with relapsed and refractory MCL. He had received three prior therapies and was refractory at the time of starting acalabrutinib. His medical history was complicated by a history of diabetes, pancreatitis and gastrointestinal bleeding. The patient responded to study therapy and had best response of PR on study day 88. He developed several TEAEs while on study to include anemia (study day 274) and peripheral ischemia of the left lower limb, which required amputation. The patient was diagnosed as having PD on study day 451 and discontinued study therapy at that time. On study day 473, the patient had a cardiopulmonary arrest and died 12 days after taking the last dose of acalabrutinib. The cause of death was listed as progressive disease and there was no autopsy.

Reviewer comment: This patient's death listed as cardiopulmonary arrest in the setting of progressive disease is likely related to disease progression. This review agrees with the investigators assessment based on the information available.

- **Patient 034-506-1401** was an 88-year-old male patient with relapsed and refractory stage 3 mantle cell lymphoma who had received two prior therapies. This patient had a significant past medical history of mild hypertension and mild aortic stenosis. The patient developed worsening hypertension (grade 2) on study day 112 which worsened on study day 117 to grade 3 resulting in acalabrutinib discontinuation. On study day 125 the patient was hospitalized for worsening aortic stenosis and died as a result of aortic stenosis on study day 175, 58 days from the last dose of acalabrutinib. The investigator concluded that the aortic stenosis was unrelated to study treatment.

Reviewer comment: This reviewer agrees with the investigator's assessment based on the information provided. This is supported by the patient's history of aortic stenosis and the natural history of aortic stenosis in this age group.

- **Patient 034-518-1447** was a 65-year-old male with relapsed and refractory mantle cell lymphoma. The patient had received one prior regimen of chemotherapy (rituximab, hyper-CVAD with rituximab maintenance, methotrexate, and ARA-C). The patient had a platelet count of 101 at screening and was reported to have platelet counts ranging from 74-114 x 10⁹/L until study day 131 when study treatment was discontinued on study day 131 due to grade 4 thrombocytopenia. On study day 184, the patient was diagnosed with MDS and was reported to have died on study day 240 due to unknown causes.

Reviewer comment: Based on the information provided, it is not possible to rule out the possibility of the thrombocytopenia that developed while on study treatment to have been related to the patient's later development of MDS. It is also unclear as to whether the MDS was the underlying cause of death as it is listed as "unknown." This reviewer's assessment is that based on the information provided, this patient's death may be secondary to a TEAE (MDS).

- **Patient 034-509-1412** was a 72-year-old male who discontinued treatment due to disease progression on day 226 and died on day 570, 344 days after the last dose of study treatment due to unknown causes.

Reviewer comment: Based upon the diagnosis of PD in this patient and the time of death from last acalabrutinib dose, this reviewer assesses that the cause of death is unlikely to be related to study therapy.

- **Patient 225-501-1419** was an 81-year-old male who discontinued study treatment on Day 186 due to an SAE of pulmonary fibrosis and died due to secondary AML on day 463, 277 days after the last dose of study treatment.

Reviewer comment: Based upon the time of death from last acalabrutinib dose, this reviewer agrees with the cause of death as other.

- **Patient 062-508-1460** discontinued study treatment on day 183 due to disease progression and died on day 246, 63 days after the last dose of study treatment due to intestinal obstruction caused by complications of removal of colorectal tumor.

Reviewer comment: Based upon the patient's history of PD and the time of death associated with surgical complication 63 days after the last acalabrutinib dose, this reviewer agrees with the cause of death as other.

As of the 90-day safety update, there were 30 deaths on the pivotal study. Twenty-two (21.8%) patients died from progressive disease, 5 within 30 days of last dose of acalabrutinib. Two deaths were attributed to a TEAE. One death, due to aortic stenosis, occurred 58 days after last dose of acalabrutinib and the second death due to non-small cell lung cancer occurred 86 days after acalabrutinib was discontinued. Both events were treatment emergent but were not considered to be related to study treatment. One death was due to intestinal obstruction of a colorectal tumor and one death was from AML. There were two additional deaths due to unknown causes in patients who had discontinued drug after a diagnosis of MDS and progressive disease, respectively.

Reviewer comment: No identified single cause of death in the pivotal study could be directly attributed to acalabrutinib therapy. Specifically, no deaths in the pivotal study were attributed to therapy-related infections, cardiac arrhythmias, or hemorrhage.

Serious Adverse Event

Serious adverse events were defined as those SAEs that occurred during treatment, within 30 days after the last dose of acalabrutinib, or SAE considered related to study drug occurring after the safety follow-up visit. SAEs were reported in 38.7% of the subjects in the primary safety population. No SAEs were reported in more than 5% of the population. The most common SOC category for SAEs was Infections and Infestations and the most common SAE by preferred term was pneumonia. SAE rates were similar to those reported in the pooled safety populations and are provided in the table below.

Table 62: Serious Adverse Events by System Organ Class and Preferred Term

System Organ Class Preferred Term	ISS-LY004 N=124 n(%)	ISS-100 N=443 n(%)	ISS-ALL N=610 n(%)
Patients with SAEs	48 (38.7)	149 (33.7)	218 (35.7)
Infections and infestations	13 (10.5)	54 (12.2)	94 (15.4)
Pneumonia	5 (4.0)	19 (4.3)	32 (5.2)
Sepsis	2 (1.6)	4 (0.9)	7 (1.1)
Arthritis bacterial	1 (0.8)	1 (0.2)	1 (0.2)
Catheter site infection	1 (0.8)	1 (0.2)	1 (0.2)
Gastroenteritis viral	1 (0.8)	1 (0.2)	1 (0.2)
Paronychia	1 (0.8)	1 (0.2)	1 (0.2)
Pharyngitis	1 (0.8)	1 (0.2)	1 (0.2)
Respiratory syncytial virus infection	1 (0.8)	1 (0.2)	1 (0.2)
Respiratory tract infection	1 (0.8)	3 (0.7)	4 (0.7)
Pneumonia	2 (1.6)	4 (0.9)	7 (1.1)
Sepsis	1 (0.8)	1 (0.2)	1 (0.2)
Gastrointestinal Disorders	6 (4.8)	20 (4.5)	25 (4.1)
Vomiting	2 (1.6)	4 (0.9)	4 (0.7)
Colitis	1 (0.8)	1 (0.2)	2 (0.3)
Diarrhea	1 (0.8)	4 (0.9)	5 (0.8)
Gastrointestinal hemorrhage	1 (0.8)	1 (0.2)	1 (0.2)
Inguinal hernia strangulated	1 (0.8)	1 (0.2)	1 (0.2)
Intestinal obstruction	1 (0.8)	1 (0.2)	1 (0.2)
Nausea	1 (0.8)	1 (0.2)	1 (0.2)
General Disorders and administration site conditions	6 (4.8)	23 (5.2)	33 (5.4)
General Physical Health Deterioration	3 (2.4)	3 (0.7)	3 (0.5)
Chest Pain	1 (0.8)	1 (0.2)	1 (0.2)
Non cardiac chest pain	1 (0.8)	3 (0.7)	4 (0.7)
Peripheral swelling	1 (0.8)	1 (0.2)	1 (0.2)
Pyrexia	1 (0.8)	11 (2.5)	14 (2.3)
Blood and Lymphatic System Disorders	5 (4.0)	18 (4.1)	29 (4.8)

System Organ Class Preferred Term	ISS-LY004 N=124 n(%)	ISS-100 N=443 n(%)	ISS-ALL N=610 n(%)
Anemia	4 (3.2)	7 (1.6)	11 (1.8)
Leukostasis Syndrome	1 (0.8)	1 (0.2)	1 (0.2)
Cardiac Disorders	4 (3.2)	11 (2.5)	15 (2.5)
Acute Coronary syndrome	1 (0.8)	1 (0.2)	1 (0.2)
Acute myocardial infarction	1 (0.8)	2 (0.5)	2 (0.3)
Cardiac failure	1 (0.8)	1 (0.2)	1 (0.2)
Cardiorespiratory arrest	1	1 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified	4 (3.2)	14 (3.2)	22 (3.6)
B cell lymphoma	1 (0.8)	1 (0.2)	1 (0.2)
Invasive ductal breast carcinoma	1 (0.8)	1 (0.2)	1 (0.2)
Metastasis to the meninges	1 (0.8)	1 (0.2)	2 (0.3)
Non-small cell lung cancer	1 (0.8)	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	4 (3.2)	8 (1.8)	11 (1.8)
Dyspnea	1 (0.8)	1 (0.2)	2 (0.3)
Interstitial lung disease	1 (0.8)	1 (0.2)	1 (0.2)
Pleural Effusion	1 (0.8)	1 (0.2)	1 (0.2)
Pulmonary Fibrosis	1 (0.8)	1 (0.2)	1 (0.2)
Injury poisoning and procedural complications	4 (3.2)	9 (2.0)	12 (2.0)
Fall	1 (0.8)	4 (0.9)	4 (0.7)
Humerus fracture	1 (0.8)	1 (0.2)	1 (0.2)
Radius fracture	1 (0.8)	1 (0.2)	1 (0.2)
Tibia fracture	1 (0.8)	2 (0.5)	2 (0.3)
Metabolism and nutrition disorders	3 (2.4)	7 (1.6)	12 (2.0)
Tumor lysis syndrome	2 (1.6)	2 (0.5)	2 (0.3)
Decreased appetite	1 (0.8)	2 (0.5)	2 (0.3)
Lactic Acidosis	1 (0.8)	1 (0.2)	1 (0.2)
Vascular disorders	3 (2.4)	6 (1.4)	10 (1.6)
Aortic stenosis	1 (0.8)	1 (0.2)	2 (0.3)
Hypotension	1 (0.8)	2 (0.5)	3 (0.5)
Peripheral ischemia	1 (0.8)	1 (0.2)	1 (1.2)
Hepatobiliary disorders	2 (1.6)	4 (0.9)	6 (1.0)
Cholecystitis	1 (0.8)	2 (0.5)	2 (0.3)
Jaundice cholestatic	1 (0.8)	1 (0.2)	1 (0.2)
Nervous system disorders	2 (1.6)	13 (2.9)	15 (2.5)
Altered state of consciousness	1 (0.8)	1 (0.2)	1 (0.2)
Headache	1 (0.8)	2 (0.5)	2 (0.3)
Renal and Urinary Disorders	1 (0.8)	2 (0.5)	6 (1.0)
Hydronephrosis	1 (0.8)	1 (0.2)	1 (0.2)
Reproductive system and breast disorders	1 (0.8)	1 (0.2)	2 (0.3)
Prostatitis	1 (0.8)	1 (0.2)	1 (0.2)

System Organ Class Preferred Term	ISS-LY004 N=124 n(%)	ISS-100 N=443 n(%)	ISS-ALL N=610 n(%)
Skin and subcutaneous tissue disorders	1 (0.8)	4 (0.9)	6 (1.0)
Acute febrile neutrophilic dermatosis	1 (0.8)	1 (0.2)	1 (0.2)

Source: Applicant ISS, FDA verified

SAEs that were higher in Study ACE-LY- 004 compared to ISS-100 and ISS-ALL were anemia (3.2% vs 1.6% and 1.8%), and general health deterioration (2.4% vs 0.9% and 1.1%). These events are not unexpected in a population of elderly patients with mantle cell lymphoma and cannot be conclusively attributed to study therapy.

Reviewer Comment: In general the SAEs across the three safety populations were similar. The slight increase in the SAEs of anemia and general health deterioration may reflect the underlying disease (MCL) or the slightly higher age of the ACE-LY-004 population age of the MCL population compared to the ISS-100 and ISS ALL populations.

