PROTOCOL

TITLE:	A Phase 1b/2 Proof-of-Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects with Hematologic Malignancies
PROTOCOL NUMBER:	ACE-LY-005
STUDY DRUG:	CALQUENCE® (acalabrutinib / ACP-196) and KEYTRUDA® (pembrolizumab)
IND NUMBER:	118717
SPONSOR MEDICAL MONITOR:	PPD PPD Phone: PPD Email: PPD
SPONSOR:	Acerta Pharma B.V. PPD 5349 AB Oss The Netherlands
PROTOCOL DATE:	Version 0.0 – 25 October 2014
AMENDMENT 1:	Version 1.0 – 14 August 2015
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AMENDMENT 4:	Version 4.0 – 16 May 2017
AMENDMENT 5:	Version 5.0 – 30 May 2018
AMENDMENT 6:	Version 6.0 – 14 March 2019
AMENDMENT 7:	Version 7.0 – 18 February 2020

Confidentiality Statement

PROTOCOL APPROVAL

Version 7.0

I have carefully read Protocol ACE-LY-005 entitled "A Phase 1b/2 Proof-of-Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects with Hematologic Malignancies" (Amendment 7.0, dated 18 February 2020). I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the sponsor, Acerta Pharma, and the IRB/ IEC must approve any changes to the protocol in writing before implementation.

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

Principal Investigator Signature

Print Name of Principal Investigator

Date (DD Month YYYY)

SUMMARY OF AMENDMENT 7

This protocol has been amended to align with new safety language in the most current acalabrutinib Investigator Brochure, and to update the medical monitor. Clarifying edits and typographical changes have been made throughout the protocol. The following substantive changes were made as part of this amendment:

Description of Change	Sections
Sponsor medical monitor was changed	• TITLE page
Current protocol number/version was updated to v7.0	• Throughout
CALQUENCE® marketing approval in the United States and other markets has been expanded to include treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma.	• Section 1.2
Updated/added language regarding continued access to study treatment and details for transitioning subjects from Study ACE-LY-005 to a rollover study	• Section 3.6
Guidelines for use of CYP-inhibiting/inducing drugs updated to reflect new language added in Section 3.10	• Section 3.9.2
Details regarding concomitant use of strong CYP3A inducers/inhibitors were consolidated within Section 3.10.7 (Guidelines for use of CYP-inhibiting/inducing drugs)	• Section 3.9.4
Language was updated and/or details were added to the following Warnings and Precautions for acalabrutinib: • Hemorrhage • Infections • Cytopenias • Second primary malignancies • Atrial fibrillation	• Section 3.10.1.2
Language was updated and/or details were added to the following Risks Associated with acalabrutinib: • Progressive multifocal leukoencephalopathy • Hepatitis B reactivation • Drug-drug interactions	 • Section 3.10.3 • Section 3.10.5 • Section 3.10.7
Additional details were provided in the Guidance and Definitions related to highly effective methods of contraception.	• Section 3.10.9.2
Hepatitis testing language was updated to match Section 3.10.5	• Section 4.1.14
Language regarding the AE reporting period was updated to align with Acerta Pharma standard protocol language	• Section 4.3

Description of Change	Sections
Language regarding the Adverse Event Reporting Period was updated to align with Acerta Pharma standard protocol language.	• Section 6.2.1
Second Primary Malignancies section added with reporting guidelines for AEs for malignant tumors; subsequent sections were renumbered	• Section 6.2.3
Appendix 7"Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law" was updated to align with Acerta Pharma standard protocol language.	• Appendix 7

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ABBREVIATIONS

Term	Definition
5PS	5-point scale
ABC	activated B-cell
ACP-196	acalabrutinib
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
anti-HBc	hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AST	aspartate aminotransferase
ASXL1	Additional Sex Combs-Like 1
AUC	area under the curve
$AUC_{0\text{-last}}$	area under the concentration-time curve, from time 0 to last quantifiable concentration
$AUC_{0\text{-inf}}$	area under the concentration-time curve, from time 0 to infinity
$AUC_{0\text{-}24}$	area under the concentration-time curve, from time 0 to 24-hour timepoint
$AUC_{0\text{-}12}$	area under the concentration-time curve, from time 0 to 12-hour timepoint
BID	twice per day (dosing)
BTK	Bruton tyrosine kinase
BUN	blood urea nitrogen
CAL-R	calreticulin
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CI	confidence interval, or clinical improvement (response)
CL/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CR	complete remission (response)
CRF	case report form
CRi	CR with incomplete blood count recovery
CSSF	Clinical Supplies Shipping Receipt Form

Term	Definition
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
EBMT	European Group for Blood and Marrow Transplant
EC_{50}	concentration of a drug that gives half-maximal response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EFD	embryofetal development
EGFR	epidermal growth factor receptor
EMH	extramedullary hematopoiesis
FDA	Food and Drug Administration
FDG	[^{18}F]fluorodeoxyglucose
FL	follicular lymphoma
FLC	free light chains
FSH	follicle stimulating hormone
GCB	germinal center B-cell
GCP	Good Clinical Practices
GI	gastrointestinal
GLP	Good Laboratory Practices
GVHD	graft-versus-host disease
Hb	hemoglobin
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HL	Hy's law
HSCT	hematopoietic stem cell transplantation
IB	Investigator Brochure
ICF	informed consent form
IC_{50}	half-maximal inhibitory concentration

Term	Definition
IEC	Independent Ethics Committee
Ig	immunoglobulin
IHC	immunohistochemistry
IMWG	International Myeloma Working Group
IMP	investigational medicinal product
iNHL	indolent non-Hodgkin lymphoma
irAE	immune-related adverse event
ITK	interleukin-2-inducible kinase
IUD	intrauterine device
IV	intravenous
IVIG	intravenous immunoglobulins
IRB	Institutional Review Board
JAK2	Janus kinase 2
LCM	left costal margin
LDH	lactate dehydrogenase
LDi	longest transverse diameter of a lesion
LFT	liver function test
mAb	monoclonal antibody
MCL	mantle cell lymphoma
CCI	CCI
MM	multiple myeloma
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
MPD	myeloproliferative disease
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MR	minor response
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
nCR	near complete response
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
NOAEL	no observable adverse effect level
non-GCB	non-germinal center B-cell
nPR	nodular remission
NSAIDS	nonsteroidal anti-inflammatory drugs

Term	Definition
ORR	overall response rate
CCI	CCI
PCR	polymerase chain reaction
PD	pharmacodynamics or progressive disease
PD-1	programmed death-1 (receptor)
PD-L1	programmed death ligand-1
PET	positron-emission topography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PO	per os (oral)
PHL	potential Hy's law
PPD	cross product of the LDi and perpendicular diameter
PR	partial remission (response)
PRL	partial remission (response) and lymphocytosis
Q3W	every 3 weeks
QD	once per day (dosing)
QM	every month
QTc	corrected QT interval
R/R	relapsed/refractory
RS	Richter's syndrome
SAE	serious adverse event
SAP	statistical analysis plan
sCR	stringent complete remission (response)
SCT	stem cell transplant
SFLC	serum-free light chains
SDi	shortest axis perpendicular to the LDi
SD	stable disease or standard deviation
SIFE	serum immunofixation electrophoresis
SLL	small lymphocytic lymphoma
SPD	sum of the product of the diameters
SPEP	serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction (report)
$t_{½}$	terminal elimination half-life

Term	Definition
T3	triiodothyronine
T4	free thyroxine
T1DM	Type 1 diabetes mellitus
T_{max}	time to maximum drug concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal
UIFE	urine immunofixation electrophoresis
UNL	upper normal limit
UPEP	urine serum protein electrophoresis
VGPR	very good partial response
V_z/F	volume of distribution values
WBC	white blood cell (count)
WHO	World Health Organization
WM	Waldenström macroglobulinemia
WOCBP	women of childbearing potential

STUDY SYNOPSIS

Protocol Number:	ACE-LY-005
Study Drugs:	CALQUENCE®/acalabrutinib (also known as ACP-196) KEYTRUDA® (pembrolizumab)
Protocol Title:	A Phase 1b/2 Proof-of-Concept Study of the Combination of ACP-196 and Pembrolizumab in Subjects with Hematologic Malignancies
Phase:	Phase 1b/2
Comparator:	None
Background and Rationale for Study	Decades of research across various oncologic diseases support the fact that multidrug regimens produce higher and more durable complete response (CR) rates than single-agent chemotherapy. However, these benefits are often outweighed with the increased toxicity associated with multidrug regimens. The high risk:benefit ratio of multidrug regimens means these regimens are less likely to be used in elderly patients or patients with comorbid conditions. The advent of highly selective, targeted agents to treat cancer, such as Bruton tyrosine kinase (BTK) inhibitors, has changed the risk:benefit paradigm traditionally associated with chemotherapy agents. However, the proportion of patients with CR when treated with single-agent BTK inhibitors is low compared with traditional polychemotherapy or chemoimmunotherapy. Also, in more aggressive histologies, the median duration of response can be brief (<12 months). The question remains as to whether "targeted combination" therapy can produce more durable responses and potentially more CRs than single agents without an associated increase in toxicity. Acerta Pharma, B.V. is developing acalabrutinib as a 2nd generation, orally administered, small-molecule inhibitor of BTK. Preclinical data indicate that acalabrutinib may offer greater potency, improved selectivity, better pharmaceutical properties, and less potential for drug-drug interactions than the 1st generation compound, ibrutinib (IMBRUVICA®). Acalabrutinib has shown clinical activity in an ongoing Phase 1/2 study in subjects with chronic lymphocytic leukemia (CLL) (NCT02029443). Improved understanding of the molecular mechanisms governing the host response to tumors has led to the identification of checkpoint signaling pathways involved in limiting the anticancer immune response. A critical checkpoint pathway responsible for mediating tumor-induced immune suppression is the programmed death-1

	(PD-1) pathway (McDermott and Atkins 2013). This proof-of-concept study will assess the clinical potential of combined BTK inhibition and checkpoint blockade by evaluating the safety, pharmacodynamics (PD), and efficacy of acalabrutinib and pembrolizumab in hematologic malignancies. To determine whether there is potential synergy between BTK inhibition and PD-1 blockade, Acerta has conducted a nonclinical study of acalabrutinib in combination with an anti-PD ligand 1 (anti-PD-L1) antibody in an orthotopic colon cancer murine model. Treatment with anti-PD-L1 as a single agent reduced tumor growth, but tumor regression was not observed. However, combined anti-PD-L1 and acalabrutinib treatment showed a further reduction in tumor growth and 6 of 9 animals displayed tumor regression (see Figure 1). These results suggest the combination therapy of BTK inhibition, and PD-1 blockade leads to greater benefit compared with PD-1 blockade alone.
Study Design:	This is a Phase 1b/2, open-label, nonrandomized study that will be conducted in 2 stages. In the first stage, Part 1 of the study will determine the safety and preliminary efficacy of acalabrutinib and pembrolizumab in a limited group of B-cell malignancies. In the second stage, Part 2 allows for possible expansion cohorts into a wider range of B-cell malignancies, and Part 3 (enrolled concurrently with Part 2) will evaluate the combination in subjects with myelofibrosis (MF). **Part 1** Six subjects will be enrolled to receive acalabrutinib in combination with pembrolizumab. If the combination is safe with ≤1 dose-limiting toxicity (DLT) (6-week observation period) in the first 6 subjects, the cohort will be expanded to up to 24 subjects to obtain additional safety information and to assess the efficacy of the combination. Part 1 of the study will include adult subjects with the following disease types: • Non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma (DLBCL) • Follicular lymphoma (FL) • CLL/small lymphocytic lymphoma (SLL) **Part 2** Part 2 will consist of expansion groups of up to 30 subjects per histology provided the safety and efficacy results from Part 1 of the study indicate that further evaluation of the combination is warranted.

	The possible expansion groups for Part 2 may include adult subjects with the following disease types:
	• Non-GCB DLBCL
	• Germinal center B-cell (GCB) DLBCL
	• Richter's syndrome (RS)
	• Mantle cell lymphoma (MCL)
	• Indolent non-Hodgkin lymphoma (iNHL)
	  ○ FL
	  ○ Waldenström macroglobulinemia (WM)
	  ○ CLL/SLL
	• Multiple myeloma (MM)
	• Other B-cell malignancy (including but not limited to: Hodgkin's lymphoma, Burkitt lymphoma, marginal zone lymphomas, mediastinal large B-cell lymphoma, and hairy cell leukemia)
	Under Amendment 3 of this protocol, subjects with MCL or iNHL (including FL, WM, and CLL/SLL) are no longer enrolled.
	Under Amendment 4 of this protocol, subjects with RS are no longer enrolled.
	Part 3
	Part 3 includes up to 30 subjects with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF with thrombocytopenia or anemia. Part 3 will run in parallel with Part 2. Subjects with MF will receive a run-in of 6 weeks of acalabrutinib alone. Subjects who are demonstrating a clinically meaningful response, in the opinion of the investigator, may continue on acalabrutinib monotherapy; those who are not will receive combination therapy with acalabrutinib and pembrolizumab.
	In Part 3, safety and response data will be reviewed after the initial 12 subjects have completed 24 weeks of treatment (i.e., the Week 25 visit) or have discontinued treatment before Week 25. The first 12 subjects will be evaluated regardless of the length of treatment with acalabrutinib alone or in combination with pembrolizumab. If <2 subjects who received acalabrutinib monotherapy or the combination with pembrolizumab have achieved a response of "clinical improvement" or better (see Table 9), the MF group will not be expanded. The decision to expand the study is multifactorial and will take into consideration the nature and quality of response, safety, and evolving competitive landscape. If the safety and response data indicate that further evaluation is warranted, up to 18 additional

	subjects with MF (for a total of up to 30 subjects) will be treated on the same adaptive regimen as was given to the first 12 subjects. Under Amendment 3 of this protocol, Part 3 is closed to enrollment. Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Treatment with acalabrutinib can continue until the end of trial, defined as 48 months after the last subject is enrolled. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may be eligible to enroll in a separate rollover study. Treatment with pembrolizumab may continue for 24 months (103 weeks) from first dose of pembrolizumab provided subjects are tolerating the drug and not progressing. In addition, pembrolizumab treatment can end for subjects with confirmed CR (or stringent CR [sCR] for MM) if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR/sCR. Subjects who have **confirmed** progressive disease will come off treatment. Note: If there is uncertainty regarding whether there is cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) pending confirmation of progression. In particular, transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred. All subjects will have bone marrow biopsy, hematology, chemistry, thyroid, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry, hematology, and thyroid function tests once weekly for the first 8 weeks, followed by a Week 10 visit and then every 3 weeks thereafter (every 6 weeks thereafter for thyroid function tests) through Week 103. For subjects who discontinue pembrolizumab at Week 103, the Week 103 visit will be followed by Week 106 and Week 109 visits, at which time the investigator will determine eligibility to continue single-agent acalabrutinib treatment. Subjects remaining on study treatment after Week 103 will have a Week 103 and Week 115 visit, and then visits for safety and tumor response assessments every 24 weeks starting at Week 127 through 3 years (for subjects with CLL/SLL histologies) or 5 years (for subjects with non-CLL/SLL histologies [i.e., DLBCL/Hodgkin lymphoma]), and then every 52 weeks thereafter (all histologies). Subjects who permanently discontinue pembrolizumab at any time during study participation must have a minimum of 2 consecutive

	study visits, 3 weeks apart, after the last dose of pembrolizumab for safety evaluation. The study visits will be scheduled as follows:
	• For all subjects except MM and CLL subjects
	  ○ If a subject discontinued pembrolizumab prior to completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 3 weeks until Week 37. After Week 37, study visits will be held every 12 weeks.
	  ○ If a subject discontinued pembrolizumab after completing 37 weeks on study and is on acalabrutinib alone, 2 consecutive study visits will be held 3 weeks apart (e.g., Week 40 and 43), after which study visits will be held every 12 weeks.
	  ○ It is acknowledged that the discontinuation timepoint of pembrolizumab (if applicable) is unique per subject. To synchronize the every 12-week study visit schedule with the radiologic tumor assessment schedule, the first 2 study visits after pembrolizumab discontinuation should be 3 and 6 weeks after pembrolizumab discontinuation and then scheduled to align with the nearest radiological timepoint.
	• For CLL subjects
	  ○ If a subject discontinued pembrolizumab prior to completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 3 weeks until Week 37. After Week 37, study visits will be held every 12 weeks.
	  ○ If a subject discontinued pembrolizumab after completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 12 weeks.
	  ○ It is acknowledged that the discontinuation timepoint of pembrolizumab (if applicable) is unique per subject. To synchronize the every 12-week study visit schedule with the radiologic tumor assessment schedule, the first study visit should be scheduled to align with the nearest radiological timepoint.
	In addition, subjects who permanently discontinue pembrolizumab for any reason (e.g., pembrolizumab toxicity, adverse event (AE), or completing the 103-week course of pembrolizumab) and remain on acalabrutinib alone at any time during study participation must have a thyroid test done every 6 weeks for 6 months after pembrolizumab discontinuation. Thyroid testing may be discontinued at 6 months if 1) testing that was performed at 6 months was normal and 2) testing that was performed 6 weeks prior to the 6-month timepoint was normal (for a total of 2 consecutive normal test results). Otherwise, thyroid testing will continue as scheduled until 2 consecutive normal test results.