One patient experienced the SAE of leukostasis syndrome and two patients experienced the SAE of tumor lysis syndrome. Narratives were provided and reviewed for these SAEs. All three of the reported tumor lysis syndrome SAEs occurred in the setting of progressive disease. No specific SAE by preferred term occurred in >5% of the patients on study ACE-LY-004. The most common SAE by preferred term was pneumonia (4%)

Table 63: SAEs by Preferred Term Occurring in > 2% patients in study ACE-LY-004

SAE Preferred Term	N = 124 n(%)
Pneumonia	5 (4.0)
Anemia	4 (3.2)
General physical health deterioration	3 (2.4)
Sepsis	2 (1.6)
Tumor Lysis Syndrome	2 (1.6)
Vomiting	2 (1.6)

Source: FDA Analysis

Dropouts and/or Discontinuations Due to Adverse Effects

In the pivotal study ACE-LY-004, 7 patients (5.6%) discontinued acalabrutinib due to an adverse event. The treatment emergent adverse events leading to drug discontinuation were not due to any one predominant cause. There was a similar, low rate of discontinuation of acalabrutinib due to AE in the ISS-100 population (6.6%) and the ISS-ALL population (6.1%). Reasons for drug discontinuation are listed in the table below.

Table 64: Summary of AEs leading to Acalabrutinib Discontinuation in ACE-LY-004, ISS-100 and ISS-ALL populations

Adverse Events Leading to Dose Discontinuation	ISS-LY-004 N = 124 n(%)	ISS-100 N = 442 n(%)	ISS-ALL N = 610 n(%)
Discontinuation due to AE	7 (5.6)	29 (6.6)	37 (6.1)
Development of EBV related malignancy	1 (0.8)	1 (0.2)	1 (0.2)
Aortic Stenosis	1 (0.8)	1 (0.2)	1 (0.2)
Dyspnea/Leukostasis	1 (0.8)	1 (0.2)	1 (0.2)
Thrombocytopenia	1 (0.8)	2 (0.5)	3 (0.5)
Pulmonary Fibrosis	1 (0.8)	1 (0.2)	1 (0.2)
Hemorrhagic bullae and petechiae	1 (0.8)	1 (0.2)	1 (0.2)
Non cardiac chest pain	1 (0.8)	1 (0.2)	1 (0.2)
Dose reduction due to AE	2 (2)	6 (2)	15 (3)
Dose/Treatment Delay due to AE	37 (30)	(140) 32	(204) 33

Source: Applicant submitted Summary of Clinical Safety page 43, FDA verified

With the submission of the 90-day safety update, 6.5% of patients discontinued due to adverse reactions.

In the pivotal study, 30% of patients had acalabrutinib dose delayed due to a TEAE. Rates and AEs leading to treatment delay are listed in the table below and were similar across the safety populations.

Table 65: Treatment Emergent Adverse Events Resulting in Acalabrutinib Treatment Delay Occurring in ≥ 2 patients

System Organ Class Preferred Term	ISS-LY-004 N = 124 n(%)	ISS-100 N = 442 n(%)	ISS-ALL N = 610 n(%)
ANY TAE	37 (29.8)	140 (31.7)	204 (33.4)
Blood and lymphatic system disorders	6 (4.8)	26 (5.9)	35 (5.7)
Neutropenia	2 (2.4)	26 (5.9)	21 (3.4)
Anemia	2 (1.6)	5 (1.1)	7 (1.1)
Infections and Infestations	13 (10.5)	45 (10.2)	46 (7.5)
Pneumonia	4 (3.2)	14 (3.2)	20 (3.3)
Herpes Zoster	3 (2.4)	4 (0.9)	4 (0.7)
Urinary Tract Infection	2 (1.6)	2 (0.5)	2 (0.3)
Gastrointestinal disorders	11 (8.9)	37 (8.4)	48 (7.0)
Vomiting	5 (4.0)	14 (3.2)	16 (2.6)
Nausea	3 (2.4)	9 (2.0)	12 (2.0)
Diarrhea	2 (1.6)	12 (2.7)	15 (2.5)
Intestinal obstruction	2 (1.6)	2 (0.5)	2 (0.3)

System Organ Class Preferred Term	ISS-LY-004 N = 124 n(%)	ISS-100 N = 442 n(%)	ISS-ALL N = 610 n(%)
Nervous System Disorders	3 (2.4)	21 (4.8)	25 (4.1)
Headache	2 (1.6)	10 (2.3)	11 (1.8)
Skin and subcutaneous disorders	3 (2.4)	7 (1.6)	12 (2.0)
Rash	2 (1.5)	2 (0.5)	3 (0.5)
Investigations	3 (2.4)	10 (2.3)	3 (0.5)
Neutrophil count decreased	2 (1.6)	2 (0.5)	3 (0.5)

Source: Applicant Integrated Summary of Safety, Table 11

Grade ≥3 TEAES

The most common grade ≥ 3TEAEs were related to bone marrow suppression. Greater than or equal to grade 3 neutropenia, anemia and thrombocytopenia were experienced in 10%, 8.9%, and 4% of patients respectively. The table below summarizes the greater than grade 3 TEAEs.

Table 66: Grade ≥3 AEs in > 2% of any analysis safety population

≥ Grade 3 AE	ISS-LY-004 N=124 n(%)	ISS-100 N=442 n(%)	ISS-ALL N=610 n(%)
Any Grade	61 (49.2)	206 (46.6)	295 (48.4)
Neutropenia	13 (10.5)	44 (10.0)	57 (9.3)
Anemia	11 (8.9)	31 (7.0)	43 (7.0)
Pneumonia	6 (4.8)	21 (4.8)	35 (5.7)
Thrombocytopenia	5 (4.0)	17 (3.8)	22 (3.6)
Diarrhea	4 (3.2)	9 (2.0)	13 (2.1)
Dyspnea	3 (2.4)	6 (1.4)	10 (1.6)
General Physical Health Deterioration	3 (2.4)	3 (0.7)	3 (0.5)
Hyperuricemia	3 (2.4)	3 (0.7)	11 (1.8)
Neutrophil count decreased	3 (2.4)	8 (1.8)	11 (1.8)
Tumor Lysis Syndrome	2 (1.6)	9 (2.0)	13 (2.1)
Syncope	2 (1.6)	9 (2.0)	13 (2.1)
Hypertension	1 (0.8)	10 (2.3)	15 (2.5)

Source: Applicant Provided Summary of Clinical Safety, page 35-36, verified by FDA

Reviewer comment: The Applicant reported an overall a low rate of grade 3 or higher AEs and only one grade 5 TEAE. No TEAE greater than grade 3 occurred in more than 11% of patients. The TEAE profile is acceptable in this patient population.

Significant Adverse Events

Adverse events of special interest (ESI) were identified by the Applicant based on non-clinical findings and emerging data from published reports of BTK inhibitors (Tang, 2017, Yun, 2016). An analysis was provided by the Applicant on the following events of clinical interest: cardiac events including a subcategory of atrial fibrillation, cytopenias, and the subcategories neutropenia, anemia and thrombocytopenia, hemorrhage including the subcategory major hemorrhage, hepatic events, hypertension, infections, interstitial lung disease, second primary malignancies, and tumor lysis syndrome. Definitions of ECIs were provided in the ISS SAP and were acceptable. For the subcategory of atrial fibrillation, preferred terms of atrial fibrillation and atrial flutter were used. Major hemorrhage was defined and any hemorrhagic event that is serious or $\geq$ grade 3 in severity or that is a central nervous hemorrhage of any grade.

Reviewer comment: The Applicant's classification of ECIs appeared acceptable to capture appropriate events for each category.

The table below provides a breakdown of the events of clinical interest.

Table 67: Events of Clinical Interests in patients in ACE-LY-004

	Any grade N=124 n (%)	$\geq$ Grade 3 N=124 n (%)
<u>Cardiac Events</u>	10 (8.1)	3 (2.4)
Atrial Fibrillation	0(0)	0(0)
<u>Anemia</u>	15 (12.1)	11 (8.9)
<u>Leukopenia</u>	16 (12.9)	16 (12.9)
Neutropenia	16 (12.9)	16 (12.9)
Other Leukopenia	1 (0.8)	1 (0.8)
<u>Thrombocytopenia</u>	7 (5.6)	6 (4.8)
<u>Hemorrhage</u>	39 (31.5)	1 (0.8)
Major Hemorrhage	1 (0.8)	1 (0.8)
<u>Hepatic Events</u>	5 (4.0)	2 (1.6)
<u>Hypertension</u>	3 (2.4)	1 (0.8)
<u>Infections</u>	66 (53.2)	16 (12.9)
<u>Interstitial Lung disease</u>	2 (1.6)	1 (0.8)
<u>Second primary malignancies</u>	8 (6.5)	4 (3.2)
Second primary malignancies, non-skin	4 (3.2)	4 (3.2)
<u>Tumor Lysis Syndrome</u>	3 (2.4)	3 (2.4)

Source: FDA Analysis of ADAE dataset

There was no grade 5 ECIs reported. There were no events of atrial fibrillation or atrial flutter in the pivotal study and one event of major hemorrhage.

The incidence of major hemorrhage was low across the safety populations, 2.3% in the ISS-100

and 2.5% in the ISS-All populations, including one fatal intracranial hemorrhage. In the ISS-ALL population, 14 patients were reported to have the AE atrial fibrillation/flutter. Thirteen of these were atrial fibrillation and one was atrial flutter.

Hemorrhage

The incidence of any hemorrhage on Study ACE-LY-004 was 31.5 % and only an 0.8% incidence of major hemorrhage. The median time to onset for all hemorrhage events was 22 days (range 2-503 days).

One patient was reported to have severe hemorrhage. Patient 215-501-1474 had a relevant medical history of gastric ulcer with hemorrhage and deep venous thrombosis prior to initiating study. This patient had lymphoma involvement of the GI tract. On study day 149, the patient was hospitalized with melena and a suspected GI bleed. At the time of admission, his platelet count was $10.6 \times 10^9/\text{dL}$, and hemoglobin was 12.7 g/L which had decreased from 15.5 g/dL. This patient was taking fondaparinux up until 7 days prior to the diagnosis of the bleeding event. The bleeding was reported resolved three days after admission and the patient was discharged. The patient resumed acalabrutinib therapy and was still receiving acalabrutinib at the time of the data cut off, approximately 8 months after the bleeding event.

In the ISS-All population the most commonly reported hemorrhagic events were contusion, petechiae, ecchymosis, epistaxis and increased tendency to bruise (all mucocutaneous). In the evaluation of the safety database of 612 patients based on the 90-day safety cut-off, grade 3 or higher bleeding events were reported in 2% of the patients. The incidence of any bleeding event in the total combined patient population (n=612) was approximately 50%.

Reviewer comment: The 30% incidence hemorrhage (mostly grade 1 or 2) is consistent with the presumed class effect of BTK inhibitors of platelet dysfunction. Risk of bleeding and caution against concomitant anticoagulant use is warranted in the UPSI.

Atrial Fibrillation and Atrial Flutter

In the combined database of 612 patients (includes 90-day safety cut-off), 2.9% of patients experienced atrial fibrillation or atrial flutter of any grade. Grade 3 atrial fibrillation or flutter occurred in 1% of these patients.

Infections:

Infections were defined as any TEAE with a PT in MedDRA SOC Infections and Infestations and occurred in 53.2% (all grades) of the patients in the study ACE-LY-004. Thirteen percent of patients on ACE-LY-004 were reported to have $\geq$ grade 3 infections. The most frequently reported infections were sinusitis (9.7%) nasopharyngitis and upper respiratory tract infection (6.5 % each) and bronchitis and pneumonia (6.5% each).

Serious infections were reported for 8% of the patients on the ACE-LY-004 study and there were no fatal infections.

In the total safety database to include two additional patients with the 90-day safety cut-off data, grade 3 or higher infections occurred in 18% of these patients. The most frequently reported infection in this population was pneumonia.

Reviewer comment: Opportunistic infections involving both fungal viral and bacterial were noted in both the ACE-LY-004 and the total safety population although there was no specific pattern or organism identified. The risk for these infections should be included in the USPI and prophylaxis should be considered for patients receiving acalabrutinib therapy.

Immunoglobulin Levels and Infections

Serum Immunoglobulins (IGG, IGM and IGA) were assessed starting at the end of cycles 6, 12, 18, 24, and then every 24 weeks.

Mean Immunoglobulin levels for IgA remained stable in the normal range until 18 months and then decreased for the 4 remaining patients who had analysis at 24 weeks, although mean values were still within normal range.

Mean Immunoglobulin levels for IgG decreased slightly during therapy although mean values remained in the normal range for the patients who had assessments at 24 weeks.

Mean Immunoglobulin levels for IgM initially decreased and then increased slightly for those patients who had assessments at 24 weeks.

There were no reports in the pivotal study of patient with any grade IgG decreased AEs. Three patients (2.4%) received immunoglobulins while on study. An analysis of low immunoglobulin levels and infectious AEs was performed and no correlation with AEs of infection and low IgG, IgA or IgM levels were identified.

Tumor Lysis Syndrome

In Study ACE-LY-004, three subjects had a tumor lysis event. In a review of the narratives, progressive disease occurred in all three patients and is potential confounder as to whether study drug or underlying disease or both are causes of the TLS.

One patient developed grade 4 TLS on Day 26 (1 day after stopping acalabrutinib). The patient stopped therapy due to progressive disease and concurrent renal failure so it is unclear if the TLS due to progressive disease or study drug.

The other two patients developed TLS on Day 277 and Day 110 of the study, respectively. In both patients, study drug had been discontinued for 3 and 8 days, respectively due to progressive disease before TLS occurred.

Reviewer Comment: All patients who developed tumor lysis on this study had progressive disease at the time of diagnosis of TLS. Tumor lysis syndrome was not noted in any patient in the first two weeks of therapy. Tumor lysis syndrome does not seem to be associated with acalabrutinib therapy although the relatively high (27%) incidence of elevated uric acid levels in patients on this study raises the possibility of sub-clinical tumor lysis syndrome and warrants further follow up.

Second Primary Malignancies (SPM)

Eight patients on ACE-LY-004 developed a second primary malignancy that was considered treatment related. Three additional patients developed a SPM 30 days after stopping acalabrutinib therapy. Of these three patients, two developed hematologic malignancies (MDS, AML). The patient who developed MDS discontinued acalabrutinib 53 days prior to the MDS diagnosis due to thrombocytopenia. In this patient, is it possible that the thrombocytopenia reflected developing MDS that occurred while on study therapy.

Table 68: SPMs occurring in patients in Study ACE-LY-004

Treatment Emergent SPM (within 30 days of stopping Acalabrutinib)	n(%)	SPM > 30 days after stopping acalabrutinib	n(%)
EBV Related Lymphoma	1 (0.8)	MDS – 53 day	1 (0.8)
Invasive ductal breast carcinoma	1 (0.8)	AML – 277 days	1 (0.8)
Metastasis to meninges *	1 (0.8)	Colorectal tumor – 63 days	1 (0.8)
NSCLC	1 (0.8)		
Basal Cell Carcinoma	2 (1.6)		
Squamous Cell Carcinoma	2 (1.6)		
Total	8 (6.4)		
Non Skin	4 (3.2)		

*progressive disease

Source: FDA analysis

In the combined database of 612 patients (includes 2 patients from 90 day safety data update), SPMs occurred in 10.6% of patients.

Reviewer Comment: There was no clear pattern for non-skin SPMs and the incidence in this small study does not appear to be significantly increased over what would be expected in patients with mantle cell lymphoma. The incidence of SPM in patients with MCL has been reported to be 8.2% in a published report of 3149 patients with median latency time of 47 months from diagnosis to development of SPM. In the population-based study, the most common SPM categories with the highest observed/expected ratios were CLL, AML, NHL, anal and rectal, skin, and thyroid (Shah, 2015). Since immune suppression can be associated with malignancies and many patients treated with acalabrutinib may be exposed for long-term

therapy, inclusion in the warnings and precautions is warranted. Additional long-term follow-up will be informative to characterize the long-term incidence of development of SPMs in patients who receive acalabrutinib.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent events were defined as AEs that occurred or worsened after the first dose of acalabrutinib administered through the safety follow up visit.

Treatment emergent adverse events were reported in 97.6 percent of patients and were mostly grade 1 or grade 2 events. The most common non-hematological TEAEs were headache (37.9%), diarrhea (30.6%), fatigue (27.4%) and myalgias (21%). The table below summarizes the Adverse Drug Reactions reported in greater than >10% of patients in the safety populations.

Table 69: Treatment Emergent Adverse Events reported in greater than 10% of the safety population

Preferred Term	ISS-LY004 N = 124		ISS-100 N = 442		ISS-ALL N = 610	
	All Grades n(%)	Grade ≥3 n(%)	All Grades n (%)	Grades ≥3 n(%)	All Grades n(%)	Grades ≥3 n(%)
Any AE	121 (97.6)	61 (49.2)	437 (99.9)	206 (46.6)	603 (98.9)	295 (48.4)
Headache	47 (37.9)	2(1.6)	186 (42.1)	7 (1.6)	258 (42.3)	8 (1.3)
Diarrhea	38 (30.6)	4 (3.2)	161 (36.4)	9 (2.0)	234 (38.4)	13 (2.1)
Fatigue	34 (27.4)	1 (0.8)	106 (24)	5 (1.1)	143 (23.4)	9 (1.5)
Myalgia	26 (21.0)	1 (0.8)	55 12.4	2 (0.5)	74 (12.1)	2 (0.3)
Cough	24 (19.4)	0(0)	89 (20.1)	0(0)	119 (19.5)	0(0)
Nausea	22 (17.7)	1 (0.8)	101 (22.9)	7 (1.6)	141 (23.1)	9 (1.5)
Pyrexia	19 (15.3)	0(0)	60 (13.6)	4 (0.9)	(100) 16.4	7 (1.1)
Asthenia	18 (14.5)	2 (1.6)	54 (5.4)	4 (0.9)	31 (5.1)	6 (1.0)
Constipation	17 (13.7)	0(0)	60 (13.6)	0(0)	91 (14.9)	0(0)
Contusion	16 (12.9)	0(0)	91 (20.6)	0(0)	132 (21.6)	0(0)
Rash	16 (12.9)	1 (0.8)	54 (12.2)	1 (0.2)	73 (12.0)	2 (0.3)
Vomiting	16 (12.9)	2 (1.6)	63 (14.3)	5 (1.1)	85 (13.9)	7 (1.1)
Anemia	15 (12.1)	11 (8.9)	11 (8.9)	31 (7)	69 (11.3)	43 (7.0)
Dizziness	15 (12.1)	0(0)	62 (14.0)	2 (0.5)	83 (13.6)	2 (0.3)
Neutropenia	13 (10.5)	13 (10.5)	47 (10.6)	44 (10.0)	61 (10.0)	57 (9.3)

Source: Applicant Submitted Summary of Clinical Safety, page 34

Laboratory Findings

For standard clinical laboratory test results, the Applicant provided summaries of absolute values over time with changes from baseline over time.

Table 70: Summary of Hematology Laboratory Abnormalities

Laboratory parameter	ISS-LY004 N = 124		ISS-100 N = 442		ISS-ALL N = 610	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Platelet Decreased	50(40.3)	10(8.1)	135 (30.5)	30 (6.8)	189 (31)	46 (7.5)
ANC Decreased	44(35.5)	16 (12.9)	168 (38.0)	38 (8.6)	281 (46.1)	65 (10.7)
Hgb Decreased	49(39.5)	8 (6.5)	192 (43.4)	90 (20.4)	248 (40.7)	132 (22.1)

Source Applicant CSR (verified by FDA)

The most common reported hematologic laboratory abnormality was platelets decreased (40%), with the majority being grade 1 or 2. The incidence of platelets decreased in the pivotal population was slightly higher than that in the ISS-100 and the ISS-ALL populations. The most common ≥ grade 3 hematologic laboratory abnormality was ANC decreased. The median time to onset for ≥ grade 3 decreased ANC was 87.5 days, with resolution to baseline or grade 1 values reported in 68.8% of patients after a median duration of 29 days.

Reviewer comment: The laboratory abnormality platelet count decreased was increased in the ACE-LY-004 population compared to the ISS-100 and ISS-ALL populations, which may be related to the higher rate of underlying bone marrow involvement in the mantle cell population in Study ACE-LY-004 compared to the other hematologic malignancies populations in the other studies. TEAEs that would be expected to be related to these findings, however (i.e. hemorrhage) were not increased in the ACE-LY-004 population compared to the larger safety populations.

Additional analyses were performed assessing both hematological adverse events and laboratory abnormalities. There was a discrepancy in the reporting of laboratory hematological abnormalities and hematology TEAEs with more laboratory abnormalities of low hemoglobin, decreased platelets and decreased ANC reported relative to the number of EAEs of anemia, thrombocytopenia and neutropenia.

The following table provides the combined incidence for laboratory and hematological TEAEs.

Table 71 Hematologic Adverse Reactions (NCI-CTCAE and laboratory measurements)

	ACE-LY-004 N=124	
	All Grades n(%)	Grade ≥3 n(%)

	ACE-LY-004 N=124	
	All Grades n(%)	Grade ≥ 3 n(%)
Hemoglobin Decreased	57(46.0)	13(10.5)
Platelets Decreased	55(44.4)	15(12.1)
Absolute Neutrophil Count Decreased	45(36.3)	18(14.5)

Reviewer Comment: Given that there may have been underreporting of the hematological TEAEs, recommend including both hematology and hematology laboratory parameters in the common adverse events given that incidence > 20% when combined.

The figures below display the mean values for ANC, Hemoglobin and Platelets over time for subjects on ACE-LY-004. Mean values for ANC decreased over the first six months of therapy and then increased for the patients remaining on treatment after 10 months. Mean hemoglobin decreased more rapidly, during the first month of therapy and then increased after two months for those remaining on therapy. Mean platelet count decreased over the first few months of therapy and remained lower than baseline throughout therapy without a clear trend toward continued decrease.

Figure 19: Mean (+/-) SEM of ANC ($10^9/L$)