	Refer to Appendix 5 and Appendix 6 for comprehensive lists of study assessments and their timing. A study schema is provided in Figure 4.
Definition of Dose-limiting Toxicity:	For Part 1, a DLT will be defined as the occurrence of any of the following study drug-related AEs (note: AEs clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs): 1. Any Grade ≥3 non-hematologic toxicity (except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy). 2. Any of the following hematologic toxicities: a. Grade 4 neutropenia lasting >7 days. b. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion. c. Grade ≥3 febrile neutropenia (temperature ≥38.5°C). d. Grade 4 anemia, unexplained by underlying disease. 3. Dosing delay due to toxicity for >28 consecutive days.
Study Objectives:	**Primary Objective:** To characterize the safety profile of acalabrutinib and pembrolizumab in subjects with hematologic malignancies **Secondary Objective:** To evaluate the activity of acalabrutinib and pembrolizumab as measured by overall response rate (ORR), duration of response, progression-free survival (PFS), overall survival, and time-to-next treatment **Exploratory Objectives:** CCI [redacted]

Safety Parameters:	Type, frequency, severity, timing of onset, duration, and relationship to study drug of any treatment-emergent AEs or abnormalities of laboratory tests; serious AEs (SAEs); events of clinical interest (ECIs), or AEs leading to discontinuation of study treatment.
Pharmacodynamic and Biomarker Parameters:	CCI [redacted]
Efficacy Parameters:	• ORR • Duration of response • Progression-free survival • Overall survival • Time-to-next treatment In addition, for Part 3 subjects with MF, an overall response will be defined as clinical improvement or better (clinical improvement, partial response [PR], or CR) as shown in Table 9. Under Amendment 3 of this protocol, Part 3 is closed to enrollment.
Sample Size:	Part 1: Up to 24 subjects Part 2: Up to 270 subjects Part 3: Up to 30 subjects Note: Under Amendment 3 of this protocol, Part 3 is closed to enrollment.

Inclusion Criteria:	**Part 1:**
	• Diagnosis of non-GCB DLBCL or iNHL as documented by medical records and with histology based on criteria established by the World Health Organization (WHO).
	  ○ If a subject has DLBCL, it is characterized as de novo non-GCB DLBCL (Hans et al 2004; Choi et al 2009).
	  ○ If the subject has iNHL, the histology shows one of the following subtypes:
	  ▪ FL Grade 1, 2, or 3a
	  ▪ CLL/SLL
	• Prior treatment for lymphoid malignancy (applies to Part 1 and Part 2):
	  ○ If the subject has DLBCL, there is no curative option with conventional therapy and the prior treatment included

	≥1 prior combination chemoimmunotherapy regimen (e.g., anthracycline based therapy with rituximab). ○ If the subject has MCL or iNHL, the prior treatment comprised any of the following: ▪ ≥1 regimen containing an anti-CD20 antibody administered for ≥2 doses, and/or ▪ ≥1 regimen containing ≥1 cytotoxic agent (e.g., bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin) administered for ≥2 cycles, and/or ▪ ≥1 regimen containing yttrium^{90}-ibritumomab tiuxetan (ZEVALIN®) or iodine^{131}-tositumomab (BEXXAR®). • Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of a ≥2.0 cm lesion, as measured in the longest dimension by computed tomography [CT] scan). Note: Not applicable to subjects with WM and MM. • Absolute neutrophil count (ANC) ≥1.5×10^9/L and platelet count ≥100×10^9/L unless due to disease involvement in the bone marrow (Part 1 only). **Part 2:** • ANC ≥0.5×10^9/L and platelet count ≥50×10^9/L unless due to disease involvement in the bone marrow (Part 2 only). **Additional Part 2 disease entry criteria including those listed in Part 1 above:** • DLBCL (GCB): Confirmed diagnosis of DLBCL with disease characterized as GCB subtype by immunohistochemistry (Hans et al 2004; Choi et al 2009) and meeting the rest of the criteria as defined above, including characterization as de novo DLBCL. • If the subject has MCL, it is characterized by documentation of monoclonal B-cell that have a chromosome translocation t(11;14)(q13;q32) and/or overexpression of cyclin D1 • Richter's syndrome: Confirmed diagnosis of and biopsy-proven DLBCL due to Richter transformation and meeting the rest of the criteria as defined above. • WM: Confirmed diagnosis of WM, which has relapsed after, or been refractory to ≥1 prior therapy for WM, and is progressing at the time of study entry and meeting the rest of the criteria as defined above. Must be able to provide archival or newly obtained bone marrow aspirate/biopsy material for biomarker analysis.

	• MM: Confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥3 prior therapies for MM, and is progressing at the time of study entry and meeting the rest of the criteria as defined above. Must be able to provide archival or newly obtained bone marrow aspirate/biopsy material for biomarker analysis. • Other B-cell malignancy (including but not limited to: Hodgkin's lymphoma, Burkitt lymphoma, marginal zone lymphomas, mediastinal large B-cell lymphoma, and hairy cell leukemia): Confirmed diagnosis of previously treated B-cell malignancy and meeting the rest of the criteria as defined above. **Part 3 (Under Amendment 3 of this protocol, Part 3 is closed to enrollment.):** • Diagnosis of primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF. • Intermediate-1, intermediate-2, or high-risk MF per Passamonti 2010 criteria and must have failed therapy with ruxolitinib. • Thrombocytopenia (platelet count ≤100×10^9/L at any time after signing informed consent) OR anemia (hemoglobin ≤8.0 g/dL). Subjects who are platelet or red blood cell transfusion-dependent are eligible; platelet counts must be ≥30×10^9/L during the screening period. • Palpable splenomegaly ≥5 cm on physical examination. • Total Symptom Score ≥13 on the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF TSS), not including the inactivity question. • No splenic irradiation within 6 months before first study dose. • No myelofibrosis therapy, including any erythropoietic or thrombopoietic agents, within 2 weeks before first study dose. • ANC ≥0.5×10^9/L. • Bone marrow blasts <10%. **All Parts:** • Men and women ≥18 years of age on day of signing informed consent. • Documented active disease. • Eastern Cooperative Oncology Group (ECOG) performance status of ≤1. • Completion of all therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer ≥4 weeks before the start of study therapy (Parts 1 and 2) and recovered (i.e., Grade ≤1 or baseline) from

	AEs associated with prior cancer therapy (all subjects). Note: Subjects with Grade ≤2 neuropathy or Grade ≤2 alopecia are an exception to the latter criterion and may qualify for the study. • Women who are sexually active and can bear children must agree to use highly effective methods of contraception during the study and for 2 days after the last dose of acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer. Note: Highly effective methods of contraception are defined in Section 3.10.9. • Men who are sexually active and can beget children must agree to use highly effective methods of contraception during the study and for 120 days after the last dose of pembrolizumab. Highly effective methods of contraception are defined in Section 3.10.9. • Men must agree to refrain from sperm donation during the study and for 120 days after the last dose of pembrolizumab. • Able to provide tissue, if available, from either an archived or newly obtained tumor sample (most recent biopsy) for biomarker and correlative analysis as appropriate for a given histology. • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).
Exclusion Criteria:	**All Parts:** • Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years. • A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk. • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) >480 msec at screening. • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.

	• Central nervous system (CNS) involvement by lymphoma/leukemia • Any therapeutic antibody within 4 weeks of first dose of study drug. • Any prior irreversible BTK inhibitor therapy. Note: Prior treatment with reversible, noncovalent BTK inhibitors is not excluded on this protocol. • Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD ligand 2 (anti-PD-L2), anti-CD137, or anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab, tremelimumab, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). • Receiving ongoing immunosuppressive therapy, including systemic or enteric corticosteroids except for minimally systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, chronic obstructive pulmonary disease, or allergic rhinitis) within 7 days before the first dose of pembrolizumab. • Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. • History of interstitial lung disease or non-infectious pneumonitis that required steroids or current pneumonitis. • History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins. • History of bleeding diathesis (e.g., hemophilia or von Willebrand disease). • Active bleeding that requires hospitalization during the screening period. • Prior allogeneic hematopoietic stem cell transplantation within the last 5 years. • Requires treatment with a strong cytochrome P450 3A (CYP3A) inhibitor/inducer. • Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug. • Requires treatment with a proton-pump inhibitor (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). • Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.

	• Major surgery within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
	• Has received a live vaccine within 30 days of planned start of study therapy.
	• History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
	• Total bilirubin >1.5× institutional upper limit of normal (ULN); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3.0× ULN.
	• Estimated creatinine clearance of <30 mL/min, calculated using the formula of Cockcroft and Gault [(140−Age) • Mass (kg)/(72 • Creatinine mg/dL); multiply by 0.85 if female].
	• Breastfeeding or pregnant or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
	• Is currently participating in a clinical trial and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
	• Immediate family members of the sponsor personnel or site staff directly involved with the conduct of this protocol are excluded from participating on this study.
	• Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
	• Active or known tuberculosis infection. Note: Tuberculosis testing is not required for this protocol.
	• Serologic status reflecting active hepatitis B or C infection:
	  ○ Subjects who are hepatitis B core antibody (anti-HBc) positive and who are surface antigen negative will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen (HBsAg) positive or hepatitis B PCR positive will be excluded.
	  ○ Subjects who are hepatitis C antibody-positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.

Dose Regimen/Route of Administration:	Acalabrutinib is provided as hard gelatin capsules for oral administration. KEYTRUDA® (pembrolizumab) for injection is provided as a 100 mg/4 mL (25 mg/mL) solution in a single-use vial or as a

	lyophilized powder for reconstitution 50 mg/vial). It is administered as an intravenous infusion over 30 minutes. **<u>Regimen (Combination Therapy):</u>** • Acalabrutinib 100 mg twice a day (BID) continuous oral dosing; and • Pembrolizumab 200 mg by intravenous (IV) infusion every 3 weeks (Q3W) Note: In Part 3, subjects with MF will receive a run-in of 6 weeks of acalabrutinib alone (100 mg BID). Subjects who are demonstrating a clinically meaningful response, in the opinion of the investigator, may continue on acalabrutinib monotherapy; those who are not will receive combination therapy with acalabrutinib (100 mg BID) and pembrolizumab (200 mg Q3W) as described above. Under Amendment 3 of this protocol, Part 3 is closed to enrollment.
Concomitant Medications:	The concomitant use of strong inhibitors/inducers of CYP3A with acalabrutinib should be avoided when possible. The effect of agents that reduce gastric acidity (e.g., antacids or proton-pump inhibitors,) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this completed study indicate subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib. Use of omeprazole, lansoprazole or esomeprazole or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib. Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.
Statistics:	Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. Depending on Part 1 and the expansion cohorts opened in Parts 2 and 3, a total of 6 to 324 evaluable subjects will be enrolled in this study. Under Amendment 4 of this protocol, the planned total enrollment is approximately 160 evaluable subjects. In Part 1 (DLT review), enrollment of 6 subjects for DLT review is consistent with sample sizes used in oncology studies for

	determination of maximum tolerated dose (MTD). The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in <33.3% of subjects). Provided ≤1 DLT occurs during the DLT review, then expansion will occur in Part 1 to include up to 24 subjects in a select group of histologies (as described in Section 3.0). The safety and preliminary efficacy results from Part 1 will be used to determine opening Part 2 and Part 3 of the protocol. In Part 2, expansion groups of up to 30 subjects per disease type will be enrolled. In Part 3, safety and response data will be reviewed after the initial 12 subjects have completed 24 weeks of treatment (i.e., the Week 25 visit) or have discontinued treatment before Week 25. The first 12 subjects will be evaluated regardless of the length of treatment with acalabrutinib alone or in combination with pembrolizumab. If <2 subjects who received acalabrutinib monotherapy or the combination with pembrolizumab have achieved a response of "clinical improvement" or better, the MF group will not be expanded. The decision to expand the study is multifactorial and needs to take into consideration the nature and quality of response, safety, and evolving competitive landscape. If the safety and response data indicate that further evaluation is warranted, up to 18 additional subjects with MF (for a total of up to 30 subjects) will be treated on the same adaptive regimen as was given to the first 12 subjects. In Part 2 (expansion groups), enrollment of 30 subjects per group offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in the selected tumor types. An ORR of ≥20% is considered the minimum value of potential interest in each of the selected indications in Part 2. If ≤2 subjects in a group experience an objective response, the probability is >0.90 that an ORR of ≥20% will be excluded for that cancer. If 2 subjects in a group experience an objective response, the upper bound of a 1-sided exact binomial 90% CI is 16.8%. In Part 3 (if MF group is expanded), enrollment of 30 subjects offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in MF. An overall response rate (clinical improvement, PR, or CR) of ≥25% within the sample size of 30 subjects with MF is considered the minimum value of potential interest in this highly unmet medical need population of MF patients with thrombocytopenia or anemia. To reject the null hypothesis of response rate ≤5% in favor of an alternative hypothesis that the response rate is ≥25%, 30 subjects will preserve approximately 90% power to detect the difference at a 0.05 level of significance by 1-sided exact test for single proportion. Under Amendment 3 of this protocol, Part 3 is closed to enrollment.

1.0 BACKGROUND INFORMATION

1.1 A CASE FOR COMBINATION BTK AND CHECKPOINT BLOCKADE FOR TREATMENT OF HEMATOLOGIC MALIGNANCIES

Through decades of clinical experience, the use of multidrug regimens has been shown to produce higher CR rates and more durable responses, resulting in improved survival in most oncology indications. However, these benefits are often outweighed with the increased toxicity associated with multidrug regimens. This high risk-benefit ratio limits the use of many effective multidrug regimens in elderly patients or patients with comorbid conditions.

The advent of highly selective, targeted agents such as BTK inhibitors has changed the risk-benefit paradigm traditionally associated with cytotoxic chemotherapy regimens. For example, ibrutinib, a first-generation oral, small-molecule BTK inhibitor, has been approved for the treatment for CLL and MCL (IMBRUVICA Package Insert). In addition, ibrutinib has shown clinical efficacy in other NHL histologies, including FL (Advani 2013), DLBCL (De Vos 2013), and in WM (Treon 2013). Preliminary data suggests that patients with MM with high BTK activity, as evidenced by phosphorylated BTK, may be particularly responsive to BTK inhibitor therapy (Liu 2014). In nonclinical studies, BTK inhibition significantly reduced MM cell growth and tumor-induced osteolysis in a murine model (Tai 2012). Despite these significant advances, the investigation of additional treatment regimens is essential to improve outcomes in hematologic malignances. A low proportion of patients achieve CR when treated with single-agent BTK inhibitors compared with conventional chemotherapy or chemoimmunotherapy regimens. Moreover, the median duration of response can be brief (<12 months) in aggressive histologies.

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of acalabrutinib, an orally administered, new chemical entity that covalently inhibits BTK and shows encouraging activity and acceptable safety in nonclinical studies. Within the class of BTK inhibitors, acalabrutinib is a more selective inhibitor of BTK than ibrutinib. Key nonclinical differentiators of acalabrutinib versus ibrutinib are:

- Acalabrutinib has been evaluated against ibrutinib in epidermal growth factor receptor (EGFR) expressing cell lines. Ibrutinib is a potent covalent inhibitor of EGFR (EC_{50}=5.3 nM). Acalabrutinib did not inhibit EGFR, even at the highest concentration tested (10 µM).

- Acalabrutinib and ibrutinib have been evaluated in natural killer (NK) cell functional assays. While ibrutinib inhibits NK cell functions including antibody-dependent cellular cytotoxicity (ADCC), lytic granule release and cytokine production (Kohrt 2014), the in vitro functional activity of acalabrutinib-treated NK cells was preserved.
- Acalabrutinib has been evaluated against ibrutinib in an in vivo thrombus formation model. Platelets from CLL patients treated with acalabrutinib had similar thrombus formation dynamics as platelets from healthy volunteers, while platelets from ibrutinib-treated CLL patients had impaired thrombus formation.

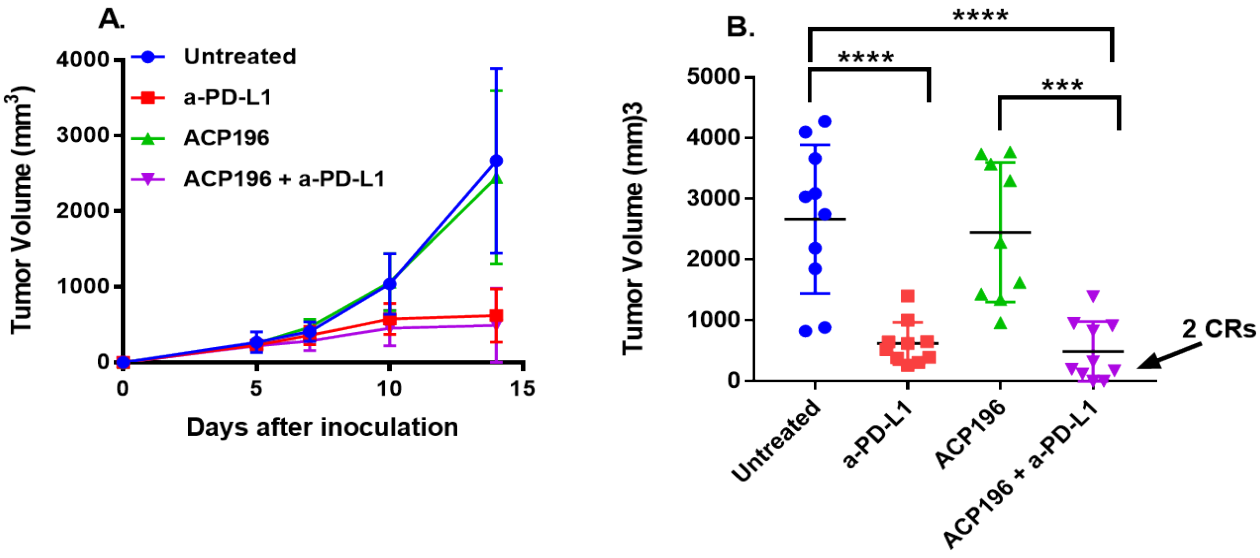
The nonclinical and toxicology results of acalabrutinib suggest it may have an improved therapeutic window relative to ibrutinib; it may be more readily combined with other agents for the treatment of cancer including monoclonal antibodies that activate effector cells.