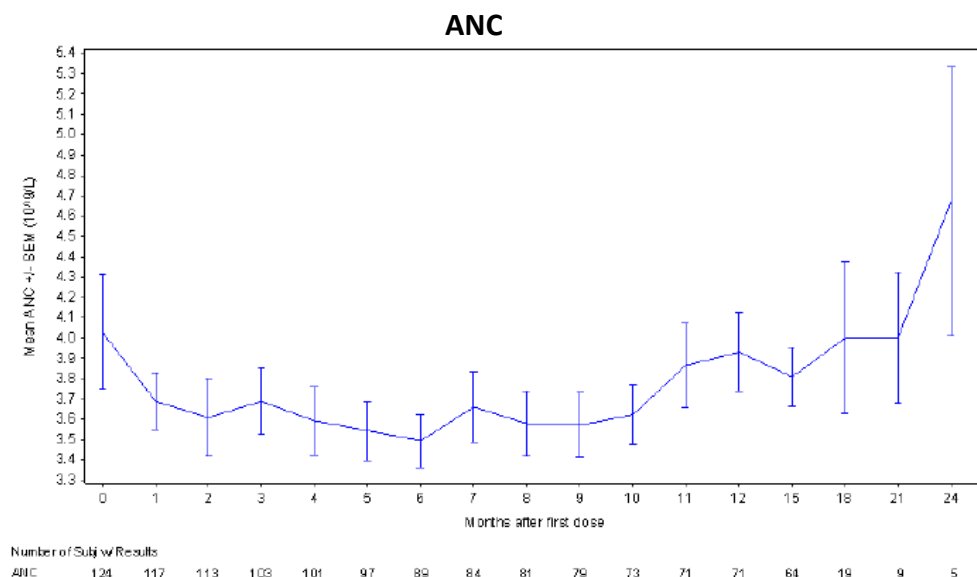


Figure 20 Mean (+/-) SEM of Hemoglobin g/L

Hemoglobin

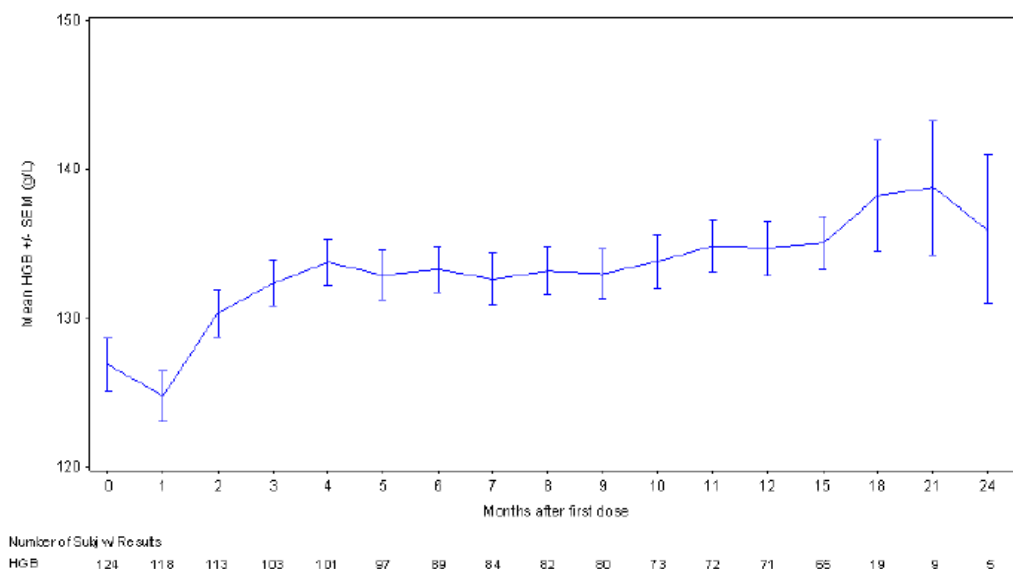
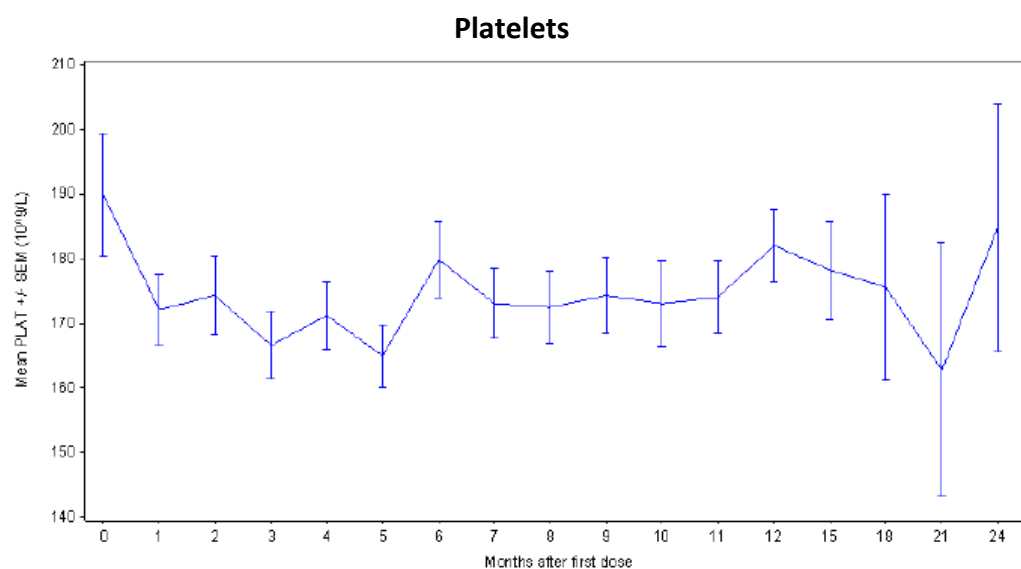


Figure 21 Mean (+/-) SEM Platelets ($10^9/L$)



Non-Hematologic Laboratory Abnormalities

The following table summarizes grade ≥ 3 non-hematologic laboratory abnormalities occurring in greater than 5% of patients in the safety populations.

Table 72: Summary of $\geq$ Grade 3 Chemistry Laboratory Abnormalities occurring in > 5% of patients

Laboratory parameter	ISS-LY004 N = 124		ISS-100 N = 442		ISS-ALL N = 610	
	All Grades N (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Uric Acid Increased	33(26.6)	33 (26.6)	74 (16.7)	74 (16.7)	94 (15.4)	94 (15.4)
Phosphate Decreased	29(23.4)	6 (4.8)	77 (17.4)	13 (2.9)	108 (17.7)	19 (3.1)

Source Applicant SCS, verified by FDA analysis

Reviewer comment: The rates of clinically relevant TEAEs associated with elevated uric acid (TLS and renal toxicity) were not reported at rates >2% in this study. Consideration was given to the inclusion in the USPI of elevated uric acid as a laboratory finding associated with acalabrutinib therapy since elevated uric acid can be associated with tumor lysis syndrome and renal toxicity, both of which may be mitigated with medical interventions (hydration, anti-hyperuricemic agents). However, given the low rates of TLS observed with acalabrutinib and the lack of correlation with the initiation of therapy, the elevation of uric acid was not considered an adverse drug reaction.

The table below summarizes selected all grades chemistry laboratory abnormalities occurring in > 20% of patients

Table 73: Summary of Selected All Grades Chemistry Laboratory Abnormalities occurring in ≥ 20% of patients

Laboratory parameter	ISS-LY004 N = 124		ISS-100 N = 442		ISS-ALL N = 610	
	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Creatinine Increased	113(91.1)	0(0)	317 (71.7)	0(0)	426 (69.8)	1 (0.2)
Uric Acid Increased	33(26.6)	33(26.6)	74 (16.7)	74 (16.7)	94 (15.4)	94 (15.4)
ALT increased	28 (22.6)	3 (2.4)	83 (18.8)	10 (2.3)	118 (19.3)	14 (2.3)
AST increased	26 (21)	1 (0.8)	71 (16.1)	7 (1.6)	109 (17.9)	10 (1.6)

Source Applicant SCS, Verified by FDA analysis

Reviewer comment: There was a high rate (91.1%) rate of grade 1 or grade 2 increase in creatinine in the ACE-LY-004 which was consistent with the ISS-100 and ISS-ALL populations although slightly higher in the ACE-LY-004 populations. This in combination with the renal toxicity noted in preclinical studies supports a potential safety signal that warrants renal

function monitoring for patients that take acalabrutinib therapy for long period. At this time, there have not been significant reports of > grade 3 elevated creatinine or renal toxicity with acalabrutinib, however since long term treatment is expected in the post marketing setting, this warrants follow up for any evidence of cumulative toxicity.

Hepatic Events

Overall, the frequency of hepatic adverse events was similar across ACE-ALY-004, ISS-100 and the ISS-ALL populations. In the ISS-LY-004 there were 4% of all grades hepatic adverse events with grade ≥ 3 hepatic events of 1.6%. In Study ACE-LY-004, the most commonly reported hepatic AE was blood bilirubin increased (1.6%). There were no reported grade 4 or 4 hepatic events and no reported serious adverse events (hepatic) in the ACE-LY-004 study.

There were 3 subjects in the ISS-ALL population who met the biochemical criteria for Hy's law of ALT or AST ≥ 3 ULN and concurrent total bilirubin $\geq 2 \times$ ULN. One patient was from Study ACE-LY-004. Brief narratives for these patients are provided below.

- Patient ACE-LY-004-062-508-1460: 62-year-old male with enlarged liver at baseline of study and was hospitalized on Study Day 182 for grade 4 cholestatic jaundice and grade 4 hydronephrosis. The patient was subsequently diagnosed with colon carcinoma and the investigator attributed the cholestatic jaundice due to the colon cancer. The events resolved on Day 188.
- Patient 15-H-001643-2403: 67-year-old female with grade 4 hepatocellular injury and grade 4 reactivation of hepatitis B viral infection on Study Day 310. Study treatment discontinued and on Study day 316, the patient died due to hepatic failure (developed hepatic encephalopathy). The investigator assessed hepatic failure as related to acute reactivation of hepatitis B and as related to acalabrutinib.
- Patient ACE-LY-002-509-118: 59-year-old female with history of moderate hyperbilirubinemia and grade 2 bilirubin elevation at screening. On Day 58, the patient met the biochemical criteria for Hy's law. On Day 86 and 350, the patients AST and ALT returned to normal limits, respectively but the bilirubin continued to remain elevated. This was not considered an AE and study treatment continued.

Reviewers Comments: Upon review of these three patient narratives, there were confounders (colon cancer, hepatitis reactivation, baseline elevated bilirubin) for each patient. This reviewer agrees with the Applicant's assessment that these three cases were not Hy's law.

Shifts in Clinical Chemistry Parameters (AST, ALT, bilirubin) for Study ACE-LY-004

Table 74: Percentage Shift increase in AST, ALT and Bilirubin from baseline in Study ACE-LY-004 (N = 124)

Grade 1 Shift	Grade 2 Shift	Grade 3 Shift	Grade 4 Shift
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	Grade 1 Shift	Grade 2 Shift	Grade 3 Shift	Grade 4 Shift
ALT	17.9%	2.4%	2.4%	0
AST	17.9%	2.4%	0.8%	0
Total bilirubin	5.7%	1.6%	1.6%	0

Source: FDA Analysis of Applicants data

In Study ACE-LY004, ALT was increased (all grades) in 28(26%) of patients, AST increased in 26(21%) of patients and bilirubin increased in 11(8.9%) of patients. There was > grade 3 increase in ALT, AST and total bilirubin in 3(2.4%), one (0.8%) and 2(1.6%) patients.

Lymphocytosis

Lymphocytosis is a class effect of BTK inhibitors and has been reported in patients taking BTK inhibitors with CLL and mantle cell lymphoma. The mechanism of action is reported to be a redistribution of lymphocytes from tissue sites to peripheral blood. In general, with BTK therapy, the lymphocytosis resolves within the first several months and in general is not associated with lymphocytosis-related AEs.

Lymphocytosis in the ACE-LY-004 study was defined as ALC increased greater than 50% over baseline and greater than $5 \times 10^9/L$. Resolution of lymphocytosis was defined as when ALC decreased to baseline or lower or achieved $< 5 \times 10^9/L$.

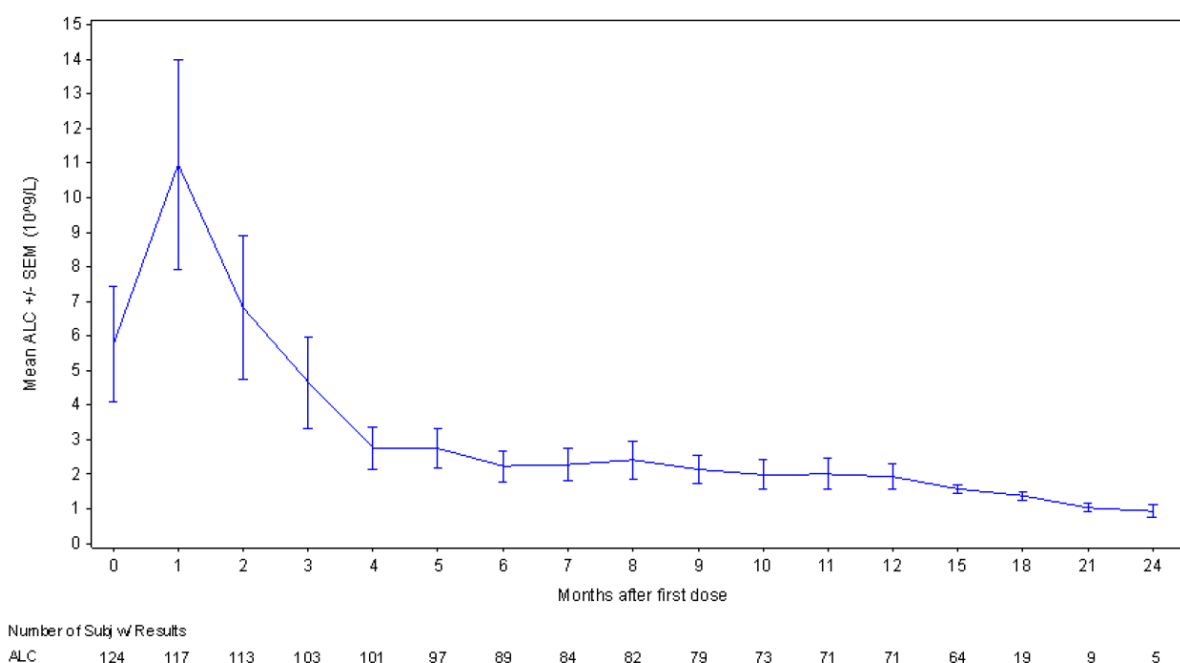
Lymphocytosis occurred in (38) 31% of patients on study ACE-LY-004. Seventy-nine percent of patients who developed lymphocytosis had resolution of lymphocytosis. Lymphocytosis occurred within the first several weeks of starting therapy. The median time to onset of lymphocytosis in the pivotal study was 1.1 weeks and the median duration of lymphocytosis was 5.6 weeks. Similar rates were noted for the additional two safety population and are displayed in table 75. Median plot of absolute lymphocyte count for patients on ACE-LY-004 over time is displayed in the figure below.