Improved understanding of the molecular mechanisms governing the host response to tumors has led to the identification of checkpoint signaling pathways involved in limiting the anticancer immune response (Topalian 2011). A critical checkpoint pathway responsible for mediating tumor-induced immune suppression is the PD-1 pathway (McDermott and Atkins 2013). This proof-of-concept study will assess the clinical potential of combined BTK inhibition and checkpoint blockade by evaluating the safety, PD, and efficacy of acalabrutinib and pembrolizumab in hematologic malignancies.

To determine whether there is potential synergy between BTK inhibition and PD-1 blockade, Acerta conducted a nonclinical study of acalabrutinib in combination with an anti–PD-L1 antibody in an orthotopic colon cancer murine model. Mice were inoculated with syngeneic CT26 colorectal cancer cells on Day 0; anti–PD-L1 (150 µg on Days 6, 9, 12, 15) and acalabrutinib (15 mg/kg BID) treatment was initiated on Day 6, when the tumor was well established. Treatment of mice with ACP-196 alone did not substantially diminish tumor growth. In comparison, there was a significant reduction in tumor volume in mice treated with the PD-L1 antibody (mean + SD of 621 +349 mm^3) or the combination of ACP-196 + PD-L1 antibody (mean + SD of 491 +489 mm^3) compared to tumor sizes in the untreated group (mean + SD of 2667 +1222 mm^3, $p<0.0001$) or ACP-196 only group (mean + SD of 2449 +1149 mm^3, $p=0.0004$) (see Figure 1). On Day 14, the average tumor growth was not significantly different between mice treated with the PD-L1 antibody or the combination of ACP-196 + PD-L1 antibody (see Figure 1). Interestingly, in the combination group, 5 of

10 tumors appeared to be smaller than any of those in the PD-L1 antibody-treated group (see Figure 1). Additionally, there were 2 complete regressions (CRs) in the combination-treated group but not in the PD-L1 antibody group (see Figure 1).

Figure 1 Acalabrutinib Enhances the Antitumor Effects of α-PD-L1 in the Orthotopic CT26 Colon Cancer Model



ACP-196=acalabrutinib; CR=complete regression; PD-L1=programmed death ligand-1.

Effects of ACP-196 or anti-PD-L1 antibody alone or in combination were evaluated in the CT26 colorectal tumor model in Balb/c mice. A) Treatment effects on tumor growth, and B) Treatment effects on Day 14. Data were available from 9 mice in the ACP-196 group and10 mice in the other groups on Day 14. Data analyzed by one-way analysis of variance (ANOVA) with Sidak's multiple comparison test (***p=0.0002 to ACP-196, ****p<0.0001 to Untreated).

Summaries of other nonclinical and clinical studies for acalabrutinib are provided below. For more detailed information refer to the acalabrutinib Investigator Brochure (IB). For detailed information on pembrolizumab refer to the pembrolizumab (MK-3475) IB.

1.2 ACALABRUTINIB

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and acalabrutinib is the S-enantiomer. Acalabrutinib is orally administered and is suitable for formulating in capsules. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

Acalabrutinib (CALQUENCE®) is an investigational product. CALQUENCE® has been approved in the United States and other markets for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy, chronic lymphocytic leukemia (CLL), and small lymphocytic lymphoma (SLL).

1.2.1 Mechanism of Action

Acalabrutinib is a highly selective, potent, covalent inhibitor of BTK. In kinase activity assays and wide kinome screens, acalabrutinib was more selective than ibrutinib (Covey 2015). For additional details, refer to the acalabrutinib IB.

1.2.2 Spontaneous Canine B-cell Lymphoma

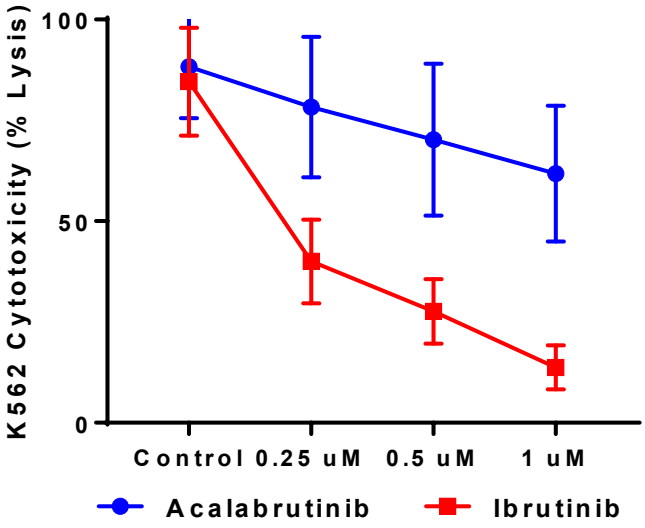
Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to BTK inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). Acalabrutinib was evaluated in a dose-escalation study in canine spontaneous B-cell lymphoma (Harrington 2016). Twenty dogs were enrolled in the clinical trial and treated with acalabrutinib at dosages of 2.5 to 20 mg/kg every 12 or 24 hours. Acalabrutinib was generally well tolerated, with AEs consisting primarily of Grade 1 or 2 anorexia, weight loss, vomiting, diarrhea, and lethargy. Per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), the ORR was 25% (5/20) with a median progression-free survival of 22.5 days. Clinical benefit was observed in 30% (6/20) of dogs. These findings suggest that acalabrutinib is safe and exhibits activity in canine B-cell lymphoma patients and support the use of canine lymphoma as a relevant model for human NHL. These findings are similar to the clinical responses observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

1.2.3 Acalabrutinib and Antibody-dependent Cell-mediated Cytotoxicity

As acalabrutinib is not an inhibitor of interleukin-2-inducible kinase (ITK), it is expected to have less activity against non-malignant cells that require ITK for development and functional activation, such as T and NK cells. ITK kinase is required for FcR-stimulated NK cell functions including calcium mobilization, lytic granule release (Khurana 2007), and overall ADCC. Anti-CD20 antibodies are standard of care drugs, often as part of combination regimens, for the treatment of CD20+ B-cell malignancies; obinutuzumab has

been specifically designed to increase Fc interactions and promote ADCC and phagocytosis of malignant CD20+ cells. Ibrutinib has been evaluated for effects on NK activity, including ADCC, using in vitro assays of cytokine release, lytic granule release, and cellular cytotoxicity (Kohrt 2014). In contrast to more specific BTK inhibitors, ibrutinib inhibited all these NK cell functions, and impaired NK activity against rituximab-coated autologous CLL cells and in mouse tumor models requiring Fc-mediated effector functions (Kohrt 2014). Acalabrutinib was tested in ADCC and natural cytotoxicity assays, using cells from healthy donors. In these in vitro tests, NK cell function was preserved with acalabrutinib treatment, whereas ibrutinib inhibited functional activity, including natural cytotoxicity against K562 cells.

Figure 2 NK Cell Natural Cytotoxicity



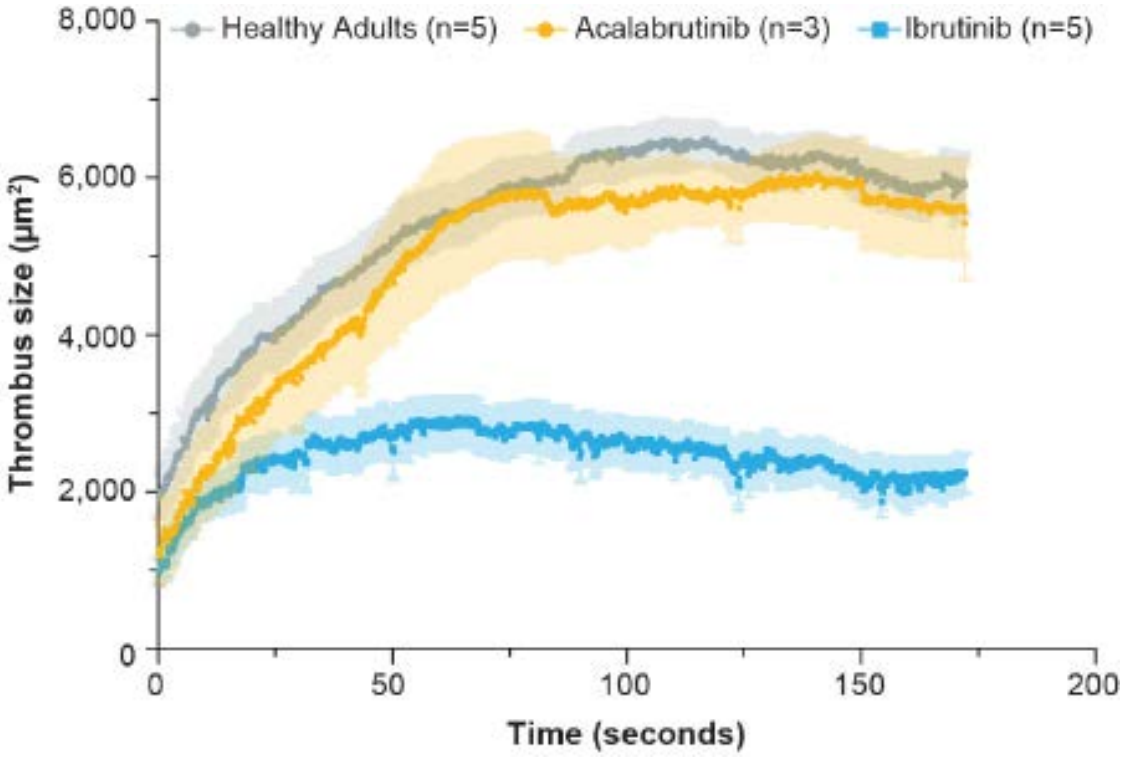
Peripheral blood mononuclear cells were cultured with ^{51}Cr labelled K562 targets at an effector-to-target (E:T) ratio of 100:1 for 4 hours. Cytotoxicity was evaluated by scintillation counting of supernatants. Treatment, dose, and interaction effect were significant in 2-way analysis of variance (ANOVA) (n=5 healthy donors; ibrutinib versus acalabrutinib $p<0.0001$; all ibrutinib doses $p<0.0001$ compared with control; $p=0.0117$ for control versus acalabrutinib 1 µM, other acalabrutinib doses not statistically different from control condition).

1.2.4 Acalabrutinib and Thrombus Formation

Ibrutinib is associated with an increased risk of bleeding (Kamel 2015). Hence, the effects of acalabrutinib and ibrutinib were evaluated on human platelet-mediated thrombus formation by using the in vivo human thrombus formation in VWF^{HA1} murine model, which has been previously described (Chen 2008). The in vivo function of platelets isolated from

blood of healthy volunteers (n=5), CLL patients treated with 420 mg once per day (QD) ibrutinib (n=5), or CLL patients treated with 100 mg BID acalabrutinib (n=3) was evaluated in the VWF^{HA1} model. Results from this study showed a reduction in platelet-vessel wall interactions of platelets from ibrutinib-treated CLL patients, but not of those from CLL patients treated with acalabrutinib (Byrd 2016).

Figure 3 In Vivo Thrombus Formation



Platelets from patients treated with ibrutinib 420 mg once per day (QD) (n=5) or acalabrutinib 100 mg twice per day (BID) (n=3) were evaluated for their ability to support thrombus formation in laser injured arterioles of VWF^{HA1} mice. Freshly isolated platelets from healthy volunteers (n=5) were used as non-drug treated controls. A minimum of 4 arterioles per mouse was used to assess thrombus formation for each patient/volunteer sample. Thrombus size as a function of time is provided in the figure (shading denotes standard error of the median).

1.2.5 Safety Pharmacology

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

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein–coupled receptors, nuclear receptors, proteases, and ion channels, acalabrutinib shows significant activity only against the A3 adenosine

receptor; follow-up dose-response experiments indicated a half-maximal inhibitory concentration (IC_{50}) of 4.6 µM, suggesting a low clinical risk of off-target effects.

The in vitro effect of acalabrutinib on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. Acalabrutinib inhibited hERG channel activity by ~25% at 10 µM, suggesting a low clinical risk that acalabrutinib would induce clinical QT prolongation as predicted by this assay (see the acalabrutinib IB for a summary of the thorough QT study in humans).

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

1.2.6 Drug-drug Interaction Potential

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

Please refer to Section 3.10.7 for guidance on drugs that may cause drug-drug interactions.

1.2.7 In Vivo General Toxicology

The systemic toxicity of acalabrutinib has been fully investigated in repeat-dose sub-chronic studies in mice, rats, and dogs. The pivotal GLP studies were 28- and 91-day repeat-dose studies in rats and dogs, each with recovery periods to assess the reversibility of observed changes.

In rats, 100 mg/kg/day was selected initially to represent the highest non-severely toxic dose; however, in subsequent studies the 100 mg/kg/day dose level was determined to be a no observable adverse effect level (NOAEL). In rats, the target organs of toxicity were the kidney, liver, and heart.

The NOAEL in the dog was 30 mg/kg/day; dose levels higher than 30 mg/kg/day were not tolerated. In dogs, the target organs of toxicity, observed only at doses exceeding the MTD, were the kidney and liver. Heart findings were also observed in 2 dogs with kidney toxicity, which were interpreted as possibly secondary to uremia, as has been reported for this species.

In rats and dogs, no adverse electrocardiogram (ECG) or histopathologic cardiovascular effects were noted at the planned conclusion of the sub-chronic studies or in the rat chronic toxicity study. However, in 5 of 6 rats from the 4-week study that died early, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts.

1.3 PEMBROLIZUMAB

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on nonclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable nonclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the pembrolizumab IB.

1.4 CLINICAL EXPERIENCE

Acalabrutinib has been studied in a broad range of clinical studies, including subjects with hematologic malignancies and solid tumors. No new safety concerns were identified for acalabrutinib monotherapy based on safety data available to date. The safety data of acalabrutinib monotherapy are consistent among studies. For more detailed and updated information on the clinical experience for acalabrutinib, refer to the acalabrutinib IB. See the KEYTRUDA package insert for details about clinical experience with pembrolizumab.

1.4.1 Pharmacokinetics and Pharmacodynamics of Acalabrutinib

ACE-HV-001 was a pharmacokinetic (PK)/PD, dose-ranging, food-effect, and drug-drug interaction study evaluating BID and QD dosing for 1 or 2 days in healthy volunteers. This study evaluated the PK/PD of acalabrutinib at various dose levels and regimens. The starting dose for acalabrutinib was 2.5 mg BID. This study has been completed and no

adverse laboratory, vital signs, or ECG findings were observed (2.5 to 50 mg BID; 50 to 100 mg QD). Three AEs related to study drug were reported. Each AE was Grade 1 and resolved without treatment. The AEs were constipation (2.5 mg BID), feeling cold (75 mg QD), and somnolence (75 mg QD).

In Part 1, PK properties of acalabrutinib were evaluated after oral administration of 2 daily divided doses of 2.5 to 50 mg and a single dose of 100 mg. Of the 30 subjects evaluated, all observed systemic concentrations of acalabrutinib. Acalabrutinib plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts and were independent of dose level. The increase in mean maximum observed plasma concentration (C_{max}) values was greater than dose proportion based on the increases of C_{max} from the first dose administered. When evaluating area under the curve from time 0 to 12-hour timepoint (AUC_{0-12}), from time 0 to 24-hour timepoint (AUC_{0-24}), or from time 0 to infinity (AUC_{0-inf}) the mean values increased in a dose-proportional manner based on the increases of the total dose administered. Mean half-life ($t_{1/2}$) values ranged from 0.97 to 2.1 hours and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (V_z/F: 233 to 612 L) appeared to be independent of the dose administered.

Acalabrutinib was not detected in the urine of subjects receiving the 2.5- or 5.0-mg BID doses of acalabrutinib. Acalabrutinib was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose-dependent manner.

In Part 2, the effect of food on the PK of acalabrutinib (75 mg) after a single oral administration was evaluated in 6 men and 6 women. Median acalabrutinib plasma T_{max} values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma acalabrutinib C_{max} fed values decreased to 27.3% of the C_{max} values observed in the fasted state. In contrast, the relative AUC exposure of acalabrutinib remained mostly unchanged in both states. This decrease in exposure is not clinically significant; therefore, acalabrutinib can be taken without regard to meals.

In Part 3, the effect of itraconazole on the PK of acalabrutinib (50 mg) after a single oral administration was evaluated in 17 subjects. No difference in acalabrutinib T_{max} values was observed in the presence or absence of itraconazole.

Mean acalabrutinib exposures (as assessed by C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-inf}}$) increased in the presence of itraconazole. The mean plasma acalabrutinib C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-inf}}$ values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and V_z/F values decreased in the presence of itraconazole (CL/F: 217 vs 44 L/h; V_z/F: 1190 vs 184 L). No differences in $t_{1/2}$ were observed (3.3 vs 2.5 hours).