Table 75: Lymphocytosis in patients receiving acalabrutinib therapy

	ISS-LY-004 N=124	ISS-100 N=442	ISS-ALL N=610
Patients who developed lymphocytosis n(%)	38 (30.6)	143 (32.8)	228 (37.4)
Median time to onset(weeks)	1.1	1.1	1.1
Median duration of lymphocytosis(days)	5.6	7.4	11.0

Source: Applicant submitted ISS, FDA confirmed

Figure 22: Mean plot of absolute lymphocyte counts over time – all treated subjects on ACE-LY-004



Source: Applicant CSR

AEs associated with Lymphocytosis

Of the 38 patients who were reported to have lymphocytosis as defined by the protocol, 28 (74%) had a greater than grade 3 TEAE reported at some time during therapy. Two of these 28 patients had a greater than grade 3 TEAE that this reviewer assessed as possibly being related to lymphocytosis based on the symptoms and the degree of lymphocytosis at the time of the AE. Both patients reportedly died of progressive disease shortly after the lymphocytosis occurred.

Table 76: Lymphocytosis related AEs on study ACE-LY-004

USUBJID	Baseline ALC	Lymphocytosis ALC / Study Day	AE / Study Day	Comments
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USUBJID	Baseline ALC	Lymphocytosis ALC / Study Day	AE / Study Day	Comments
ACE-LY-004 055-501 -1421	120 X 10 ⁹ /L	284 x 10 ⁹ / Day 22	Dyspnea / Day 22 Leukostasis / Day 22	Pt had elevated ALC on screening and on day 1 – discontinued therapy and died of PD after discontinuing therapy
ACE-LY-004 091 503 1502	1 x 10 ⁹ /L	37 x 10 ⁹ / Day 22	TLS / Day 26 Renal Failure / Day 26	Tumor lysis syndrome may have been related to lymphocytosis related to therapy

Source: FDA Analysis

Reviewer comment: Lymphocytosis is associated with acalabrutinib therapy at similar rates across all safety populations and a variety of hematologic conditions. The longer duration of lymphocytosis noted in the ISS-ALL population may be related to the higher number of patients with CLL in that population. The TEAEs that occurred in patients with lymphocytosis did not appear to be related to the lymphocytosis. For the two patients that did have TEAEs that could be attributed to the lymphocytosis, the concomitant report of progressive disease at the time of the lymphocytosis creates some uncertainty of the relationship of symptoms.

Any FDA analysis of the most common AE for the study, headache, which may be predicted to be related to lymphocytosis, did not appear to be related to lymphocytosis. Eleven of the 38 (30%) of patients who were reported to have lymphocytosis had an AE of headache, which is similar to the incidence of headache reported in the overall study population (37.9%)

Reviewer Comment: It is warranted to include lymphocytosis in the USPI so that prescribers and physicians can monitor for any potential ADRs related to lymphocytosis and so that there is knowledge of this event to prevent unnecessary discontinuance of potentially effective therapy as long as lymphocytosis is not associated with serious AEs.

Vital Signs

The Applicant provided a record of the vital signs and a description of the changes in vital signs during treatment with acalabrutinib. A review of blood pressure, weight, heart rate, and temperature did not reveal any identified safety signals.

Hypertension

Hypertension is a reported TEAE with other BTK inhibitors. Hypertension TEAEs were reported for 2.4% of the ISS-LY004 patients which was slightly lower than the ISS-100 (6.1%) and ISS-ALL (7.5%). There were no treatment discontinuations due to hypertension. The table below displays maximum post-baseline grades for systolic and diastolic blood pressure.

Table 77 Hypertension in Study ACE-LY-004

Vital Sign	N	Baseline grade ^a	Maximum postbaseline grade ^b			
			0 n (%)	1 n (%)	2 n (%)	3 n (%)
Systolic Blood Pressure (mmHg) ^c	123	0	6 (4.9%)	17 (13.8%)	14 (11.4%)	2 (1.6%)
		1	1 (0.8%)	17 (13.8%)	28 (22.8%)	10 (8.1%)
		2	0	3 (2.4%)	13 (10.6%)	7 (5.7%)
		3	0	0	1 (0.8%)	4 (3.3%)
Diastolic Blood Pressure (mmHg) ^d	123	0	32 (26.0%)	25 (20.3%)	21 (17.1%)	1 (0.8%)
		1	1 (0.8%)	18 (14.6%)	15 (12.2%)	4 (3.3%)
		2	0	1 (0.8%)	4 (3.3%)	0
		3	0	0	1 (0.8%)	0

^a Baseline = pretreatment value closest to the first dose.

^b The maximum toxicity grade experienced by each subject up to the Safety Follow-up Visit or 30 days after the last dose, whichever was later.

^c Systolic Blood Pressure: Grade 0 (≤ 119 mmHg), Grade 1 (120-139 mmHg), Grade 2 (140-159 mmHg), Grade 3 (≥ 160 mmHg).

^d Diastolic Blood Pressure: Grade 0 (≤ 79 mmHg), Grade 1 (80-89 mmHg), Grade 2 (90-99 mm Hg), Grade 3 (≥ 100 mmHg).

Source: Applicant CSR Table 51, page 157

Electrocardiograms (ECGs)

ECGs were obtained only obtained at baseline on Study ACE-LY004.

Cardiac AEs were reported for 10 (8%) of patients on the pivotal study and 9.7% and 11.8% in the ISS-100 and ISS All populations. Five patients had a TEAE of arrhythmia reported on ACE-LY-004. There was one grade 4 ventricular arrhythmia and cardiac arrest and the remainder were grade 1 bradycardia, tachycardia, premature ventricular contraction, and extrasystoles. There were no reports of atrial fibrillation or flutter in Study ACE-LY-004.

QT

A thorough QT/QTc study was conducted in 48 healthy adult subjects and reviewed by the QT Interdisciplinary Team. Subjects received acalabrutinib at doses of 100mg, 400mg, placebo and moxifloxacin in this randomized, double-blind, double dummy 4-way crossover study.

No significant QTc prolongation effect of acalabrutinib was detected in the thorough QT study. The largest upper bounds of the 2-sided 90% confidence interval for the main differences between acalabrutinib and placebo were below 10ms, the threshold for regulatory concern as described in ICH E-14 guidelines.

The QT-IRT recommend the following language for Section 12.2 of the USPI: The effect of acalabrutinib on the QTc interval was evaluated in a randomized, double-blind, double-dummy, placebo-and positive-controlled, 4-way crossover thorough QTc study in 48 healthy adult subjects. Administration of a single dose of acalabrutinib that is the 4-fold maximum recommended single dose did not prolong the QTc interval to any clinically relevant extent

Refer to the QT-IRT review dated October 12, 2017 for additional details.

Immunogenicity

There is no immunogenicity data about acalabrutinib in this application.

8.2.5. Analysis of Submission-Specific Safety Issues

There was no additional analysis of submission-specific safety issues.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

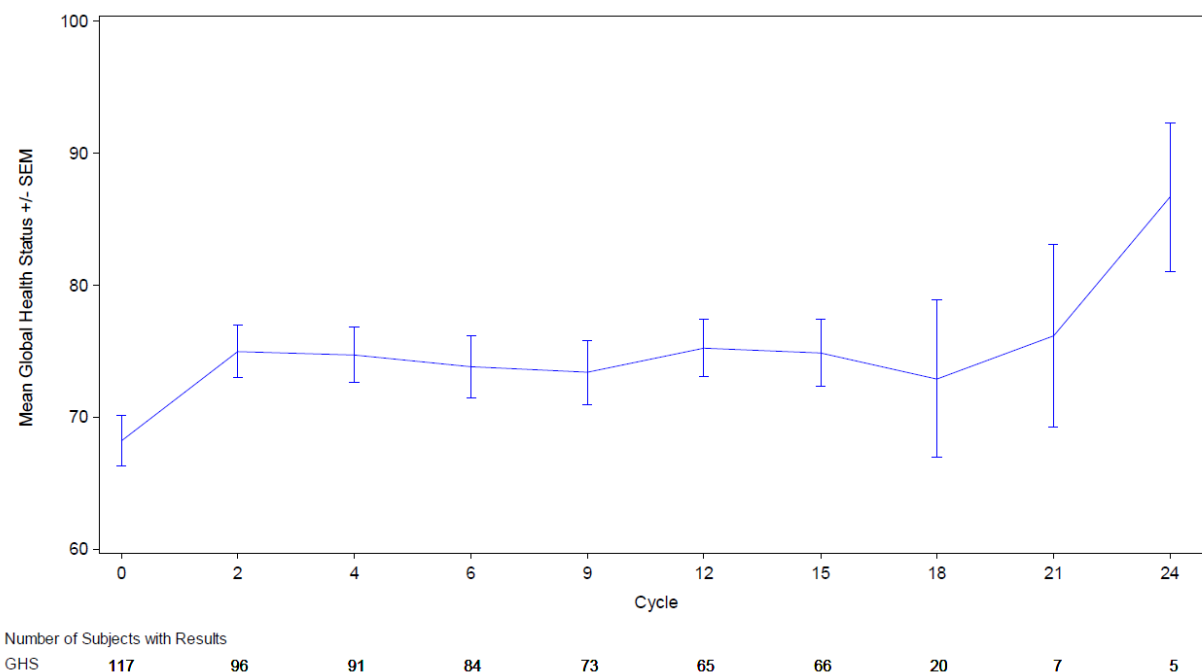
Health-related quality of life questionnaires (EORTC (European Organization for Research and Treatment of Cancer, Core Quality of life questionnaire [QLQ-C30]) was administered to subjects at screening, at the end of the cycle 2, 4 and 6 and then every 12 weeks until PD or use of alternative therapy. The compliance rate for PRO completion is detailed in the table below.

Visit	Eligible	Percent Completed
Baseline	124	95%
Cycle 2 Day 28	116	83%
Cycle 4 Day 28	101	90%
Cycle 6 Day 28	95	88%
Cycle 9 Day 28	82	89%
Cycle 12 Day 28	75	87%
Cycle 15 Day 28	74	89%
Cycle 18 Day 28	21	100%
Cycle 21 Day 28	9	78%
Cycle 24 Day 28	5	100%

Source: Applicant CSR, Table 11.2.6.2 , p 320-321

As displayed in the figure below, mean global health status and quality of life scores improved slightly over therapy.

Figure 23: Mean plot of EORTC QLQ-C30 over time, global health status/quality of life (all treated subjects)



Source: Applicant CSR

Mean functional scales remained stable throughout therapy and mean symptom scales for fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial problems in general, remained stable through therapy. There did appear to be an increase in symptom scores for insomnia, diarrhea, and constipation after cycle 18, although the small number of patients in this group makes drawing meaningful clinical conclusions challenging.