The PD of acalabrutinib was evaluated using a BTK occupancy assay and correlated with a functional assay that determines the level of BTK inhibition by measuring expression of CD69 and CD86 on B cells. A dose-dependent increase in BTK occupancy and corresponding decrease in CD69/86 expression was observed in this study. Full BTK occupancy (≥90%) and complete CD86 and CD69 inhibition (≥90%) occurred at the 75- and 100-mg single dosed cohorts 1 to 3 hours after administration. However, only the 100-mg cohort maintained high BTK occupancy (91.5%) and high BCR functional inhibition (CD86: 86 ±3% and CD69: 78 ±8%) at 24 hours. For subjects receiving a second dose of acalabrutinib 12 hours after the first administration, full BTK target occupancy was observed 3 hours after the second dose for the 50-mg dosed cohort (BTK occupancy 97 ±4%).

ACE-HV-004 was a 3-part drug interaction study. Each part was conducted as an open-label, 2-period, fixed sequence study under fasting conditions. The study design was as follows:

- Part 1: In Period 1, a single oral dose of acalabrutinib (100 mg) was administered followed by PK sampling for 24 hours. In Period 2, a single oral dose of calcium carbonate (1 g) was coadministered with a single oral dose of acalabrutinib (100 mg) followed by PK sampling for 24 hours.
- Part 2: In Period 1, a single oral dose of acalabrutinib (100 mg) was administered followed by PK sampling for 24 hours. In Period 2, oral doses of omeprazole (40 mg) were administered QD for 5 consecutive days with a single oral dose of acalabrutinib (100 mg) coadministered on Day 5. PK sampling for acalabrutinib and omeprazole were done for 24 hours after dosing on Day 5.
- Part 3: In Period 1, a single oral dose of acalabrutinib (100 mg) was administered followed by PK sampling for 24 hours. In Period 2, oral doses of rifampin (600 mg) were administered QD for 9 consecutive days with a single oral dose of acalabrutinib (100 mg)

coadministered on Day 1 and Day 9. PK sampling for acalabrutinib and rifampin were done for 24 hours after dosing on Day 1 and Day 9.

Seventy-two healthy volunteers enrolled in the study. Acalabrutinib administration was well tolerated. Three AEs were reported as related to study drug. These were generalized pruritus, dyspepsia, and abdominal pain. All were considered mild and resolved without treatment. No drug-related AEs led to discontinuation from the study. No severe AEs or SAEs occurred on this study.

Coadministration of the gastric pH-modifiers calcium carbonate or omeprazole decreased mean C_{max} to 25% and 21% and AUC to 47% and 43%, respectively, of values obtained with acalabrutinib dosed alone. Rifampin dosed at 600 mg QD for 9 days decreased AUC to 23% of values obtained with acalabrutinib dosed alone. Results from Part 1 of this study suggest that subjects should avoid the use of calcium carbonate-containing drugs or supplements (e.g., antacids and calcium supplements) for a period of at least 2 hours before and after taking the study drug.

1.4.2 Safety of Acalabrutinib

This section includes preliminary safety in Study ACE-LY-005. Additional safety details in studies with healthy subjects and in subjects with malignancies are available in the acalabrutinib IB.

1.4.2.1 Safety of Acalabrutinib in Combination with Pembrolizumab for Subjects with B-Cell Malignancies (ACE-LY-005)

Study ACE-LY-005 is a Phase 1b/2, multicenter, open-label proof-of-concept study in subjects with B-cell malignancies. Safety data from 161 subjects are available as of the data cutoff date of 03 September 2017. Median exposure was 3.4 months (range 0.2 to 30.2 months).

All 161 subjects (100.0%) experienced at least 1 AE of any grade. The most frequently reported AEs were diarrhea (44.1%), headache (35.4%), fatigue (33.5%), cough (26.7%), nausea (26.7%), decreased appetite (24.8%), and vomiting (22.4%).

Nine subjects (5.6%) had Grade 5 (fatal) events, including 2 subjects with Grade 5 sepsis and 3 subjects with Grade 5 respiratory failure. One subject with DLBCL had Grade 5 neutropenic sepsis, which was considered by the investigator to be related to acalabrutinib.

Two other subjects had Grade 5 events of respiratory failure and sepsis which were considered by the investigator to be related to pembrolizumab.

SAEs were reported for 73 subjects (45.3%). The most commonly reported SAEs were sepsis (5 subjects [3.1%]) and lung infection and AST increased (4 subjects [2.5%] each). Five subjects had SAEs reported by the investigator as related to only acalabrutinib of lymphoma, tumor flare, neutropenic sepsis (fatal event described above), nausea, and syncope.

Fifteen subjects had SAEs that were attributed to both acalabrutinib and pembrolizumab treatment. Of these 15 subjects, 1 subject experienced multiple related events of mental status change, pyrexia, lactic acidosis, and AST increased (Grade 3). Other SAEs related to both acalabrutinib and pembrolizumab were hypotension, dehydration, septic shock, systemic inflammatory response syndrome, ALT increased, Herpes zoster, lymphadenitis, cytokine release syndrome, lymphocyte count decreased, platelet count decreased, pancreatitis, pneumonitis, lymphoma, gastrointestinal hemorrhage, retroperitoneal mass, anemia, hyponatremia, upper gastrointestinal hemorrhage, enteritis, and neck pain.

Sixteen subjects had SAEs reported by the investigator to be related to only pembrolizumab, including AST increased, anemia, bronchitis, vertigo, orthostatic hypotension, drug-induced liver injury, platelet count decreased, sepsis, lung infection, pneumonitis, respiratory failure, respiratory distress, colitis, hyponatremia, pyrexia, tubulointerstitial nephritis, and systemic inflammatory response syndrome. The AE of drug-induced liver injury was attributed to pembrolizumab due to the known risk for pembrolizumab of immune-mediated hepatitis, and occurred in a subject in whom initial corticosteroid therapy was likely not adequate. The event improved when corticosteroids were again administered per guidance in the pembrolizumab prescribing information (Immune-Mediated Hepatitis, pembrolizumab prescribing information).

A total of 40 subjects (24.8%) had AEs that led to study drug discontinuation, the most frequent of which included ALT increased (8 subjects [5.0%]) and AST increased (7 subjects [4.3%]). One subject discontinued study drug due to an AE of lymphoma, considered by the investigator to be related to acalabrutinib only. Five subjects discontinued study drug due to AEs considered to be related to both acalabrutinib and pembrolizumab, including ALT increased in 2 subjects, and cytokine release syndrome, pneumonitis, and AST increased in 1 subject each. Thirteen subjects discontinued treatment due to AEs considered related

only to pembrolizumab, including 1 or more AEs of ALT increased, AST increased, pneumonitis, deafness neurosensory, neutropenia, bursitis, pneumonitis, colitis, and diarrhea.

1.4.3 Efficacy of Acalabrutinib

Preliminary efficacy data as of 03 April 2017 have been evaluated for subjects with CLL, including subjects with R/R CLL (N=134), treatment-naive subjects (N=99), ibrutinib-intolerant subjects (N=33), and subjects with Richter's syndrome or PLL transformation (N=29). The ORRs for the 4 populations were 96.9%, 99.0%, 80.6%, and 37.0%, respectively. Efficacy data through 28 February 2017 are also available on the first 124 sequentially enrolled subjects with R/R MCL who were treated with acalabrutinib monotherapy. With a median follow-up of 15.2 months, the ORR was 80.6%, with CR in 39.5% of subjects. See the acalabrutinib IB for details.

1.5 BENEFIT/RISK OF ACALABRUTINIB

Acalabrutinib is a potent, orally administered small-molecule inhibitor of BTK. Preliminary efficacy and safety data from ongoing studies suggest that acalabrutinib is well tolerated and has robust activity as monotherapy and combination therapy.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To characterize the safety profile of acalabrutinib and pembrolizumab in subjects with hematologic malignancies.

2.2 SECONDARY OBJECTIVE

To evaluate the activity of acalabrutinib and pembrolizumab as measured by response rate, duration of response, progression-free survival, overall survival, and time to next treatment.

2.3 EXPLORATORY OBJECTIVES

CCI

CCI

[redacted]

3.0 STUDY DESIGN

This is a Phase 1b/2, open-label, nonrandomized study that will be conducted in 2 stages. In the first stage, Part 1 of the study will determine the safety and preliminary efficacy of acalabrutinib and pembrolizumab in a limited group of B-cell malignancies. In the second stage, Part 2 allows for possible expansion cohorts into a wider range of B-cell malignancies, and Part 3 (enrolled concurrently with Part 2) will evaluate the combination in subjects with myelofibrosis (see Figure 4).

Part 1

Six subjects will be enrolled to receive acalabrutinib in combination with pembrolizumab. If the combination is safe with ≤1 DLT (6-week observation period) in the first 6 subjects, the cohort will be expanded up to 24 subjects to obtain additional safety information and to assess the efficacy of the combination.

Part 1 of the study will include adult subjects with the following disease types:

- Non-GCB DLBCL
- FL
- CLL/SLL

Part 2

Part 2 consists of expansion groups of up to 30 subjects per histology provided the safety and efficacy results from Part 1 of the study indicate that further evaluation of the combination is warranted. The possible expansion groups for Part 2 could include adult subjects with the following disease types:

- Non-GCB DLBCL
- GCB DLBCL
- Richter syndrome
- MCL

- iNHL
    - FL
    - WM
    - CLL/SLL
- MM
- Other B-cell malignancy (including but not limited to: Hodgkin's lymphoma, Burkitt lymphoma, marginal zone lymphomas, mediastinal large B-cell lymphoma, and hairy cell leukemia)

Under Amendment 3 of this protocol, subjects with MCL or iNHL (including FL, WM, and CLL/SLL) are no longer enrolled. Under Amendment 4, subjects with RS are no longer enrolled.

Part 3

Part 3 includes up to 30 subjects with primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF with thrombocytopenia or anemia. Part 3 will run in parallel with Part 2. Subjects with MF will receive a run-in of 6 weeks of acalabrutinib alone. Subjects who are demonstrating a clinically meaningful response, in the opinion of the investigator, may continue on acalabrutinib monotherapy; those who are not will be treated with combination therapy with acalabrutinib and pembrolizumab.

In Part 3, safety and response data will be reviewed after the initial 12 subjects have completed 24 weeks of treatment (i.e., the Week 25 visit) or have discontinued treatment before Week 25. The first 12 subjects will be evaluated regardless of the length of treatment with acalabrutinib alone or in combination with pembrolizumab. If <2 subjects who received acalabrutinib monotherapy or the combination with pembrolizumab have achieved a response of "clinical improvement" or better (see Table 9), the MF group will not be expanded. The decision to expand the study is multifactorial and will take into consideration the nature and quality of response, safety, and evolving competitive landscape. If the safety and response data indicate that further evaluation is warranted, up to 18 additional subjects with MF (for a total of up to 30 subjects) will be treated on the same adaptive regimen as was given to the first 12 subjects.

Under Amendment 3 of this protocol, Part 3 is closed to enrollment.

All Parts

Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Treatment with acalabrutinib can continue until the end of trial, defined as 48 months after the last subject is enrolled. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may be eligible to enroll in a separate rollover study of acalabrutinib monotherapy. In the event that a rollover or safety extension study is available at the time of the final data cutoff and database closure, subjects who remain in Study ACE-LY-005 may be transitioned to such a study. Once all active subjects are eligible for and move to a rollover or safety extension study, Study ACE-LY-005 would be considered closed. The rollover or safety extension study would ensure treatment continuation, with visit assessments per the rollover or extension protocol. Any subject who would be proposed to move to a rollover or safety extension study would be asked to sign an Informed Consent Form (ICF) for the rollover or safety extension study.

Treatment with pembrolizumab may continue for 24 months (103 weeks) from first dose of pembrolizumab, provided subjects are tolerating the drug and not progressing. In addition, pembrolizumab treatment can end for subjects with confirmed CR (or sCR for MM) if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR/sCR. Subjects who have **confirmed** progressive disease will come off treatment. Note: If there is uncertainty regarding whether there is cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) pending confirmation of progression. In particular, transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

All subjects will have bone marrow biopsy, hematology, chemistry, thyroid, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry, hematology, and thyroid function tests, once weekly for the first 8 weeks, followed by a Week 10 visit and then every 3 weeks

thereafter (every 6 weeks thereafter for thyroid function tests) through Week 103. For subjects who discontinue pembrolizumab at Week 103, the Week 103 visit will be followed by Week 106 and Week 109 visits, at which time, the investigator will determine eligibility to continue single-agent acalabrutinib treatment. Subjects remaining on study treatment after Week 103 will have a Week 103 and Week 115 visit, and then visits for safety and tumor response assessments every 24 weeks starting at Week 127 through 3 years (for subjects with CLL/SLL histologies) or 5 years (for subjects with non-CLL/SLL histologies [i.e., DLBCL/Hodgkin lymphoma]), and then every 52 weeks thereafter (all histologies).

Subjects who permanently discontinue pembrolizumab at any time during study participation must have a minimum of 2 consecutive study visits, 3 weeks apart, after the last dose of pembrolizumab for safety evaluation. The study visits will be scheduled as follows:

- For all subjects except MM and CLL subjects
    - If a subject discontinued pembrolizumab prior to completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 3 weeks until Week 37. After Week 37, study visits will be held every 12 weeks.
    - If a subject discontinued pembrolizumab after completing 37 weeks on study and is on acalabrutinib alone, 2 consecutive study visits will be held 3 weeks apart (e.g., Week 40 and 43), after which study visits will be held every 12 weeks.
    - It is acknowledged that the discontinuation timepoint of pembrolizumab (if applicable) is unique per subject. To synchronize the every 12-week study visit schedule with the radiologic tumor assessment schedule, the first 2 study visits after pembrolizumab discontinuation should be 3 and 6 weeks after pembrolizumab discontinuation and then scheduled to align with the nearest radiological timepoint.

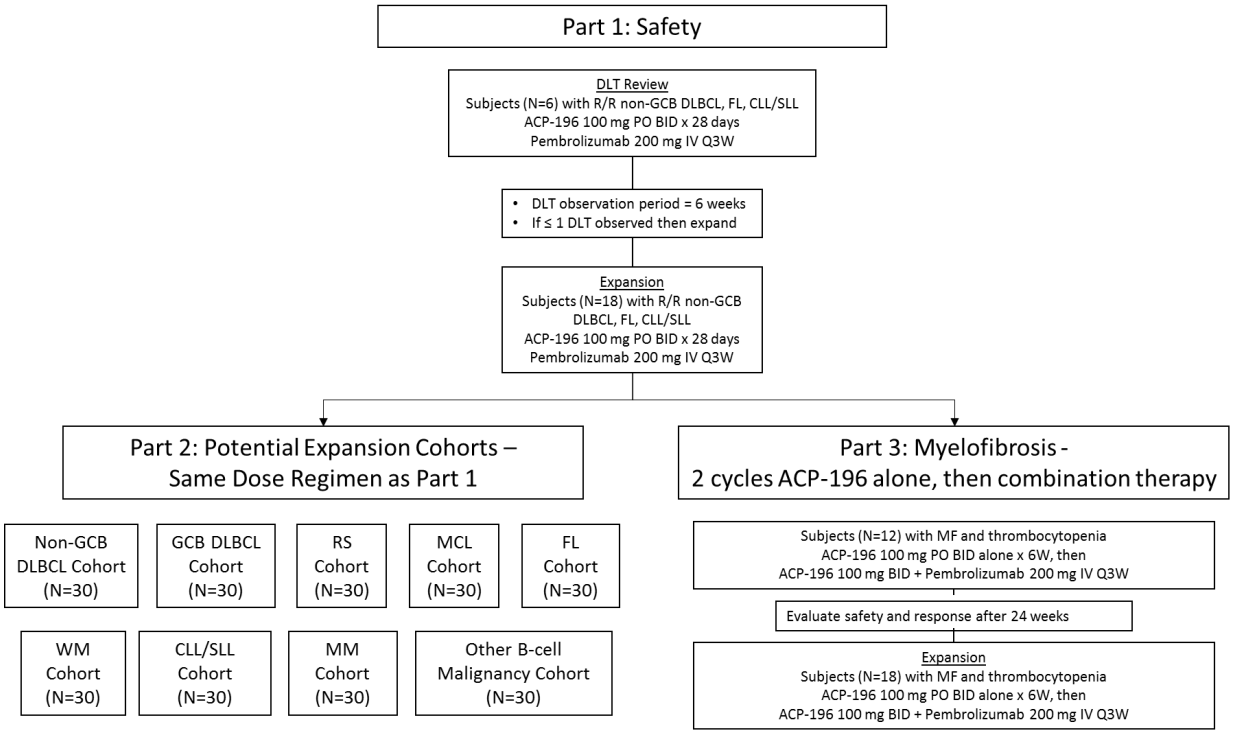
- For CLL subjects
    - If a subject discontinued pembrolizumab prior to completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 3 weeks until Week 37. After Week 37, study visits will be held every 12 weeks.
    - If a subject discontinued pembrolizumab after completing 37 weeks on study and is on acalabrutinib alone, study visits will be held every 12 weeks.
    - It is acknowledged that the discontinuation timepoint of pembrolizumab (if applicable) is unique per subject. To synchronize the every 12-week study

visit schedule with the radiologic tumor assessment schedule, the first study visit should be scheduled to align with the nearest radiological timepoint.

In addition, subjects who permanently discontinue pembrolizumab for any reason (e.g., pembrolizumab toxicity, AE, or completing the 103-week course of pembrolizumab) and remain on acalabrutinib alone at any time during study participation must have a thyroid test done every 6 weeks for 6 months after pembrolizumab discontinuation. Thyroid testing may be discontinued at 6 months if 1) testing that was performed at 6 months was normal and 2) testing that was performed 6 weeks prior to the 6-month timepoint was normal (for a total of 2 consecutive normal test results). Otherwise, thyroid testing will continue as scheduled until 2 consecutive normal test results.

Refer to Appendix 5 and Appendix 6 for a comprehensive list of study assessments and their timing.

Figure 4 Study Schema



ACP-196=acalabrutinib; BID=twice per day; CLL/SLL= chronic lymphocytic leukemia/small lymphocytic lymphoma; DLT=dose-limiting toxicity; FL= follicular lymphoma; GCB=germinal center B-cell diffuse large B-cell lymphoma; iNHL=indolent non-Hodgkin lymphoma; IV=intravenous; MF=myelofibrosis (per Amendment 3, Part 3, MF was not opened for this study); MM=multiple myeloma; non-GCB DLBCL=non-germinal center B-cell diffuse large B-cell lymphoma; PO=oral; Q3W=every 3 weeks; RS=Richter's syndrome (under Amendment 4, subjects with RS are no longer enrolled); WM=Waldenström macroglobulinemia.

3.1 STUDY PARAMETERS

3.1.1 Safety Parameters

The safety of acalabrutinib and pembrolizumab will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug(s) of any treatment-emergent AEs or abnormalities of laboratory tests; SAEs; ECIs, or AEs leading to discontinuation of study treatment.

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

3.1.2 Pharmacodynamic and Biomarker Parameters

CCI

3.1.3 Efficacy Parameters

Standardized response and progression criteria have been established for B-cell malignancies including WM (Bladé 1998; Durie 2006; Hallek 2008; Owen 2013; Tefferi 2013; Cheson 2014); assessments of acalabrutinib and pembrolizumab efficacy in this study will be based on these criteria. Efficacy endpoints will include:

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

For Part 3 subjects with MF, an overall response will be defined as clinical improvement or better (clinical improvement, PR, or CR) see Table 9. An additional analysis will evaluate

response when defined as CR + PR only. Under Amendment 3 of this protocol, Part 3 is closed to enrollment.

3.2 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.4, acalabrutinib is currently being evaluated in a Phase 1/2 study in subjects with CLL (ACE-CL-001). In this study, subjects have received oral dosages of 100 to 400 mg QD and 100 to 200 mg BID of acalabrutinib. All tested dose levels have been well tolerated and, to date, no DLTs have been observed. Robust clinical responses have been observed with dosages as low as 100 mg QD. Preliminary PK data from ACE-CL-001 suggests a plateauing of exposure after 250 mg QD. PD results from this study also show 100 mg BID has the highest BTK occupancy at 24 hours of all the regimens evaluated. Therefore, 100 mg BID maintains full target coverage over 24 hours, while lowering the C_{max} and AUC of acalabrutinib suggesting this regimen is preferred when acalabrutinib is being administered with other agents to lower the potential risk of drug-drug interactions. Therefore, based on PK/PD and efficacy results of the Phase 1/2 study, a 200-mg total daily dose, administered 100 mg BID, will be evaluated in this protocol.

Because acalabrutinib has not yet been evaluated in subjects with MF, an adaptive regimen will be used in Part 3. Preliminary data in CLL suggest that responses to acalabrutinib occur rapidly; in study ACE-CL-001, some subjects obtained PRs after only 2 cycles (8 weeks) of therapy. Thus, subjects in Part 3 will receive at least 6 weeks run-in with acalabrutinib alone before beginning combination therapy with pembrolizumab. The adaptive dosing regimen allows for the reasonable possibility that robust activity will be seen in MF using acalabrutinib as a single agent, while providing combination therapy of acalabrutinib plus pembrolizumab for subjects who do not show a clinically meaningful response to acalabrutinib alone. Under Amendment 3 of this protocol, Part 3 is closed to enrollment.

The dose of pembrolizumab planned to be studied in this trial is 200 mg Q3W. The dose recently approved in the United States and several other countries for treatment of melanoma subjects is 2 mg/kg Q3W. Information on the rationale for selecting 200 mg Q3W is summarized below.

KEYNOTE-001 was an open-label Phase 1 study conducted to evaluate the safety, tolerability, PK and PD, and anti-tumor activity of pembrolizumab when administered as monotherapy. The dose escalation portion of this trial evaluated 3 dose levels, 1 mg/kg,

3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) and dose expansion cohorts evaluated 2 mg/kg Q3W and 10 mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no DLTs were observed. This first-in-human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No MTD has been identified. In addition, 2 randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed, and 1 randomized cohort evaluating 10 mg/kg Q3W versus 10 mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of important differences in efficacy or safety profile across doses.

An integrated body of evidence suggests that 200 mg Q3W is expected to provide similar response to 2 mg/kg Q3W, 10 mg/kg Q3W and 10 mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2 mg/kg and 10 mg/kg. Exposures of 200 mg Q3W are expected to lie within this range and will be close to those obtained with the 2 mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed. The PK profile of pembrolizumab is consistent with that of other humanized monoclonal antibodies, which typically have a low clearance and a limited volume of distribution. The distribution of exposures from the 200 mg fixed dose is predicted to considerably overlap those obtained with the 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. PK properties of pembrolizumab, and specifically the weight-dependency in clearance and volume of distribution are consistent with no meaningful advantage to weight-based dosing relative to fixed dosing.

In translating to other tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available PK results in subjects with melanoma, NSCLC, and other tumor types support a lack of meaningful difference in PK exposures obtained at tested doses

among tumor types. Thus the 200 mg Q3W fixed-dose regimen is considered an appropriate fixed dose for other tumor indications as well.

A fixed-dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed-dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage. The existing data suggest 200 mg Q3W as the appropriate dose for pembrolizumab.

As described in Section 1.1, Acerta Pharma has conducted a nonclinical study to evaluate the potential synergy of BTK inhibition with PD-1 blockade and has seen encouraging results which warrant testing the hypothesis in a clinical trial.

3.3 SELECTION OF STUDY POPULATION

3.3.1 Inclusion Criteria

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

Part 1

1) Diagnosis of non-GCB DLBCL or iNHL as documented by medical records and with histology based on criteria established by the WHO.
    a) If the subject has DLBCL, it is characterized as de novo non-GCB DLBCL (Hans 2004; Choi 2009).
    b) If the subject has iNHL, the histology shows one of the following subtypes:
        i) FL Grade 1, 2, or 3a
        ii) CLL/SLL
2) Prior treatment for lymphoid malignancy (applies to Part 1 and Part 2 of the protocol):
    a) If the subject has DLBCL, there is no curative option with conventional therapy and the prior treatment included ≥1 prior combination chemoimmunotherapy regimen (e.g., anthracycline based therapy with rituximab).
    b) If the subject has MCL or iNHL, the prior treatment comprised any of the following:
        i) ≥1 regimen containing an anti-CD20 antibody administered for ≥2 doses, and/or
        ii) ≥1 regimen containing ≥1 cytotoxic agent (e.g., bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin) administered for ≥2 cycles, and/or

iii) ≥1 regimen containing yttrium^{90}-ibritumomab tiuxetan (ZEVALIN®) or iodine^{131}-tositumomab (BEXXAR®).

3) Presence of radiographically measurable lymphadenopathy or extranodal lymphoid malignancy (defined as the presence of a ≥2.0-cm lesion as measured in the longest dimension by CT scan). Note: Not applicable to subjects with WM and MM.

4) ANC ≥1.5×10^9/L or platelet count ≥100×10^9/L unless due to disease involvement in the bone marrow (Part 1 only).

Part 2

5) ANC ≥0.5×10^9/L and platelet count ≥50×10^9/L unless due to disease involvement in the bone marrow (Part 2 only).

Additional Part 2 disease entry criteria including those listed in Part 1 above

6) DLBCL (GCB): Confirmed diagnosis of DLBCL with disease characterized as GCB subtype by immunohistochemistry (Hans 2004; Choi 2009) and meeting the rest of the criteria as defined above, including characterization as de novo DLBCL.

7) If the subject has MCL, it is characterized by documentation of monoclonal B cells that have a chromosome translocation t(11;14)(q13;q32) and/or overexpress cyclin D1.

8) Richter's syndrome: Confirmed diagnosis of and biopsy-proven DLBCL due to Richter transformation and meeting the rest of the criteria as defined above.

9) MM: Confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥3 prior therapies for MM, and is progressing at the time of study entry and meeting the rest of the criteria as defined above. Must be able to provide archival or newly obtained bone marrow aspirate/biopsy material for biomarker analysis.

10) WM: Confirmed diagnosis of WM, which has relapsed after, or been refractory to ≥1 prior therapy for WM, and is progressing at the time of study entry and meeting the rest of the criteria as defined above. Must be able to provide archival or newly obtained bone marrow aspirate/biopsy material for biomarker analysis.

11) Other B-cell malignancy (including but not limited to Hodgkin's lymphoma, Burkitt lymphoma, marginal zone lymphomas, mediastinal large B-cell lymphoma, and hairy cell leukemia): Confirmed diagnosis of previously treated B-cell malignancy and meeting the rest of the criteria as defined above.

Part 3 (Under Amendment 3 of this protocol, Part 3 is closed to enrollment.)

12) Diagnosis of primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF.

13) Intermediate-1, intermediate-2, or high-risk MF per Passamonti 2010 criteria and must have failed therapy with ruxolitinib.

14) Thrombocytopenia (platelet count ≤100×10^9/L at any time after signing informed consent) OR anemia (hemoglobin ≤8.0 g/dL). Subjects who are platelet or red blood cell transfusion-dependent are eligible; platelet counts must be ≥30×10^9/L during the screening period.

15) Palpable splenomegaly ≥5 cm on physical examination.

16) Total Symptom Score ≥13 on the MPN-SAF TSS, not including the inactivity question.

17) No splenic irradiation within 6 months before first study dose.

18) No myelofibrosis therapy, including any erythropoietic or thrombopoietic agents, within 2 weeks before first study dose.

19) ANC ≥0.5×10^9/L.

20) Bone marrow blasts <10%.

All Parts

21) Men and women ≥18 years of age on day of signing informed consent.

22) Documented active disease.

23) ECOG performance status of ≤1.

24) Completion of all therapy (including surgery, radiotherapy, chemotherapy, immunotherapy, or investigational therapy) for the treatment of cancer ≥4 weeks before the start of study therapy (Parts 1 and 2) and recovered (i.e., Grade ≤1 or baseline) from AEs associated with prior cancer therapy (all subjects). Note: Subjects with Grade ≤2 neuropathy or Grade ≤2 alopecia are an exception to the latter criterion and may qualify for the study.

25) Women who are sexually active and can bear children must agree to use highly effective methods of contraception during the study and for 2 days after the last dose of

acalabrutinib or 120 days after the last dose of pembrolizumab, whichever is longer. Note: Highly effective methods of contraception are defined in Section 3.10.9.

26) Men who are sexually active and can beget children must agree to use highly effective methods of contraception during the study and for 120 days after the last dose of pembrolizumab. Note: Highly effective methods of contraception are defined in Section 3.10.9.

27) Men must agree to refrain from sperm donation during the study and for 120 days after the last dose of pembrolizumab.

28) Able to provide tissue, if available, from either an archived or newly obtained tumor sample (most recent biopsy) for biomarker and correlative analysis as appropriate for a given histology.

29) Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.

30) Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

3.3.2 Exclusion Criteria

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

All Parts

1) Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cancer, or other cancer from which the subject has been disease free for ≥2 years.
2) A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of acalabrutinib, or put the study outcomes at undue risk.
3) Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc >480 msec at screening.

4) Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach, or extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
5) CNS involvement by lymphoma/leukemia.
6) Any therapeutic antibody within 4 weeks of first dose of study drug.
7) Any prior irreversible BTK inhibitor therapy. Note: Prior treatment with reversible, noncovalent BTK inhibitors is not excluded on this protocol.
8) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab, tremelimumab, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
9) Receiving ongoing immunosuppressive therapy, including systemic or enteric corticosteroids except for minimally systemically absorbed treatments (such as inhaled or topical steroid therapy for asthma, chronic obstructive pulmonary disease, or allergic rhinitis) within 7 days before the first dose of pembrolizumab.
10) Active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
11) History of interstitial lung disease or non-infectious pneumonitis that required steroids or current pneumonitis.
12) History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
13) History of bleeding diathesis (e.g., hemophilia or von Willebrand disease).
14) Prior allogeneic hematopoietic stem cell transplantation (HSCT) within the last 5 years.
15) Requires treatment with a strong CYP3A inhibitor/inducer.
16) Requires or receiving anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon) within 7 days of first dose of study drug.
17) Requires treatment with a proton-pump inhibitor (e.g., omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
18) Known history of HIV or active infection with HCV or HBV or any uncontrolled active systemic infection.

19) Major surgery within 28 days of first dose of study drug. Note: If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug.
20) Has received a live vaccine within 30 days of planned start of study therapy.
21) History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
22) Active bleeding that requires hospitalization during the screening period.
23) Total bilirubin >1.5×ULN; AST or ALT >3.0×ULN.
24) Estimated creatinine clearance of <30 mL/min, calculated using the formula of Cockcroft and Gault [(140-Age) • Mass (kg)/(72 • creatinine mg/dL); multiply by 0.85 if female].
25) Breastfeeding or pregnant or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
26) Is currently participating in a clinical trial and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.
27) Immediate family members of the sponsor personnel or site staff directly involved with the conduct of this protocol are excluded from participating on this study.
28) Presence of a gastrointestinal ulcer diagnosed by endoscopy within 3 months before screening.
29) Active or known tuberculosis infection. Note: Tuberculosis testing is not required for this protocol.
30) Serologic status reflecting active hepatitis B or C infection:
    a) Subjects who are anti-HBc positive and who are surface antigen negative will need to have a negative PCR result before enrollment. Those who are HBsAg positive or hepatitis B PCR positive will be excluded.
    b) Subjects who are hepatitis C antibody-positive will need to have a negative PCR result before enrollment. Those who are hepatitis C PCR positive will be excluded.

3.3.3 Replacement of Subjects

Subjects will not be replaced on this study except if needed to complete the DLT assessment in Part 1 (N=6). However, subjects who discontinue from the study due to a DLT during the DLT assessment period will not be replaced.

3.3.4 Enrollment Procedures

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

- The study center will notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled into the study.
- To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the sponsor confirms enrollment.
- The sponsor will aim to fax/email a completed Enrollment Confirmation Form to the study center within 24 hours.

Treatment must begin within the screening window (see Section 4.1) and after the site has received the Enrollment Confirmation Form from the sponsor.

3.4 STUDY DRUGS

3.4.1 Premedications

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

Events of tumor lysis syndrome, consistent with disease-related events, have been reported in subjects exposed to acalabrutinib in both monotherapy and in combination with other agents (acalabrutinib IB). Whether there could be an increased likelihood of tumor lysis syndrome when co-administering acalabrutinib and pembrolizumab is unknown. Investigators are at liberty to consider additional monitoring and prophylaxis for tumor lysis syndrome according to local practices (see Section 3.9).

As general precautions considering the subject population, institution of antibiotic prophylaxis for *Pneumocystis (carinii) jiroveci* and use of intravenous immunoglobulin (Ig) may be considered in selected study subjects (see Section 3.9.1).

3.4.2 Formulation, Packaging, and Storage

Acalabrutinib

Acalabrutinib is manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. Acalabrutinib should be stored according to the instructions on the label that is affixed to the package of the drug product. Acalabrutinib will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative. Refer to the acalabrutinib IB for additional information regarding the drug products to be used in this trial.

Pembrolizumab

Pembrolizumab clinical supplies will be provided by the sponsor as summarized in Table 1.

Table 1 Pembrolizumab Clinical Supplies

Product Name and Potency	Dosage Form
MK-3475 50 mg	Lyophilized Powder for Injection
MK-3475 100 mg/ 4mL	Solution for Injection

Information on the formulation, packaging and storage of pembrolizumab is provided in the pembrolizumab Pharmacy Manual and the pembrolizumab (MK-3475) Investigator Brochure.

3.4.3 Administration of Study Drug

Investigators are prohibited from supplying acalabrutinib to any subjects not properly enrolled in this study. The investigator must ensure that subjects receive acalabrutinib or pembrolizumab only from personnel who fully understand the procedures for administering the drugs.

Acalabrutinib 100 mg is intended to be administered orally BID with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice and Seville orange juice due to CYP3A inhibition). Doses should be administered 12 hours apart (a window of ±1 hour is allowed). Acalabrutinib can be taken with or without food. The capsules should be swallowed intact. Subjects should not attempt to open capsules or dissolve them in water.

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

Guidance on co-administration of acalabrutinib with agents that affect gastric pH is provided in Section 3.10.7.

Pembrolizumab will be administered as a dose of 200 mg using a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes -5 minutes/ +10 minutes). Detailed information on preparation of pembrolizumab for infusion is provided in the pembrolizumab (MK-3475) Pharmacy Manual.