Reviewer comment: In general PRO measures in this study were consistent with well-tolerated therapy and no clear signal for a negative impact of acalabrutinib on quality of life and other PRO measures. Although the numbers are small in patients completing questionnaires after 24 weeks, the increase in mean global health status scores, supports the favorable safety profile of acalabrutinib. Given exploratory nature of analysis and lack of control arm in Study ACE-LY-004, no inclusion of PRO data in the USPI is recommended.

8.2.7. Safety Analyses by Demographic Subgroups

The single arm study (ACE-LY004) is not adequately powered to reach conclusions regarding the safety among the demographic subgroups (sex, age and race).

TEAEs were analyzed for age groups <65 and $\geq$ 65 in the ISS-ALL population and the pivotal study population

Fatal TEAEs were more common (5.7% vs 1.9%) in the $\geq$ 65 year population compared to the < 65 year in analysis of the ISS-ALL population but were not due to any one predominant cause. Pneumonia was the most common grade 5 TEAE in both the $\geq$ 65 and < 65 population.

Across the 7 pooled studies, 419(69%) of male subjects and 191 (31.3%) female subjects were enrolled and all (100%) of female subjects and 98.3% of male subjects had an AE.

Across the 7 pooled studies, 523(86%) white subjects and 87(14%) non-white subjects were enrolled. The most frequently reported TEAEs (> 10% of patients in either category) contusion was reported more by whites(23%) than non-whites(10%) patients and asthenia was reported more by non-white(16%) than white(3%) patients.

Reviewer Comments: Although the pooled study database is larger than single arm study, there was no comparator arm and the individual studies not adequately powered to detect differences in demographic subgroups. No conclusions can be drawn from findings.

8.2.8. Specific Safety Studies/Clinical Trials

There were no special safety studies or clinical trials in this application.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

An evaluation of second primary malignancies was conducted. See the section 8.2.4.

Pediatrics and Assessment of Effects on Growth

There were no children enrolled in any of the studies submitted with this application. The safety of acalabrutinib in pediatric patients has not been established.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There was no experience of overdose reported in the clinical studies of acalabrutinib. Acalabrutinib is intended to be prescribed by specialists in hematology and oncology. There is no evidence that acalabrutinib produces physical or psychological dependence in patients with hematologic malignancies.

8.2.10. **Safety in the Postmarket Setting**

Safety Concerns Identified Through Postmarket Experience

Acalabrutinib is not marketed in any country. No postmarketing safety data is available.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application. Although, since it is expected that some patients may take acalabrutinib for an indefinite period of time, safety with long-term use of acalabrutinib will need to be closely monitored since the median duration of treatment was 16.6 months at the time cut off of the 90-day safety update.

8.2.11. **Integrated Assessment of Safety**

The safety of acalabrutinib as monotherapy was evaluated in 124 patients with relapsed or refractory mantle cell lymphoma. The median duration of exposure was 13.8 months at the primary analysis and 16.6 months at the time of the 90-day safety update. The population of patients for the pivotal study was representative of the expected demographic population for mantle cell lymphoma with a median of 2 prior therapies variety of prior chemotherapy and immunotherapies. Safety data from an additional 486 patients with hematologic malignancies who received acalabrutinib monotherapy at any dose supported the safety conclusions from the primary safety population.

The most common non-hematological adverse reactions of any grade were headache (37.9%), diarrhea (30.6%), fatigue (27.4%), and myalgia (21.0%) and bruising. None of these common events led to drug discontinuation. The most common hematological adverse events (hematologic TEAEs and laboratory events) were anemia (46.0%), thrombocytopenia (44.4%) and absolute neutrophil count decreased (36.3%) when evaluating laboratory and hematological adverse reactions.

Treatment discontinuation occurred due to any adverse reaction was reported in 6.5% of patients. No one adverse reaction was predominant in leading to treatment discontinuation.

Serious adverse events were reported in 38.7% of patients. The most frequent SAEs were pneumonia (5%), anemia (4%), and general physical health deterioration. All other SAEs occurred in less than 2 (1.6%) of patients each.

The following adverse events of special interest were also identified: and

Cytopenias: Cytopenias as adverse reactions including neutropenia (12.9%), anemia (12.1%), and thrombocytopenia (5.6%), were reported in patients receiving acalabrutinib therapy.

Hematologic laboratory abnormalities occurred in > 20% of the population for ANC decreased (35.5%), Hemoglobin decreased (41.9%), and Platelets decreased (41.1) and these were more frequently reported than the related AEs. The incidence of hematologic laboratory abnormalities is clinically relevant and should be included in the USPI. Mean ANC and hemoglobin values decreased after initiating therapy but improved for patient remaining on therapy. Mean platelet counts decreased initially and generally did not return to baseline but remained greater than $100 \times 10^9/L$ for those patients remaining on therapy. CBCs should be monitored monthly on study.

Atrial fibrillation and atrial flutter: Although there were no reported events in the pivotal study there were cases reported in the ISS-100 (2.5%) and ISS-ALL (2.9%) populations. Atrial fibrillation is an AE associated with the BTK inhibitor class and should be included in warnings and precautions.

Hemorrhage: Reports of severe hemorrhage were low in this study (0.8%), however serious hemorrhagic events including fatal hemorrhage were reported in the larger safety database (approximately 50%). Mild hemorrhage (ecchymosis and bleeding) was relatively common in the pivotal study, reported in 30% of patients on the pivotal study. The mechanism of bleeding is not well understood but thought to be related to platelet dysfunction, supported by in vitro evidence of thrombin generation inhibition in patients receiving acalabrutinib and in healthy volunteers. This warrants inclusion in warnings and precautions and supports recommendations for withholding acalabrutinib prior to major surgery.

Infections: Serious infections to include bacterial, viral and fungal infections occurred in the combined safety data base of patients. In the larger database of patients, grade 3 or higher infections occurred in 18% of patients with the most common grade 3 or 4 infection of pneumonia.

Second Malignant Neoplasm: Patients with MCL have an increased risk for second malignancies. In this small study with relatively short follow up the rate of second malignancies appears to be similar to what would be expected in this population. Since early detection of some of this SPM may benefit patients, it is appropriate to include this in warnings and precautions.

In addition, lymphocytosis occurred in the first weeks of treatment however the lymphocytosis were not associated with AEs and resolved within the first several weeks of treatment, at least one patient developed marked lymphocytosis and leukostasis syndrome approximately two weeks after starting acalabrutinib therapy in the setting of PD. Lymphocytosis occurred in 30% of patients on study, typically within the first two weeks.

Reviewer comment: A comprehensive review of the safety data demonstrates that acalabrutinib demonstrated a favorable safety profile and was well tolerated in both the pivotal

trial and in the ISS-100 and ISS-ALL populations with a manageable adverse event profile and a low rate of drug discontinuation due to AEs.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

This was an open label single-arm trial which limits the interpretability of time to event analysis. Analysis of efficacy and safety on subpopulations are considered exploratory. Efficacy of acalabrutinib will require confirmation in a randomized controlled trial. Although the safety profile of acalabrutinib appears to be favorable compared to 1st generation BTK inhibitor therapy studied in a similar population, conclusions with regards to a favorable safety profile cannot be determined without a direct comparison.

8.4. Conclusions and Recommendations

Relapsed and refractory mantle cell lymphoma is a serious and life-threatening condition for which acalabrutinib demonstrated clinical activity. In the single arm trial, ACE-LY004, the ORR was 80.6% (95% CI: 30.9%, 48.7%) based on investigator assessment per the Lugano 2014 classification. The median DOR has not been reached with median follow-up of 15.2 months (range 0.3 to 23.7). In addition, the CR rate was 39.5%. The efficacy results from this trial indicated that acalabrutinib has clinical activity in patients with relapsed and refractory MCL.

Overall, acalabrutinib was well tolerated with the most frequently reported grade 3 or 4 AEs of neutropenia (12.9%) and anemia (8.9%). The overall incidence of SAEs was 38.7%. Most of the deaths on the study were due to progressive disease and few patients discontinued study drug due to adverse events (6.5%). There were no reports of atrial fibrillation or atrial flutter in Study ACE-LY-004.

This reviewer recommends Accelerated Approval for acalabrutinib. Section 21 CFR 314.50 addresses approval based on a clinical endpoint other than survival or irreversible mortality. Accelerated approval is subject to the requirement that the Applicant study the drug further, to verify and describe the clinical benefit, where there is uncertainty as to the relationship of the surrogate endpoint to clinical benefit or of the observed clinical benefit to the ultimate outcome.

Because multiple therapies are now approved for mantle cell lymphoma, a comprehensive characterization of the efficacy of anti-neoplastic agents, disease course and determination of adequacy of long-term follow up is important. Important questions remain regarding the treatment of mantle cell lymphoma such as optimal use of combination treatments, characterization of disease course (nodal, extranodal sites, BM involvement), and evaluation of treatment effect on time-to-event endpoints including progression free survival and overall

survival.

The rationale for the recommendation of accelerated approval for acalabrutinib is founded upon the following considerations:

- Uncertainty as to the relationship of ORR and DOR to ultimate outcome of overall survival. Although the ORR was 80.6% per investigator assessment, 32% of patients discontinued treatment due to progressive disease and 18% of patients died due to progressive disease.
 - The most optimal use of acalabrutinib for the treatment of mantle cell lymphoma is not known. The Applicant's ongoing randomized controlled trial of acalabrutinib + bendamustine and rituximab versus bendamustine + rituximab in patients with mantle cell lymphoma (b) (4) would allow for adequate evaluation of time-to-event endpoints and the role of acalabrutinib in combination regimens.

In conclusion, the benefit-risk assessment is favorable for the use of acalabrutinib as monotherapy for patients with mantle cell lymphoma who have received at least one prior therapy. This reviewer recommends accelerated approval for acalabrutinib.

X

X

Jingjing Ye, Ph.D
Primary Statistical Reviewer

Lei Nie, Ph.D.
Statistical Team Leader

X

X

Margret Merino M.D.
Primary Clinical Reviewer

Tanya Wroblewski M.D.
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncologic Drug Advisory Committee or any other external consultants because the application did not raise significant efficacy or safety issues for the proposed indication.

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10 Pediatrics

Patients less than 18 years of age were excluded from Applicant sponsored clinical studies of acalabrutinib. The proposed indication, mantle cell lymphoma, is not reported to occur in the pediatric population. The efficacy and safety of acalabrutinib in pediatric patients has not been studied.

11 Labeling Recommendations

11.1. Prescribing Information

The following summarizes the major changes to the acalabrutinib prescribing information proposed based on this review.

- **HIGHLIGHTS:** Add myalgia and fatigue to adverse reactions as these occurred in > 20% of patients on this study. Include anemia, thrombocytopenia and neutropenia(combined laboratory and hematologic adverse reactions) as part of common adverse events.
- **2 DOSAGE AND ADMINISTRATION:** Revision of table of dose modification recommendations to more clearly describe recommendations for AEs warranting dose interruption and reduction.
- **5 WARNINGS AND PRECAUTIONS:** Include only percentages when describing rates of AEs and remove reference to total safety pool population number. Clarify specific percentage of AEs for bleeding. Include opportunistic infections with recommendations to consider prophylaxis. Clarify that CBC monitoring occurred monthly on study. Include guidelines to monitor for atrial fibrillation.
- **6 ADVERSE REACTIONS:** Provide rates of all grades and grade ≥ 3 in the ADR table. Include most common cytopenias in the ADR table.
- **14 CLINICAL STUDIES:** Remove (b) (4) Remove subgroup ORR reference as these are considered exploratory endpoints. Include a description of lymphocytosis including rates of lymphocytosis, time of onset and duration of lymphocytosis.

11.2. Patient Labeling

The following summarizes the major changes to the patient information proposed based on this

review:

- Included fatigue and muscle aches as a common side effect of acalabrutinib.

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12 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies needed beyond recommended labeling.