3.4.4 Assuring Subject Compliance

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

Pembrolizumab infusions will be administered only at the clinics per the study schedule. Missed doses of pembrolizumab should not be made up, with the next dose occurring in agreement with the original schedule (from the first dose of drug administered to the subject) for this agent (every 3 weeks).

Subject compliance with acalabrutinib dosing will be assessed at every visit. The subject will be instructed to bring the diary and any remaining capsules to the clinic at their next visit. The study staff will review the diary and ask the subject if all of the capsules were administered. Any remaining or returned capsules will be counted and recorded as

described in Section 7.6. Returned capsules must not be redispensed. Only a sufficient quantity of capsules will be dispensed to reach the next protocol-specified visit unless approved by the medical monitor. Subjects on treatment who are on yearly visits (see Appendix 5) may return to the clinic to receive a 6-month supply between yearly visits, if they are unable to get a 1-year supply at a time.

3.5 STUDY DRUG DOSING

Acalabrutinib 100 mg BID will be orally administered. Pembrolizumab 200 mg will be administered every 3 weeks by IV infusion. In Part 3, subjects with MF will receive a run-in of 6 weeks with acalabrutinib alone (100 mg BID). Subjects who are demonstrating a clinically meaningful response, in the opinion of the investigator, may continue on acalabrutinib monotherapy; those who are not will receive combination therapy with acalabrutinib (100 mg BID) and pembrolizumab (200 mg Q3W) as described above.

3.6 DURATION OF THERAPY

Subjects may continue to receive acalabrutinib treatment until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Treatment with acalabrutinib can continue until the end of trial, defined as 48 months after the last subject is enrolled. Subjects who are still on treatment at the end of the study and deriving clinical benefit from acalabrutinib treatment may continue treatment. At the time of the final data cutoff and database closure, subjects who remain in this study may be transitioned to a separate rollover study or remain within this study for continued access to study drug. Once all active subjects are eligible to continue to receive acalabrutinib and after database closure, this study would be considered closed. There will be no further data collection other than reporting of SAEs (see Section 6.2). Access within this study will enable continued treatment with visit assessments per standard of care, whereas the separate rollover study will enable treatment continuation with visit assessments and data collection per the rollover study protocol.

Treatment with pembrolizumab may continue for 24 months (103 weeks) from first dose of pembrolizumab provided subjects are tolerating the drug and not progressing. In addition, pembrolizumab treatment can end for subjects with confirmed CR (or sCR for MM) if treatment has been administered for at least 24 weeks and 2 doses of pembrolizumab have been administered after confirmation of CR/sCR. Subjects who have **confirmed**

progressive disease will come off treatment. Note: If there is uncertainty regarding whether there is cancer progression, the subject may continue study treatment and remain under close observation (e.g., evaluated at 4- to 8-week intervals) pending confirmation of progression. In particular, transient worsening of disease during temporary interruption of study therapy (e.g., for drug-related toxicity or intercurrent illness) may not indicate disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessments should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

3.7 ASSESSMENT OF DOSE-LIMITING TOXICITY

In Part 1 the first 6 subjects enrolled will be evaluated for DLT. The DLT review period is the first 6 weeks on treatment. A DLT will be defined as the occurrence of any of the following study-drug-related AEs (note: AEs clearly related to disease progression or the subject's current medical history and associated comorbidities will not be considered DLTs):

1. Any Grade ≥3 non-hematologic toxicity (except Grade 3 nausea, vomiting, or diarrhea that respond to supportive therapy)
2. Any of the following hematologic toxicities:
    a. Grade 4 neutropenia lasting >7 days.
    b. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion.
    c. Grade ≥3 febrile neutropenia (temperature ≥38.5°C).
    d. Grade 4 anemia, unexplained by underlying disease.
3. Dosing delay due to toxicity for >28 consecutive days.

3.8 DOSING DELAYS AND MODIFICATIONS

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate acalabrutinib- or pembrolizumab-related toxicity. If a subject experiences a treatment-related DLT or other intolerable AE during the course of therapy, then acalabrutinib, pembrolizumab, or both drugs should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree. In cases where pembrolizumab is held, pembrolizumab should be restarted in agreement with its original dosing schedule

(every 3 weeks). As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (e.g., once per week) until abnormalities have recovered to Grade ≤1.

Whenever possible, please discuss plans for delays or dose modifications with the medical monitor before implementation.

Note: Temporary withholding of study treatment for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.6 for more information on assessing disease progression under these circumstances.

3.8.1 Dose Modifications for Acalabrutinib

After the DLT review is cleared, the actions in Table 2 should be followed for the following toxicities:

- Grade 4 neutropenia (<500/μL) for >7 days (neutrophil growth factors are permitted per American Society of Clinical Oncology [ASCO] guidelines [Smith 2015] and use must be recorded on the case report form [CRF]).
- Grade 3 thrombocytopenia in presence of significant bleeding.
- Grade 4 thrombocytopenia.
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy.
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

Table 2 Drug Discontinuation Actions for Acalabrutinib

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

If acalabrutinib is reduced for apparent treatment-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of acalabrutinib for ≥28 days then the dose may be increased to the next higher dose level, at the discretion of the investigator. Such

re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not treatment-related. However, the maximum dose of acalabrutinib is 100 mg BID for this protocol.

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

For treatment-emergent hepatotoxicity in the combination arm only: Important guidelines for treatment-emergent hepatotoxicity are provided in Section 3.8.2 for pembrolizumab. In the combination arm, treatment with acalabrutinib should be withheld for Grade 3 or 4 hepatitis. For Grade 4 events, acalabrutinib may be restarted only after discussion with the medical monitor. For Grade 3 events, treatment with acalabrutinib can be considered after the liver function test (LFT) laboratory values have returned to Grade ≤1 or to baseline.

3.8.2 Dose Modifications and Toxicity Management for Immune-Related AEs Associated with Pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 3.

Table 3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General Instructions

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity Grade or Conditions (CTCAE v4.0)	Action Taken to Pembrolizumab	irAE Management with Corticosteroid and/or Other Therapies	Monitor and Follow-up
Pneumonitis	Grade 2	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of pneumonitis Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). Participants with Grade ≥2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Table 3	**Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab**			
Immune-related AEs	**Toxicity Grade or Conditions (CTCAE v4.0)**	**Action Taken to Pembrolizumab**	**irAE Management with Corticosteroid and/or Other Therapies**	**Monitor and Follow-up**
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	Initiate insulin replacement therapy for participants with T1DM Administer anti-hyperglycemic in participants with hyperglycemia	Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	Administer corticosteroids and initiate hormonal replacements as clinically indicated.	Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hypothyroidism	Grade 2 to 4	Continue	Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	Monitor for signs and symptoms of thyroid disorders.

Table 3	**Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab**			
Immune-related AEs	**Toxicity Grade or Conditions (CTCAE v4.0)**	**Action Taken to Pembrolizumab**	**irAE Management with Corticosteroid and/or Other Therapies**	**Monitor and Follow-up**
Nephritis and renal dysfunction	Grade 2	Withhold	Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper.	Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	Based on severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	Based on type and severity of AE administer corticosteroids	Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

a Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GI=gastrointestinal; irAE=immune-related AE; IV=intravenous; T1DM=Type 1 diabetes mellitus.

Note: For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to Grade ≤2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

3.8.3 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined below. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Section 3.8.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**
    - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3 to 4 (or recurrent Grade 2) events**, permanently discontinue pembrolizumab; immediately treat with IV steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Diarrhea/Colitis**

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider gastrointestinal consultation and endoscopy to confirm or rule out colitis.
    - For **Grade 2 diarrhea/colitis**, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis**, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or Grade ≥3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM or Grade 3 to 4** hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3 to 4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
- **Hypophysitis**
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3 to 4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Hyperthyroidism or Hypothyroidism**

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 2 to 4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g., propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3 to 4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**
    - For **Grade 2** events, treatment with pembrolizumab should be withheld. Administer corticosteroids (initial dose of 0.5 to 1 mg/kg/day prednisone or equivalent) (KEYTRUDA package insert). When LFT laboratory values resolve to baseline or return to Grade ≤1, then taper the corticosteroids over no fewer than 4 weeks while continuing to monitor LFTs at least weekly. Further treatment with pembrolizumab can be considered after the LFT laboratory values have returned to Grade ≤1 or to baseline either during the steroid taper or after stopping corticosteroids.
    - For **Grade 3 to 4** events, permanently discontinue pembrolizumab. Treat with corticosteroids (initial dose 1 to 2 mg/kg/day prednisone or equivalent) (KEYTRUDA package insert) until LFT laboratory values resolve to baseline or return to Grade ≤1, and then taper the corticosteroids over no fewer than 4 weeks while continuing to monitor LFTs at least weekly.
- **Renal Failure or Nephritis**
    - For **Grade 2** events, treat with corticosteroids.
    - For **Grade 3 to 4** events, treat with systemic corticosteroids.
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**
    - Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.
    - Table 4 shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 4 Infusion Reaction Treatment Guidelines [a]

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5 hours (±30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg po (or equivalent dose of antihistamine). • Acetaminophen 500 to 1000 mg po (or equivalent dose of antipyretic).

Table 4 Infusion Reaction Treatment Guidelines [a]

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics • Oxygen • Pressors • Corticosteroids • Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing

a Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.

IV=intravenous; NCI-CTCAE=National Cancer Institute–Common Terminology Criteria for Adverse Events; NSAIDS=nonsteroidal anti-inflammatory drugs; po=by mouth.

3.9 CONCOMITANT THERAPY

3.9.1 Permitted Concomitant Therapy

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

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

For subjects at risk for pneumonitis: In selected subjects (e.g., those with a history of recurrent pneumonias), anti-infectious prevention should be considered. Initiation of antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning before study drug administration may be warranted. Such support may also offer the benefit of reducing the risk for other bacterial infections (Stern 2014). Prophylaxis with IV immunoglobulins (IVIG) may be appropriate in subjects with

low Ig levels (Raanani 2009). Local practices or guidelines regarding infection prophylaxis may be followed.

For subjects at risk for infections: Bacterial/viral/fungal prophylaxis is allowed per institutional standards.

3.9.2 Guidelines for Use of CYP Inhibiting/Inducing Drugs

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, as discussed in Section 1.4.1, concomitant administration of acalabrutinib with a strong CYP3A inhibitor increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer has the potential to decrease acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors or inducers of CYP3A (see Appendix 2) should be avoided when possible. If a subject requires treatment with a strong/moderate CYP3A inhibitor or strong CYP3A inducer while on-study, follow the acalabrutinib treatment/dosing instructions described in Section 3.10.7 and monitor the subject closely for potential toxicities.

3.9.3 Guideline for Use of Drugs that Affect Gastric pH

The effect of agents that reduce gastric acidity (e.g., antacids or proton-pump inhibitors) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results from this completed study indicate that subjects should avoid the use of calcium carbonate containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib.

Use of omeprazole, esomeprazole, lansoprazole or any other proton pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib.

Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

3.9.4 Prohibited or Restricted Concomitant Therapy

Any chemotherapy, anticancer immunotherapy, corticosteroids (at dosages equivalent to prednisone >20 mg/day), warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon), experimental therapy, and radiotherapy are prohibited.

At study entry, subjects may be using topical or inhaled corticosteroids or low-dose steroids (≤10 mg of prednisone or equivalent per day) as therapy for comorbid conditions but use of corticosteroids as therapy of the lymphoid cancer is not permitted. During study participation, subjects may also receive systemic or enteric corticosteroids at any required dosage as needed for treatment-emergent immune-mediated adverse reactions associated with pembrolizumab therapy (see Section 3.8).

Live vaccines within 30 days before the first dose of trial treatment and while participating in the trial are prohibited. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., FLUMIST®) are live attenuated vaccines and are not allowed.

Use of calcium carbonate-containing drugs or supplements and short-acting H2-receptor antagonists should be avoided for at least 2 hours before or after acalabrutinib administration (see Section 3.10.7).For additional information on drugs with potential drug-drug interactions, refer to Section 3.10.7.

3.10 RISKS ASSOCIATED WITH STUDY TREATMENT

3.10.1 Risks Associated with Acalabrutinib

The following summarizes the experience with acalabrutinib in hematological cancer studies. Full details regarding the clinical safety of acalabrutinib are presented in the acalabrutinib IB.

3.10.1.1 Contraindications

No contraindications are known for acalabrutinib.

3.10.1.2 Warnings and Precautions

- **Hemorrhage**

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

Subjects receiving antithrombotic agents may be at increased risk of hemorrhage. Use caution with antithrombotic agents and consider additional monitoring for signs of bleeding when concomitant use is medically necessary. As a precaution, it is suggested that acalabrutinib be withheld for at least 3 days pre- and post-surgery (see Section 3.10.8).

Subjects with hemorrhage should be managed per institutional guidelines with supportive care and diagnostic evaluations or as clinically indicated.

- **Infections**

  Serious infections (bacterial, viral, and fungal), including fatal events, have occurred in clinical studies with acalabrutinib. The most frequent reported Grade ≥3 infection was pneumonia (preferred term). Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Consider prophylaxis in subjects who are at increased risk for opportunistic infections. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate.

  HBV reactivation and progressive multifocal leukoencephalopathy (PML) have occurred in clinical studies with acalabrutinib; see Section 3.10.5 and Section 4.1.14 for additional information and monitoring guidance for viral hepatitis, and see Section 3.10.3 for additional information and management guidance for signs and symptoms of PML.

- **Cytopenias**

  Treatment-emergent Grade 3 or 4 cytopenias, including neutropenia, anemia, and thrombocytopenia, have occurred in clinical studies with acalabrutinib. Blood counts should be monitored as specified in the Schedule of Assessments (Appendix 5 and Appendix 6) and as medically appropriate. Refer to Section 3.8 for study drug modification guidance. Subjects with cytopenias should be managed according to institutional guidelines with maximal supportive care and diagnostic evaluations as clinically indicated.

- **Second Primary Malignancies**

  Second primary malignancies, including solid tumors and skin cancers, have been reported in patients treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (basal cell carcinoma). Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a second primary malignancy should be managed according to institutional guidelines with diagnostic

evaluations as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the medical monitor. Please refer to Section 6.2.3 for second primary malignancy reporting guidance.

- **Atrial Fibrillation**

  Atrial fibrillation or flutter have occurred in clinical studies with acalabrutinib, particularly in subjects with cardiac risk factors, hypertension, diabetes mellitus, acute infections, and a previous history of atrial fibrillation. Monitor for symptoms of atrial fibrillation and atrial flutter (e.g., palpitations, dizziness, syncope, chest pain, dyspnea) and obtain an ECG as appropriate. Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluation as clinically indicated.

3.10.2 Risks Associated with Pembrolizumab

The following summarizes significant risks with pembrolizumab based on KEYTRUDA Prescribing Information Contraindications and Warnings & Precautions. For additional information, please refer to the KEYTRUDA Prescribing Information.

3.10.2.1 Contraindications

No contraindications are known for pembrolizumab.

3.10.2.2 Warnings and Precautions

- **Immune-Mediated Pneumonitis**

  Pembrolizumab can cause immune-mediated pneumonitis, including fatal cases. Monitor subjects for signs and symptoms of pneumonitis. Evaluate subjects with suspected pneumonitis with radiographic imaging and follow the treatment guidance in Section 3.8.3.

- **Immune-Mediated Colitis**

  Pembrolizumab can cause immune-mediated colitis. Monitor subjects for signs and symptoms of colitis and follow the treatment guidance in Section 3.8.3.

- **Immune-Mediated Hepatitis**

  Pembrolizumab can cause immune-mediated hepatitis. Monitor subjects for changes in liver function and follow the treatment guidance in Section 3.8.3.

- **Immune-Mediated Endocrinopathies**
    - Hypophysitis: Pembrolizumab can cause hypophysitis. Monitor subjects for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) and follow the treatment guidance in Section 3.8.3.
    - Thyroid disorders: Pembrolizumab can cause thyroid disorders, including hyperthyroidism, hypothyroidism and thyroiditis. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders, and follow the treatment guidance in Section 3.8.3.
    - Type 1 diabetes mellitus: Pembrolizumab can cause type 1 diabetes mellitus, including diabetic ketoacidosis. Monitor subjects for hyperglycemia or other signs and symptoms of diabetes and follow the treatment guidance in Section 3.8.3.

- **Immune-Mediated Nephritis and Renal Dysfunction**

  Pembrolizumab can cause immune-mediated nephritis. Monitor subjects for changes in renal function and follow the treatment guidance in Section 3.8.3.

- **Immune-Mediated Skin Adverse Reactions**

  Immune-mediated rashes, including Stevens-Johnson syndrome, toxic epidermal necrolysis (some cases with fatal outcome), exfoliative dermatitis, and bullous pemphigoid can occur. Monitor subjects for suspected severe skin reactions and exclude other causes. Based on the severity of the adverse reaction, withhold or permanently discontinue pembrolizumab and administer corticosteroids. For signs or symptoms of Stevens-Johnson syndrome or toxic epidermal necrolysis, withhold pembrolizumab and refer the subject for specialized care for assessment and treatment. If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue pembrolizumab.

- **Other Immune-Mediated Adverse Reactions**

  Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue in patients receiving pembrolizumab. While immune-mediated adverse reactions usually occur during treatment with PD-1/PD-L1 blocking antibodies, they may occur after discontinuation of treatment. For suspected immune-mediated adverse reactions, ensure adequate evaluation to confirm etiology or exclude other causes. Based on the severity of the adverse reaction, withhold pembrolizumab and administer corticosteroids. Upon improvement to Grade 1 or less, initiate corticosteroid

taper and continue to taper over at least 1 month. Based on limited data from clinical studies in subjects whose immune-related adverse reactions could not be controlled with corticosteroid use, administration of other systemic immunosuppressants can be considered. Resume pembrolizumab when the immune-mediated adverse reaction remains at Grade 1 or less following corticosteroid taper. Permanently discontinue pembrolizumab for any Grade 3 immune-mediated adverse reaction that recurs and for any life-threatening immune-mediated adverse reaction. In organ transplant recipients, consider the benefit of treatment with pembrolizumab versus the risk of possible organ rejection.

- **Infusion-Related Reactions**

  Pembrolizumab can cause severe or life-threatening infusion-related reactions, including hypersensitivity and anaphylaxis. Monitor subjects for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever. Follow the treatment guidance in Section 3.8.3.

- **Complications of Allogeneic HSCT**

  Allogeneic HSCT after treatment with pembrolizumab: Immune-mediated complications, including fatal events, occurred in patients who underwent HSCT after being treated with pembrolizumab. Monitor for hepatic veno-occlusive disease, Grade 3 or 4 acute graft-versus-host disease (GVHD) including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.

  Allogeneic HSCT prior to treatment with pembrolizumab: In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with pembrolizumab. Patients who experienced GVHD after their transplant procedure may be at increased risk for GVHD after treatment with pembrolizumab. In subjects with a history of allogeneic HSCT, consider the benefit of treatment with pembrolizumab versus the risk of GVHD.

- **Increased Mortality in Patients with Multiple Myeloma When Pembrolizumab is Added to a Thalidomide Analogue and Dexamethasone**

  Treatment of subjects with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

- **Embryo-Fetal Toxicity**

  Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. Advise women of reproductive potential of the potential risk to a fetus and to use effective method of contraception during treatment and for 120 days after the last dose of pembrolizumab (see Section 3.10.9).

3.10.3 Progressive Multifocal Leukoencephalopathy

Cases of PML have occurred in clinical studies with acalabrutinib. Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties. If PML is suspected, hold further treatment with acalabrutinib until PML is excluded. A diagnostic evaluation may include (but is not limited to):

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

If PML is confirmed, permanently discontinue acalabrutinib.

3.10.4 Transaminase Elevations for Acalabrutinib in Combination with Pembrolizumab

Serum transaminase elevations (including elevations of AST and/or ALT) may be increased in severity and frequency in subjects exposed to the combination of acalabrutinib and pembrolizumab, as compared with subjects exposed to pembrolizumab monotherapy and subjects exposed to acalabrutinib monotherapy. Routine monitoring for serum transaminase elevations must follow the Schedule of Assessments (serum chemistry laboratory assessments in Appendix 5 and Appendix 6). Dosing delays and modifications for subjects with serum transaminase elevations must follow guidance provided in Section 3.8.

3.10.5 Hepatitis B Reactivation

Cases of hepatitis B virus (HBV) reactivation have occurred in clinical studies with acalabrutinib. Therefore, subjects with a history of HBV infection should be monitored every 3 months with a quantitative PCR test for HBV DNA. Monitoring every 3 months should continue until 12 months after the last dose of acalabrutinib. Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation

with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

3.10.6 Dietary Restrictions

Acalabrutinib can be taken with or without food. Because acalabrutinib is metabolized by CYP3A, subjects should be strongly cautioned against excessive consumption of grapefruit, grapefruit juice, or Seville orange juice (which contain potent CYP3A inhibitors) or using herbal remedies or dietary supplements (in particular, St John's wort, which is a potent CYP3A inducer).

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

3.10.7 Drug-Drug Interactions

At the systemic exposure levels expected in this study, acalabrutinib inhibition of CYP metabolism is not anticipated. However, acalabrutinib is metabolized by CYP3A. Concomitant administration of acalabrutinib with a strong CYP3A and P-glycoprotein (P-gp) inhibitor, itraconazole increased exposure by approximately 5-fold. Conversely, concomitant administration of acalabrutinib with a strong CYP3A inducer, rifampin, decreases acalabrutinib exposure and could reduce efficacy. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A (see Appendix 2) should be avoided when possible.

If a subject requires short-term treatment with a strong or moderate CYP3A inhibitor (such as anti-infectives for up to 7 days), interrupt acalabrutinib treatment.

If a subject requires treatment with a strong CYP3A inducer, increase the acalabrutinib dose to 200 mg BID during concomitant administration with the strong inducer and return to recommended dose of 100 mg BID after stopping the strong CYP3A inducer. See Appendix 2 for a list of strong CYP3A inhibitors/inducers.

Based on these considerations, subjects who require therapy with drugs listed in Appendix 2 should not be enrolled into the study. If medically justified, subjects may be enrolled if such inhibitors or inducers can be discontinued or alternative drugs that do not affect these enzymes can be substituted within 7 days before first dose of study drug. If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential drug-related toxicities.

The effect of agents that reduce gastric acidity (e.g., antacids or proton-pump inhibitors,) on acalabrutinib absorption was evaluated in a healthy volunteer study (ACE-HV-004). Results

from this completed study suggest subjects should avoid the use of calcium carbonate-containing drugs or supplements for a period of at least 2 hours before and at least 2 hours after taking acalabrutinib.

Use of omeprazole, lansoprazole or esomeprazole or any other proton-pump inhibitors while taking acalabrutinib is not recommended due to a potential decrease in study drug exposure. However, the decision to treat with proton-pump inhibitors during the study is at the investigator's discretion, with an understanding of the potential benefit to the subject's gastrointestinal condition and a potential risk of decreased exposure to acalabrutinib.

Although the effect of H2-receptor antagonists (such as famotidine or ranitidine) on acalabrutinib absorption has not been evaluated, if treatment with an H2-receptor antagonist is required, the H2-receptor antagonist should be taken approximately 2 hours after an acalabrutinib dose.

No formal PK drug interaction studies have been conducted with pembrolizumab.

3.10.8 Surgery

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

3.10.9 Reproductive Toxicity

3.10.9.1 Reproductive Toxicity Summaries for Study Drugs

Acalabrutinib

Acalabrutinib has been evaluated in a combined definitive fertility and embryofetal development (EFD) study in rats. Effects of acalabrutinib on embryofetal development was also evaluated in a definitive EFD study in rabbits. No effects on fertility or EFD were observed in rats at exposures 16 times the human exposure at the recommended dose. In rabbits, acalabrutinib was not teratogenic at any dose level. Decreased fetal body weight and delayed ossification were observed at exposure levels that produced maternal toxicity, which were approximately 4-fold greater than the human exposure levels at the recommended dose. Refer to the current acalabrutinib IB for further details.

There has been one reported pregnancy in a subject exposed to acalabrutinib; the subject was exposed during the first trimester. Acalabrutinib was discontinued, and the subject gave birth to a live, full-term male infant by cesarean section.

The potential for acalabrutinib to be excreted in breast milk of nursing mothers is unknown. In studies of lactating rats, acalabrutinib and its metabolite ACP-5862 were measured in milk and in the plasma of nursing pups on Postnatal Day 12.

There have been no positive genotoxicity findings during development of acalabrutinib. In addition, based on modeled estimates of fetal exposures to active product ingredient levels in ejaculated material using assumptions for small molecules, direct embryofetal exposure (i.e., female partner exposure following a vaginal dose of estimated seminal concentration) and male-mediated developmental risk with acalabrutinib treatment is considered to be very low, and risk mitigation measures for male-mediated developmental risk are therefore not required for acalabrutinib.

Pembrolizumab

Based on its mechanism of action, pembrolizumab can cause fetal harm when administered to a pregnant woman. There are no available human data informing the risk of embryo-fetal toxicity. In animal models, the PD-1/PD-L1 signaling pathway is important in the maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue (see KEYTRUDA Prescribing Information). Human IgG4 (immunoglobulins) are known to cross the placenta; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing fetus.

3.10.9.2 Guidance and Definitions

Guidance

For acalabrutinib: Women of childbearing potential (WOCBP) must use highly effective forms of contraception while in the study and for 2 days after the last dose of acalabrutinib. For male subjects with a pregnant or non-pregnant WOCBP partner, no contraception measures or restrictions are required with regard to acalabrutinib. Contraception measures and restrictions on sperm donation are not required for male subjects who are treated with acalabrutinib only.

For pembrolizumab: WOCBP must use highly effective forms of contraception while in the study and for 120 days after the last dose of pembrolizumab. Male subjects must use highly effective forms of contraception with the addition of a barrier method (condom) during the study and for 120 days after the last dose of pembrolizumab. Even with medical confirmation of vasectomy surgical success, vasectomized male subjects should still use a barrier method (condom) with WOCBP partners during the same timeframe, to prevent possible direct exposure

of a developing fetus to pembrolizumab in seminal fluid. Sperm donation is not permitted during the same timeframe.

Subjects in clinical studies should promptly notify the investigator if they or their partner become pregnant during the study or within 2 days after the last dose of acalabrutinib, or 120 days after the last dose of pembrolizumab, whichever is longer. If a female subject becomes pregnant during the treatment period, she must discontinue acalabrutinib. Pregnancy in a subject or a male subject's partner must be reported as outlined in Section 6.2.4.

Definitions for WOCBP and for Subjects of Non-Reproductive Potential

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

Women will be considered of non-reproductive potential if they meet any of the following criteria:

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

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

Definition for Highly Effective Methods of Contraception

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

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injectable, or implantable

- Intrauterine device (IUD) or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomy of a female subject's sole male partner (with medical assessment and confirmation of vasectomy surgical success)
- Sexual abstinence (only if refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)

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

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

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

3.10.10 Overdose Instructions

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an AE unless it results in untoward medical effects. Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF. All AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

For any subject experiencing an acalabrutinib overdose, observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose

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

There is no information on over dosage with KEYTRUDA (refer to KEYTRUDA Prescribing Information).

3.11 WITHDRAWAL OF SUBJECTS FROM STUDY TREATMENT

Subjects may be withdrawn from study treatment for the following reasons:

- Progressive disease
- Completed treatment
- Start of alternative anticancer therapy
- Pregnancy
- Adverse event
- Investigator decision
- Subject's withdrawal of consent from the study
- Decision by sponsor to terminate the study
- Subject lost to follow-up
- Death
- Other

3.12 REASONS FOR STUDY EXIT

Reasons for study exit are:

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

3.13 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's pharmacovigilance procedures. AEs and SAEs will be reviewed internally on an ongoing basis to identify safety concerns.

Periodic conference calls with the investigators and applicable site staff will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (i.e., AEs leading to dose reductions, related SAEs, and deaths). In addition, in Part 1, a mandatory safety teleconference will occur before Part 1 is expanded to up to 24 subjects. In Part 2, teleconferences with investigators and applicable site staff will be conducted or written communications sent to discuss study progress, obtain investigator feedback and exchange, and discuss “significant safety events” (i.e., AEs leading to dose reductions, related SAEs, and deaths) on an as needed basis.

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 5 for Parts 1 and 2, and Appendix 6 for Part 3. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.4.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. This study will primarily use central laboratory testing for safety laboratory evaluations. Samples from sites’ local laboratories will be used if central laboratory testing is unavailable.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

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

4.1.2 Medical History

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

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1. The AE reporting period is described in Section 6.2.1. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

Document all concomitant medications and procedures from within 28 days before the start of study drug administration through 30 days after the last dose of study drug.

For subjects with MF, record all transfusions of blood products (e.g., red blood cells or platelets) within 12 weeks before the first study dose and throughout the study period.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed as described in Section 3.3. All screening procedures, unless otherwise indicated, should be completed within 28 days of the first dose of study drug.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 1.

4.1.7 Physical Examination, Vital Signs, Height, and Weight

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

Physical examinations will be done during the treatment period and at the safety follow-up visits. For all subjects except those with MM or MF, the following B symptoms will be collected at each examination:

- Unintentional weight loss of normal body weight over a period of ≤6 months
- Disease-associated intermittent fevers ≥38°C
- Drenching sweats, especially at night

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

4.1.8 Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at screening or up to 60 days before the first dose of study drugs for all subjects. Per the current response criteria (Bladé 1998; Durie 2006; Hallek 2008; Owen 2013; Tefferi 2013; Cheson 2014), a bone marrow aspirate/biopsy will also be required at any time on study to confirm a CR, and may be used to confirm a PR in some cases (see Section 4.2). A bone marrow aspirate and biopsy will also be done at Week 52 and as clinically indicated. Note that the Tefferi criteria for response in MF (see Table 9) require that, for all response categories, the benefit must last for ≥12 weeks to qualify as a response; thus, a second bone marrow evaluation must be done ≥12 weeks later to confirm CR or bone marrow PR response. For subjects with MF it might only be possible to obtain a bone marrow biopsy as sometimes excessive fibrosis prevents bone marrow aspiration. Bone marrow testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's Form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

With subject consent, biomarker and correlative studies on excess bone marrow (if available) will be done by the sponsor or designee; per the protocol, bone marrow will be collected at screening, on study, and at Week 52. Refer to the study manual for sample handling and shipment instructions.

4.1.9 Electrocardiogram

Subjects should be in supine position and resting for at least 10 minutes before the Screening ECG. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing.

4.1.10 Urine or Serum Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. Women of childbearing potential must have a negative urine or serum pregnancy testing within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.11 Hematology

Hematology studies must include complete blood count (CBC) with peripheral blood smear and differential, including, but not limited to white blood cell (WBC) count, hemoglobin, hematocrit,

platelet count, ANC, and absolute lymphocyte count (ALC). Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.12 Serum Chemistry

Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine, c-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (i.e., calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.13 Thyroid Panel

The thyroid panel will include total triiodothyronine (T3), free thyroxine (T4), and thyroid stimulating hormone (TSH). Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.14 Hepatitis B and C Testing

Hepatitis serology testing must include HBsAg, hepatitis B surface antibody (anti-HBs), anti-HBc, and hepatitis C antibody. In addition, any subjects testing positive for any hepatitis serology must have PCR testing during screening and on study (see Appendix 5 and Appendix 6 and exclusion criterion #30). Testing will be done by a local or central laboratory.

Subjects who are anti-HBc positive (or have a known history of HBV) should have quantitative PCR testing for HBV DNA performed during screening and every 3 months as described in Section 3.10.5. Following study drug discontinuation, monitoring should continue every 3 months until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Because IVIGs may cause false positive hepatitis serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. Additional PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

Subjects with a known history of hepatitis C or who are hepatitis C antibody-positive should have quantitative PCR test for HCV DNA performed during screening and at Weeks 13 and 25. No further testing beyond Week 25 is necessary if PCR results are negative.

Refer to Section 3.10.5, Appendix 5, and Appendix 6 regarding monitoring of subjects who are anti-HBc positive or hepatitis C antibody-positive, or who have a known history of HBV or HCV infection.

4.1.15 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, N-terminal telopeptide, protein, blood, and glucose. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.16 T/B/NK Cell Count

Flow cytometry testing for CD3+, CD4+, CD8+, CD19+, and CD16/56+ cells. Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.17 Serum Immunoglobulin

Testing for IgG, IgM, and IgA will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.18 Disease Markers for Subjects with MM, WM, and MF

MM Subjects

Testing for serum M-protein levels (by serum protein electrophoresis [SPEP] and serum immunofixation electrophoresis [SIFE]), serum-free light chains (SFLC), urine M-protein levels (by urine serum protein electrophoresis [UPEP] and urine immunofixation electrophoresis [UIFE]), and serum β2-microglobulin will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

WM Subjects

Serum M-protein levels (by SPEP and SIFE) will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

MF Subjects

Molecular disease markers (Janus kinase 2 [JAK2], calreticulin [CAL-R], and Additional Sex Combs-Like 1 [ASXL1]) to be done at baseline and repeated as clinically indicated (at the

investigator's discretion) to assess molecular response (see Section 4.2). Testing will be done by a local or central laboratory as listed on the investigator's Form FDA 1572.

4.1.19 Skeletal Survey for MM Subjects

Standard lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femur, and humerus are required at screening or baseline (i.e., before the first dose of study drug), at Week 52, and as clinically indicated. Radiographic imaging and analysis will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's Form FDA 1572.