Recommendations on REMS

Review of the application and of the findings from the review teams, the Division of Risk Management in the Office of Surveillance and Epidemiology agree that a REMS is not needed to ensure the benefits of acalabrutinib exceed its risk. Therefore, the subsequent sections are not applicable for this review and have been omitted.

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13 Postmarketing Requirements and Commitments

The following post marketing requirements are recommended:

1. Accelerated Approval PMR Description:
To verify the clinical benefit of acalabrutinib, submit the complete final report and datasets demonstrating clinical efficacy and safety from a randomized, double-blind, placebo-controlled, clinical trial of CALQUENCE® in combination with standard immunochemotherapy versus immunochemotherapy alone in patients with mantle cell lymphoma.
2. Food and Drug Administration Amendments Act of 2007(FDAAA) PMR Description
In order to characterize the safety of acalabrutinib with long term, chronic use, conduct a study to characterize the long-term safety of CALQUENCE® monotherapy. Submit interim and complete final reports showing long-term safety with a minimum of 24 months of follow-up from study ACE-LY-004 in patients with mantle cell lymphoma.
3. FDAAA Hepatic Impairment Description
Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of acalabrutinib in patients with severe hepatic impairment. This trial should be designed and conducted in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling

14 Appendices

14.1. References

Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017

Swerdlow, S. H. (2016). The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood*, 127(20), 2375-2390.

Hoster, E., Dreyling, M., Klapper, W., Gisselbrecht, C., van Hoof, A., Kluin-Nelemans, H. C. for the European Mantle Cell Lymphoma, (2008). A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma. *Blood*, 111(2), 558-565.

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Yun, S., Vincelette, N. D., Acharya, U., & Abraham, I. (2017). Risk of Atrial Fibrillation and Bleeding Diathesis Associated With Ibrutinib Treatment: A Systematic Review and Pooled Analysis of Four Randomized Controlled Trials. *Clin Lymphoma Myeloma Leuk*, 17(1), 31-37.

14.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): ACE-LY-004, ACE-LY-001

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>494 (52 Principle Investigators and 442 sub investigators)</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>1</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in S Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>5</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

14.3. Nonclinical Pharmacology/Toxicology

14.4. OCP Appendices (Technical documents supporting OCP recommendations)

14.4.1. Summary of Bioanalytical Method Validation and Performance

Acalabrutinib and ACP-5862 concentrations in plasma or urine were assayed in clinical trials. As outlined in **Error! Reference source not found.**, 5 methods were developed and validated, including the measurement of acalabrutinib / [¹⁴C]acalabrutinib in plasma or urine and ACP-5862 in plasma. ACP-5862 concentrations were measured in Studies **ACE-HV-005** (TQT) and **ACE-HV-113** (gastric pH). During validation of all assays, no analytically significant interferences from endogenous matrix components were observed. All the bioanalytical methods appeared to be validated appropriately and met in-study performance criteria requirements according to the FDA Bioanalytical Method Validation Guidance. Validation accuracy, precision, and stability summary data for the bioanalytical methods are presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

Table 78 Validated bioanalytical methods for acalabrutinib and ACP-5862 in human biological samples

Method	Analyte	Matrix	Report Number ^a	LLOQ ng/mL	Linear range ng/mL ^c
SAP.1802	acalabrutinib	Lithium Heparin Plasma	1000-131802-1	1.00	1.00 to 1000
SAP.1826	acalabrutinib	Urine	1000-141826-1	50.0	50.0 to 5000
160.002.01	[¹⁴ C]acalabrutinib	Lithium Heparin Plasma	160/002V	0.0881 dpm/mL 0.314 pg/mL ^b	0.0881 to 10.1 dpm/mL 0.314 to 35.9 pg/mL ^b
160.002.02	[¹⁴ C]acalabrutinib	Urine	160/002V	0.0881 dpm/mL 0.314 pg/mL ^b	0.0881 to 10.1 dpm/mL 0.314 to 35.9 pg/mL ^b
SAP.1974	acalabrutinib	Lithium Heparin Plasma	1000-171974-1	1.00	1.00 to 1000
	ACP-5862	Lithium Heparin Plasma	1000-171974-1	5.00	5.00 to 5000

^a Refers to Method Validation Report, located in [Module 5.3.1.4](#).

^b The mass concentrations quoted are based on the specific radioactivity of the [¹⁴C]acalabrutinib in the certificate of analysis (0.280055896 dpm/pg).

^c Units for methods SAP.1802, SAP.1826 and SAP.1974

Abbreviations: LLOQ = Lower limit of quantification

Source: Table 2 from Applicant's Summary of Biopharmaceutical Studies and Associated Analytical Methods

Table 79 Validation accuracy, precision, stability data for bioanalytical methods for acalabrutinib in human biological samples

	Plasma Method (SAP.1802)	Urine Method (SAP.1826)
Between-run accuracy (%)	-2.5 - 1.1	-0.8 - 3
Between-run precision (%)	1.3-3.5	1.1 - 3.2
Within-run accuracy (%)	1 - 3.7	-1 - 5.2
Within-run precision (%)	2.1 - 8.8	3.1 - 5.2
Stability in matrix, acceptable up to:	2 hours ^a	24 hours
Stability at room temperature acceptable up to:	24 hours	24 hours
Long term stability ^{b,c} acceptable up to:	6 days at -20°C and -80°C	18 days at -20°C and -80°C

^a Stability in whole blood at room temperature

^b Plasma stability determination is ongoing as part of the validation report (1000-131802-1). Currently, acalabrutinib stability has been demonstrated for up to 785 days storage at ≤-80°C. Refer to stability report 1000-131802-2 in [Module 5.3.1.4](#).

^c Long term stability in plasma at ≤15°C up to 367 days was demonstrated in report 503604 (refer to [Module 5.3.1.4](#)). This method was never applied to acalabrutinib clinical samples.

Source: Table 3 from Applicant's Summary of Biopharmaceutical Studies and Associated Analytical Methods

Table 80 Validation accuracy, precision, stability data for bioanalytical methods for acalabrutinib and ACP-5862 in human biological samples

	Method SAP.1974 Acalabrutinib	Method SAP.1974 ACP- 5862
Between-run accuracy (%)	-14.5 - -2.3	-9.6 - 2.7
Between-run precision (%)	0.8 - 3.9	0.9 - 4.5
Within-run accuracy (%)	-12.8 - -2.9	-8.6 - -1.6
Within-run precision (%)	1.1 - 4.1	1.7 - 4.4
Stability in matrix, acceptable up to:	2 hours ^a	2 hours ^a
Stability at room temperature acceptable up to:	66 hours	66 hours
Long term stability ^b acceptable up to:	5 days at -20°C 13 days at -80°C	5 ^c days at -20°C 13 ^c days at -80°C

^a Stability in whole blood at room temperature

^b Ongoing plasma stability data are being collected as part of the validation completed on 21 February 2017. Data available in May 2017 indicate acalabrutinib and ACP-5862 stability for up to 99 days storage at ≤-80°C.

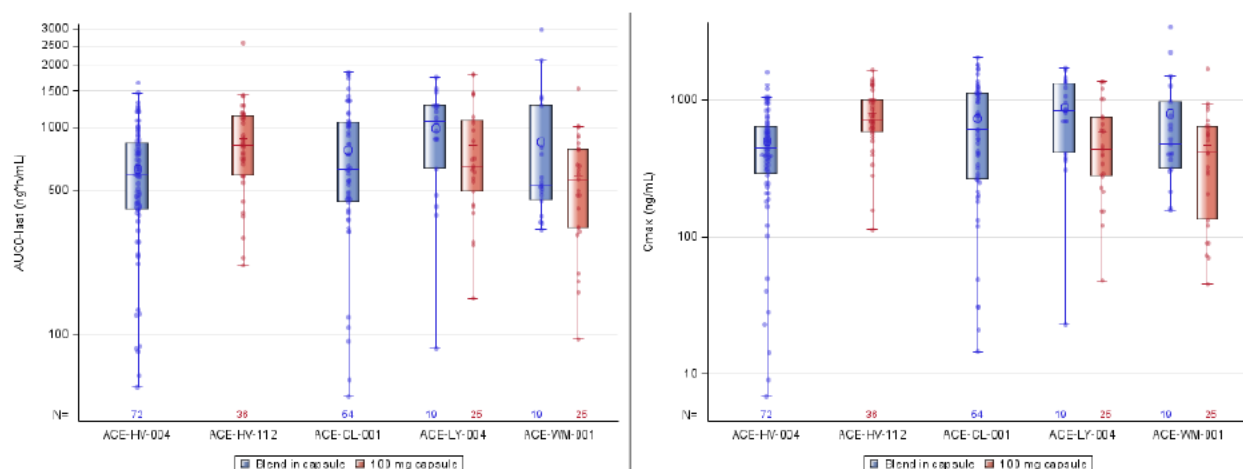
^c Within-range long term matrix stability criteria were met; however, over-range long term stability quality control samples failed at these time points. Data available in May 2017 indicate over-range and within-range stability for up to 99 days storage at ≤-80°C.

Source: Table 4 from Applicant's Summary of Biopharmaceutical Studies and Associated Analytical Methods

14.4.2. Relative Bioavailability of Acalabrutinib Formulations

Comparison of acalabrutinib AUC and C_{MAX} achieved following 100 mg using the early capsule formulation vs. 100 mg using the to-be-marketed capsule formulation in healthy subject and patient clinical studies is shown in Error! Reference source not found.. The data indicate that acalabrutinib PK is generally comparable between the two formulations in healthy subjects and patients.

Figure 24 Comparison of AUC and C_{MAX} by formulation in various clinical studies



Healthy Subject Studies = ACE-HV-004, ACE-HV-112; Patient Studies = ACE-CL-001, ACE-LY-004, ACE-WM-001

Source: Figure 5 from Applicant's Summary of Biopharmaceutic Studies and Associated Analytical Methods

14.4.3. Supplemental Tables and Figures

Appendix Table 1: List of acalabrutinib and ACP-5862 PBPK model parameters

Compound Name Acalabrutinib			Compound Name ACP-5862 (M27)		
PhysChem and Blood Binding			PhysChem and Blood Binding		
Mol Weight (g/mol)	465.50		Mol Weight (g/mol)	481.50	
log P	2.03	in-vitro value	log P	2.72	in-vitro value
pKa 1	3.54	in-vitro value	pKa 1	3.41	in-vitro value
BP input type	User		BP input type	User	
B/P	0.79	in-vitro value	B/P	0.65	in-vitro value
fu	0.03	in-vitro value	fu	0.01	in-vitro value
Absorption	1st order		Absorption	NA	
fu(Gut)	0.03	Equal to fup			
Q(Gut) Input	12.33	Predicted			
Pe _{eff,man} (x 10 ⁻⁴ cm/s)	4.00	Optimized			
Permeability Method	Mechanistic Model				
Distribution	Minimal PBPK Model		Distribution Model	Minimal PBPK Model	

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}

Clearance Type	Enzyme Kinetics		Clearance Type	Enzyme Kinetics	
In vitro metabolic system	Recombinant		In vitro metabolic system	HLM	
CYP3A4 CLint (μl/min/pmol)	9.63	derived with retrograde based on clinical PK			
Pathway	Pathway 1		Pathway	Pathway 1	
Enzyme	CYP3A4		Enzyme	CYP3A4	
Vmax	4.13	in-vitro value	CLint (μL/min/mg)	23.60	in-vitro value
Km	2.78	in-vitro value			
Forms Metabolite	Pri Met 1				
Pathway	Pathway 2				
Enzyme	CYP3A4				
CLint (μL/min/pmol of isoform)	8.14				
Additional HLM CLint	289.52				
CL R (L/h)	1.33	Clinical PK	CL R (L/h)	0.30	Clinical PK
CYPs and/or UGTs Interaction			CYPs and/or UGTs Interaction		
CYP2C8 Ki (μM)	20.60	in-vitro value	CYP2C8 MBI KI (μM)	4.00	in-vitro value
CYP2C9 Ki (μM)	11.30	in-vitro value	CYP2C8 MBI Kinact (1/h)	0.72	in-vitro value
CYP3A4/5 Ki (μM)	23.90	in-vitro value	CYP2C9 Ki (μM)	3.30	in-vitro value
CYP3A4/5 MBI KI (μM)	10.10	in-vitro value	CYP2C19Ki (μM)	8.50	in-vitro value
CYP3A4/5 MBI Kinact (1/h)	1.11	in-vitro value			

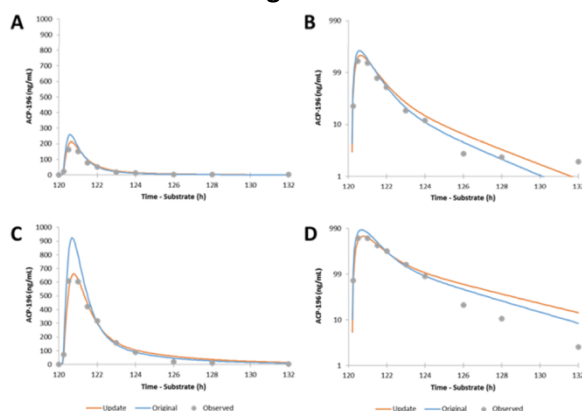
Appendix Table 2. List of applicant's itraconazole PBPK model parameters

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}

	ITZ	OH-ITZ	Reference
MW	705.6	721.6	
log P	4.5	4.5	
Compound type	Base	Base	
pKa	4.3	4.3	
fu	0.016	0.016	Ishigam <i>et al.</i> , (2001)
B:P ratio	0.58	0.58	Heykants <i>et al.</i> , (1989)
fa	0.6	n/a	Derived from van Peer <i>et al.</i> , (1989)
ka (h ⁻¹)	0.6	n/a	Derived from van Peer <i>et al.</i> , (1989)
MDCK P _{app} (x10 ⁻⁶ cm/s)	57.1	n/a	Polli <i>et al.</i> , (2001)
V _{ss} (L/kg)	2.5	1.04	Predicted – Method 1
Kp scalar	0.3	0.12	Fitted using Barone <i>et al.</i> , (1998)
CL _R (L/h)		1.39	Fitted using Barone <i>et al.</i> , (1998)
CYP3A4			
V _{max} (pmol/min/pmol P450)	0.065	0.13	Isoherranen <i>et al.</i> , (2004)
K _{m,u} (uM)	0.0039	0.027	Isoherranen <i>et al.</i> , (2004)
CYP1A2			
CL _{int,u} (ul/min/pmol P450)	1		Isoherranen <i>et al.</i> , (2004)
CYP3A4			
K _i (uM)	0.0013	0.0023	Isoherranen <i>et al.</i> , (2004)

*extracted from Applicant's
first PBPK model Table 21 [2]

Appendix Figure 1. PBPK model simulated vs observed acalabrutinib plasma concentration-time profiles following a single dose of acalabrutinib 50 mg and itraconazole 200mg bid



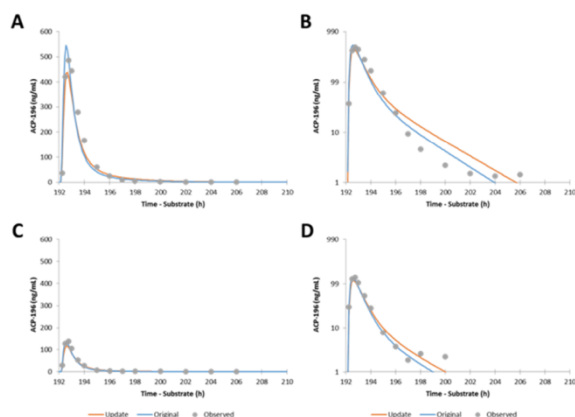
- A. acalabrutinib alone, linear scale;
- B. acalabrutinib alone, semi-log scale.
- C. acalabrutinib + itraconazole, linear scale;
- D. acalabrutinib + itraconazole, semi-log scale.

Simulated values are displayed as lines. Blue line is simulation from first acalabrutinib model [2], orange line is simulation from the updated PBPK model [3]. Observed mean values from Clinical Study ACE-HV-001 are displayed as dots.

*Extracted from Applicant's PBPK report Figure 3 [3]

Appendix Figure 2. PBPK model simulated vs observed acalabrutinib plasma concentration-time profiles following a single dose of acalabrutinib 100 mg and rifampin 600mg qd

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 210259}
{CALQUENCE, acalabrutinib}



- A. acalabrutinib alone, linear scale;
B. acalabrutinib alone, semi-log scale.
C. acalabrutinib + rifampicin, linear scale;
D. acalabrutinib + rifampicin, semi-log scale.

Simulated values are displayed as lines. Blue line is simulation from first acalabrutinib model [2], orange line is simulation from the updated PBPK model [3]. Observed mean values from Clinical Study ACE-HV--004 part 3 are displayed as dots.

**Extracted from Applicant's PBPK report Figure 4 [3]*

References

1. AstraZeneca, "Summary of Clinical Pharmacology Studies"
2. AstraZeneca, "A PBPK M&S Evaluation (Using the SIMCYP Population-Based Simulator) of the Potential Drug-Drug Interactions Between Midazolam (a CYP3A4 Substrate), Moderate Inhibitors and Inducers of CYP3A and Oral Doses of ACP-196" (AstraZeneca Study R2016001)
3. AstraZeneca, "Physiologically Based Pharmacokinetic Modeling using SIMCYP(version 14) to Evaluate Potential Drug-Drug Interactions with Acalabrutinib and its Metabolite ACP-5862" (AstraZeneca Study D8220C00003)
4. Response to FDA information request regarding PBPK (Email date 7/25/2017).
5. Response to FDA information request regarding PBPK (Email date 8/11/2017).
6. AstraZeneca, "Nonclinical Pharmacokinetics Summary"
7. AstraZeneca's proposed prescription information (USPI)

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15 Division Director (DHOT)

X

John Leighton Ph.D.
Division Director, DHOT

16 Division Director (OCP)

X

Atiqur Rahman, Ph.D.
Director, DCP V

17 Division Director (OB)

X

Rajeshwari Sridhara Ph.D.

18 Division Director (Clinical)

On June 13, 2017, Acerta Pharma submitted NDA 210259 which requested approval of acalabrutinib (Calquence) for the following indication: treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This request relied upon ACE-LY-004, which was a phase 2 single arm study of 124 patients who had relapsed after treatment or were refractory to one or more but not greater than 5 lines of prior therapy, and who had failed to achieve at least a partial response to the most recent treatment. Treatment with acalabrutinib at 100 mg bid was continued until unacceptable toxicity or progression.

Efficacy Results: The overall response rate (ORR) based on investigator assessment, which was the primary endpoint, was 80.6% (95%CI: 72.6%, 87.2%). The complete response (CR) rate by investigator assessment was 39.5% (95% CI: 30.9%, 48.7%). There was excellent concordance (91%) between the ORR as determined by investigator assessment and independent review committee. The percentage of patients who achieved a CR or PR and who were still in remission at 12 months, was 72.1% (95% CI: 61.6%, 80.2%) by investigator assessment. The median duration of remission has not been reached with 15 months of follow-up.

Safety Results: In Study ACE-LY-004, there were no deaths attributed to acalabrutinib. The toxicities observed, which included serious adverse events (39%), adverse events leading to discontinuation (6.5%), and adverse events leading to dose reductions (1.6%) were acceptable and manageable for the intended patient population.

Post Marketing Requirements (PMR): PMR#1: Submit the final report of Study ACE-LY-308, a randomized, double-blind, placebo-controlled, clinical trial of acalabrutinib in combination with standard immunochemotherapy versus immunochemotherapy alone in patients with MCL. PMR#2: Conduct a study to characterize the long-term safety of acalabrutinib monotherapy, with a minimum of 24 months of follow-up from study ACE-LY-004 in patients with MCL. PMR#3: Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of acalabrutinib in patients with severe hepatic impairment.

Benefit Risk Discussion: The response profile (ORR of 80.6% and CR of 39.5%) based on investigator assessment was favorable when compared to the toxicities of therapy. The clinical benefit of acalabrutinib in MCL will need to be confirmed in a phase 3 trial (see PMR #1 above).

Final Regulatory Recommendation of Supervisory Associate Division Director, DHP: This reviewer agrees with the review team's conclusion that the benefit/risk profile is favorable and with the recommendation for approval by the accelerated approval pathway.

X

Albert Deisseroth, MD, PhD

19 Office Director (or designated signatory authority)

This application was reviewed under the auspices of the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. The risk-benefit profile was also assessed by Drs. Deisseroth, Wroblewski and Merino who recommend approval. I also recommend approval of this application. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

My signature below also represents the approval decision of this application under CDER.

X

Richard Pazdur, MD

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/s/

ASHLEY S LUCCI VAUGHN
10/27/2017

MARGRET E MERINO
10/27/2017

BRENDA J GEHRKE
10/27/2017

CHRISTOPHER M SHETH
10/27/2017

JOHN K LEIGHTON
10/27/2017

WENCHI HSU
10/27/2017

GENE M WILLIAMS
10/27/2017

YUAN XU
10/27/2017

JIANG LIU
10/27/2017

YUCHING N YANG
10/27/2017

YANING WANG
10/27/2017

NAM ATIQUUR RAHMAN
10/27/2017

I concur.

LEI NIE on behalf of JINGJING YE
10/27/2017

LEI NIE
10/27/2017

RAJESHWARI SRIDHARA
10/27/2017

TANYA M WROBLEWSKI
10/27/2017

ALBERT B DEISSEROTH
10/27/2017

RICHARD PAZDUR
10/27/2017

Statistical Review and Evaluation

NDA/BLA: NDA 210259

Drug Name: Acalabrutinib

Indication: for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy

Sponsor: Acerta Pharma B.V.

Reviewer: Jingjing Ye

Date of Receipt: June 13, 2017

On June 13, 2017, Acerta submitted the results of their pivotal study ACE-LY-004 in Acalabrutinib to support approval for treatment of patients with mantle cell lymphoma who have received at least one prior therapy. This document briefly reviews the submitted material and conclusions made for the submission. More detailed information can be found in the unireview.

The pivotal trial ACE-LY-004 was a phase II, open-label, single-arm, multi-center study of the acalabrutinib (ACP-196) for the treatment of subjects with histologically documented MCL, who had relapsed after ≥ 1 (but not > 5) prior treatment regimens. Approximately 124 patients were enrolled in the trial and took 100 mg of acalabrutinib twice per day in repeated 28-day cycles until disease progression or an unacceptable treatment-related toxicity occurred.

Analysis datasets, SDTM tabulations, and software codes are located at:

<\\CDSESUB1\evsprod\NDA210259\0000\m5\datasets>

The primary efficacy endpoint was the ORR (objective response rate), defined as the proportion of subjects achieving either a partial response (PR) or complete response (CR) per the Lugano classification for non-Hodgkin lymphoma (NHL). The study ACE-LY-004 showed that the ORR for investigator-assessed was 80.6% with 95% CI [72.6%, 87.2%]. The ORR for IRC assessed was 79.8% with 95% CI [71.7%, 86.5%]. Secondary endpoints of duration of response (DoR), progression-free survival (PFS) and overall survival (OS) were also evaluated. The results showed that the median of DoR, PFS and OS had not been reached yet. The range of DoR for investigator assessed was 0.59 to 20.27+; range of PFS was 0.03+ to 22.08+ and range of OS was 0.26 to 22.28+.

The pivotal study ACE-LY-004 has achieved ORR of about 80% for both investigator-assessed and IRC-assessed responses. The analysis results of secondary endpoints showed that the median DoR and median PFS, OS had not been reached yet. Overall, the study showed efficacy of acalabrutinib in treatment of patients with histologically documented MCL, who had relapsed after ≥ 1 (but not > 5) prior treatment regimens.

APPEARS THIS WAY ON ORIGINAL

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/s/

JINGJING YE
10/02/2017

LEI NIE
10/04/2017

THOMAS E GWISE
10/04/2017