4.1.20 Pharmacodynamics and Biomarker Studies

CCI

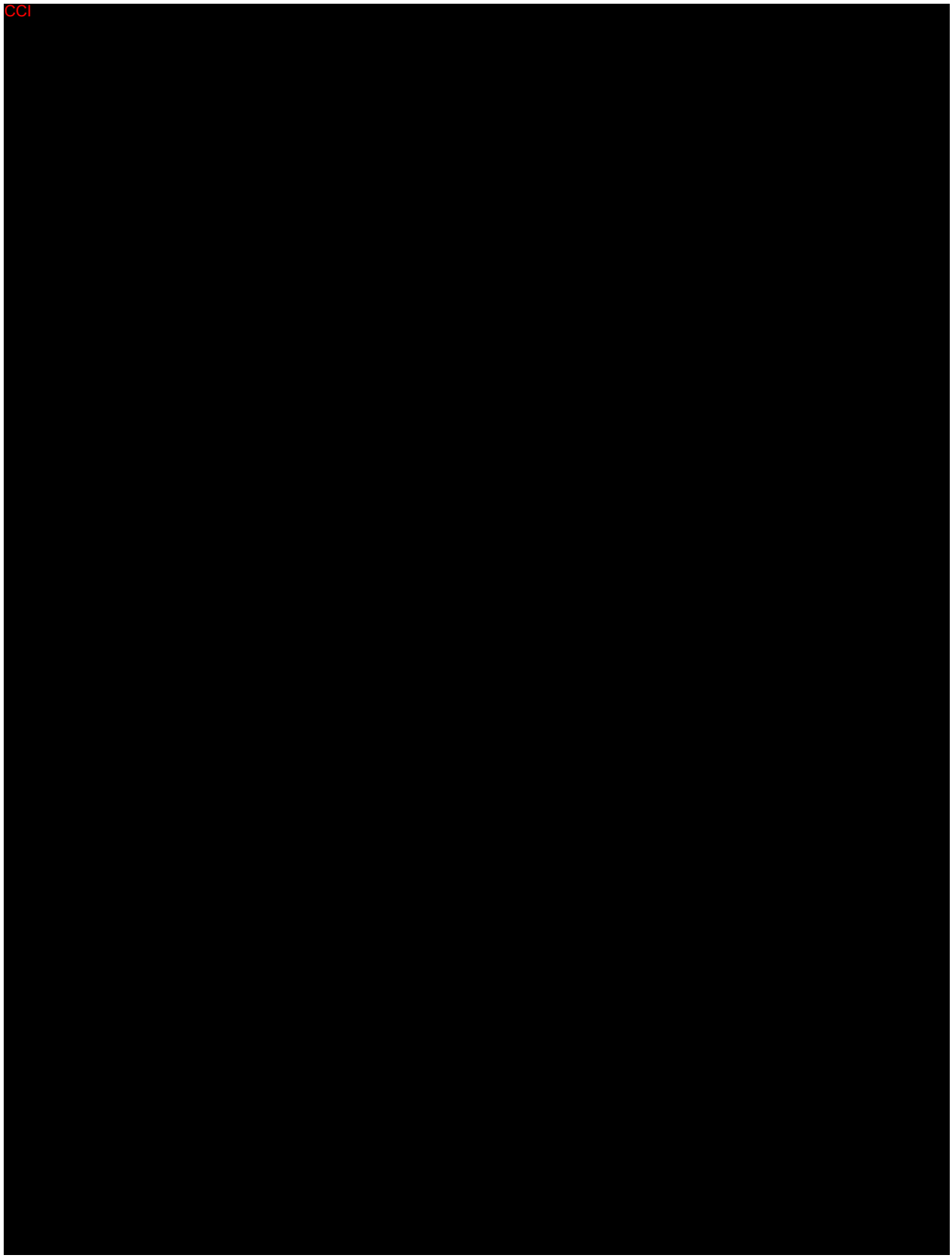
[redacted]

4.1.21 CCI

CCI

[redacted]

CCI



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[redacted]

4.1.22 Follow-up Post Allogenic Stem Cell Transplant

For subjects who have an allogeneic stem cell transplant (SCT) within 24 months of last dose of pembrolizumab, transplant parameters will be collected, and specific events will be collected for 18 months from the date of the allogeneic transplant, to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the investigator's discretion. If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

4.1.23 Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score

MPN-SAF TSS will be assessed for subjects with MF (Part 3 only) on the same schedule as MRI/CT scans (i.e., at the end of Week 6, end of Week 15, end of Week 24, every 9 weeks through Week 52, and every 12 weeks thereafter, or more frequently at investigator discretion). Please refer to the MPN-SAF TSS Manual for this study for instructions on administering this questionnaire.

4.1.24 Early Termination Visit

An early termination visit is required for safety assessments as outlined in the Schedules of Assessments (see Appendix 5 and Appendix 6). The early termination visit is not required for subjects who discontinue from the study within 10 days after a scheduled study visit.

4.1.25 Study Drug Accountability

See Section 7.6.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

The investigator must rate the response of the subjects as outlined below:

- NHL, Hodgkin lymphoma, or RS refer to Table 5
- CLL/SLL refer to Table 6
- WM refer to Table 7
- MM refer to Table 8
- MF refer to Table 9

Table 5 Response Assessment Criteria for Lymphoma

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

Table 5 Response Assessment Criteria for Lymphoma

Response and Site	PET-CT-Based Response	CT-Based Response
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least one of the following
Individual target nodes/nodal masses	Score 4 or 5 with increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase

Table 5 Response Assessment Criteria for Lymphoma

Response and Site	PET-CT-Based Response	CT-Based Response
		by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Cheson 2014.

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

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

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

Table 6 Response Assessment Criteria for CLL/SLL

Response	Lymphocytes	Bone Marrow	Physical Examination [b] (Nodes, Liver, Spleen)	Peripheral Blood
CR [a]	Lymphocytes <4×10^9/L	Normocellular <30% lymphocytes No B-lymphoid nodules	Normal (e.g., no lymph nodes >1.5 cm)	ANC >1.5×10^9/L [c] Platelets >100×10^9/L [c] Hemoglobin >11.0 g/dL (untransfused) [b]
CRi	Lymphocytes <4×10^9/L	Hypocellular <30% lymphocytes	Normal (e.g., no lymph nodes >1.5 cm)	Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity
nPR	CR with the presence of lymphoid nodules in the bone marrow which reflect residual disease			
PR [a]	Lymphocytes <5×10^9/L Or ≥50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy [d] and/or in spleen or liver enlargement	ANC >1.5×10^9/L Or Platelets >100×10^9/L or ≥50% improvement over baseline [b] Or Hemoglobin >11.0 g/dL or ≥50% improvement over baseline (untransfused) [c]
PRL [a]	Lymphocytes ≥5×10^9/L And <50% decrease from baseline	Not assessed	≥50% reduction in lymphadenopathy [d] and/or in spleen or liver enlargement	ANC >1.5×10^9/L Or Platelets >100×10^9/L or ≥50% improvement over baseline [c] Or Hemoglobin >11.0 g/dL or ≥50% improvement over baseline (untransfused) [c]

Table 6 Response Assessment Criteria for CLL/SLL

Response	Lymphocytes	Bone Marrow	Physical Examination [b] (Nodes, Liver, Spleen)	Peripheral Blood
SD	Absence of PD and failure to achieve at least a PR			
PD [a]	Lymphocytes ≥50% increase over baseline	Not assessed (except to confirm PD as assessed by progressive cytopenias)	Appearance of any new lesion or de novo appearance of hepatomegaly or splenomegaly Or Increase ≥50% in lymphadenopathy Or Increase ≥50% in hepatomegaly Or Increase ≥50% in splenomegaly	Platelets decrease of ≥50% from baseline secondary to CLL or <100,000 µL and worsening bone marrow due to CLL Or Hemoglobin decrease of >2 g/dL from baseline secondary to CLL or decrease to <100 g/L and worsening bone marrow due to CLL

Modified From Hallek 2008.

ANC=absolute neutrophil count; CLL= chronic lymphocytic leukemia; CR=complete remission (response); CRi=CR with incomplete bone marrow recovery; nPR=nodular partial response; PD=progressive disease; PR=partial remission (response); PRL=partial remission (response) with lymphocytosis; SD=stable disease.

a CR: all of the above CR criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR: at least two of the above PR criteria for lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes plus one of the criteria for ANC, platelets or hemoglobin have to be met; PRL: presence of lymphocytosis, plus ≥50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for ANC, platelets or hemoglobin have to be met; PD: at least one of the above PD criteria has to be met or transformation to a more aggressive histology (e.g., Richter's syndrome). For PD as assessed by progressive cytopenias, a bone marrow biopsy is required for confirmation. Note: Isolated elevation of treatment-related lymphocytosis by itself will not be considered PD unless patient becomes symptomatic from this per Cheson 2012.

b Computed tomography (CT) scan of abdomen, pelvis, and thorax may be used if previously abnormal.

c Without need for exogenous growth factors.

d In the sum products of ≤6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes.

Table 7 Response Assessment Criteria for WM

Response	Definition
Complete response (CR)	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	• Monoclonal IgM protein is detectable • ≥90% reduction in serum IgM level from baseline [a] • Complete resolution of extramedullary disease i.e., lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Partial response (PR)	• Monoclonal IgM protein is detectable • ≥50% but <90% reduction in serum monoclonal IgM level from baseline [a] • Reduction in extramedullary disease i.e., lymphadenopathy/splenomegaly if present at baseline • No new signs for symptoms of active disease
Minor response (MR)	• Monoclonal IgM protein is detectable • ≥25% but <50% reduction in serum monoclonal IgM level from baseline [a] • No new signs for symptoms of active disease
Stable disease (SD)	• Monoclonal IgM protein is detectable • <25% reduction and <25% increase in serum monoclonal IgM level from baseline* • No progression in extramedullary disease i.e., lymphadenopathy/splenomegaly • No new signs for symptoms of active disease
Progressive disease	• ≥25% increase in serum IgM level [a] from lowest nadir (requires confirmation on ≥2 consecutive measurements at least 4 weeks apart). AND • Progression of clinical features attributable to the disease per Owen 2013.

Owen 2013.

IgM=immunoglobulin M; WM=Waldenström macroglobulinemia.

a Sequential changes in IgM levels may be determined either by M protein quantitation or total serum IgM quantitation by nephelometry.

Table 8 Response Criteria for MM (incorporating EBMT and IMWG)

Response Subcategory	Response Criteria[a]
Complete response (CR)	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • <5% plasma cells in bone marrow[b].
Stringent complete response (sCR)	• CR as defined above plus • Normal FLC ratio and • Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c].
Near complete response (nCR)	• Meeting the criteria for CR, except that the persistence of original monoclonal protein by immunofixation while absence of monoclonal protein on serum or urine protein electrophoresis.
Very good partial response (VGPR)	• Serum and urine M-component detectable by immunofixation but not on electrophoresis or • ≥90% reduction in serum M-component plus urine M-component <100 mg/24 h.
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg/24 h • If the serum and urine M-protein are unmeasurable at baseline, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are unmeasurable at baseline, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
Minor response (MR)	• MR includes subjects in whom some, but not all, criteria for PR are fulfilled providing the remaining criteria satisfy the requirements for MR. • Requires all of the following: o ≥25% to ≤49% reduction in the level of serum monoclonal protein for ≥2 determinations 6 weeks apart. o If present, a 50% to 89% reduction in 24-hour light chain excretion, which still exceeds 200 mg/24 h, for ≥2 determinations 6 weeks apart. o 25% to 49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for ≥6 weeks. o No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease - SD (not recommended for use as an indicator of response; stability of disease is best described by providing the	• Not meeting criteria for CR, VGPR, MR, PR or progressive disease

Table 8 Response Criteria for MM (incorporating EBMT and IMWG)

Response Subcategory	**Response Criteria[a]**
time to progression estimates)	
Progression Subcategory	**Progression Criteria[d]**
Progressive disease[a] — To be used for calculation of duration of response and progression-free survival end points for all subjects including those in CR (includes primary progressive disease and disease progression on or off therapy)[g]	Laboratory or biochemical relapse or progressive disease: requires the occurrence of ≥1 of any of the following: • Increase of ≥25% from lowest response value in serum M-component and/or (the absolute increase must be ≥0.5 g/dL)[e]. • Urine M-component and/or (the absolute increase must be ≥200 mg/24 h). • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL. • Bone marrow plasma cell percentage: the absolute % must be ≥10%[f]. • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

EBMT: Bladé 1998; IMWG: Durie 2006.

EBMT=European Group for Blood and Marrow Transplant; FLC=(serum) free light chains; IMWG=International Myeloma Working Group; MM=multiple myeloma.

Note: * Note clarification to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such subjects is defined as a >90% decrease in the difference between involved and uninvolved free light chain FLC levels

a. All response categories require 2 consecutive assessments made at ≥4 weeks after the start of study therapy and any time before the institution of any new therapy after study therapy; CR and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
b. Confirmation with repeat bone marrow biopsy not needed
c. Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.
d. All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.
e. For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
f. Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
g. For purposes of calculating time to progression and progression-free survival, CR subjects should also be evaluated using criteria listed above for progressive disease.

Table 9 Response Assessment Criteria for MF

Response Categories	Required Criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)
Complete response (CR)	• Bone marrow:* Age-adjusted normocellularity; <5% blasts; Grade ≤1 MF† and • Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1×10^9/L and <UNL; • Platelet count ≥100×10^9/L and <UNL; <2% immature myeloid cells‡ and • Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Partial response (PR)	• Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1×10^9/L and <UNL; platelet count ≥100×10^9/L and <UNL; <2% immature myeloid cells‡ and • Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or • Bone marrow:* Age-adjusted normocellularity; <5% blasts; Grade <1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1×10^9/L and <UNL; platelet count ≥50, but <100×10^9/L and <UNL; <2% immature myeloid cells‡ and • Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	• The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	• Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level‖ • Transfusion-dependent patients: becoming transfusion-independent{
Spleen response	• A baseline splenomegaly that is palpable at 5 to 10 cm, below the LCM, becomes not palpable# or • A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≤50%# • A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response • A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction**
Symptoms response	• A ≥50% reduction in the MPN-SAF TSS††

Table 9 Response Assessment Criteria for MF

Response Categories	Required Criteria (for all response categories, benefit must last for ≥12 weeks to qualify as a response)
Progressive disease	• Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or‡‡ • A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or‡‡ • A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or‡‡ • Leukemic transformation confirmed by a bone marrow blast count of ≥20% or • A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1×10^9/L that lasts for at least 2 weeks
Stable disease	• Belonging to none of the above listed response categories
Relapse	• No longer meeting criteria for at least CI after achieving CR, PR, or CI, or • Loss of anemia response persisting for at least 1 month or • Loss of spleen response persisting for at least 1 month
Recommendations for assessing treatment-induced cytogenetic and molecular changes	
Cytogenetic remission	• At least 10 metaphases must be analyzed for cytogenetic response evaluation and • requires confirmation by repeat testing within 6 months window • CR: eradication of a pre-existing abnormality • PR: ≥50% reduction in abnormal metaphases • (partial response applies only to patients with at least ten abnormal metaphases at baseline)
Molecular remission	• Molecular response evaluation must be analyzed in peripheral blood granulocytes and • requires confirmation by repeat testing within 6 months window • CR: Eradication of a pre-existing abnormality • PR: ≥50% decrease in allele burden • (partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/ molecular relapse	• Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

Tefferi 2013.

EMH=extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM=left costal margin; UNL=upper normal limit.

* Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

† Grading of MF is according to the European classification
Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;90:1128.

It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis.
It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

‡ Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

§ See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25 000×10^9/L and absolute neutrophil count of ≥0.5×10^9/L.

|| Applicable only to patients with baseline hemoglobin of <100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

{ Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive “rolling” 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

** Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

†† Symptoms are evaluated by the MPN-SAF TSS (Emanuel 2012). The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡ Progressive disease assignment for splenomegaly requires confirmation my MRI or computed tomography showing a ≥25% increase in spleen volume from baseline.

Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

4.3 SAFETY FOLLOW-UP VISIT

Each subject should be followed for 30 days (+7) after his or her last dose of study drug (i.e., the “safety follow-up visit”) to monitor for resolution or progression of AEs (see Section 6.2.7) and to document the occurrence of any new events, regardless of whether the subject receives a new anticancer therapy or demonstrates disease progression within this timeframe; after this period, investigators should report SAEs or other AEs of concern that are believed to be related to prior treatment with acalabrutinib (see Section 6.2.1). Subjects who withdraw consent for study treatment should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated if subject consent for further study participation is withdrawn. The Schedules of Assessments (Appendix 5 and Appendix 6) describe the procedures required for safety follow-up.

4.4 TIME-TO-NEXT TREATMENT AND SURVIVAL

Subjects who discontinue study therapy will continue to be followed for assessment of time-to-next therapy unless they withdraw consent for further follow-up. After discontinuing study therapy, subjects will also be contacted approximately every 12 weeks until death, withdrawal of consent by subject, loss to follow-up, or study termination by the sponsor, whichever comes first.

4.5 MISSED EVALUATIONS

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

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions and CIs for discrete variables) will be used to summarize data as appropriate. As appropriate, analyses will be performed by cancer type or overall. Depending on Part 1 and the number of expansion cohorts opened in Parts 2 and 3, a total of 6 to 324 evaluable subjects will be enrolled in this study. Under Amendment 4 of this protocol, the planned total enrollment was approximately 160 evaluable subjects; enrollment was closed in May 2017 with a total of 161 evaluable subjects.

5.2 SAMPLE SIZE JUSTIFICATION

In Part 1 (DLT review), enrollment of 6 subjects for DLT review is consistent with sample sizes used in oncology studies for determination of MTD. The trial employs the standard National Cancer Institute definition of MTD (dose associated with DLT in <33.3% of subjects). Provided ≤1 DLT occurs during the DLT review, then expansion will occur in Part 1 to include up to 24 subjects in a select group of histologies (as described in Section 3.0). The safety and preliminary efficacy results from Part 1 will be used to determine opening Part 2 and Part 3 of the protocol.

In Part 2 (expansion groups), enrollment of 30 subjects per group offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in the selected tumor types. An ORR of ≥20% is considered the minimum value of potential interest in each of

the selected indications. If <2 subjects per cohort experience an objective response, the probability is >0.90 that an ORR of ≥20% will be excluded for that cancer. If 2 subjects in a group experience an objective response, the upper bound of a 1-sided exact binomial 90% CI=16.8%.

In Part 3, safety and response data will be reviewed after the initial 12 subjects have completed 24 weeks of treatment (i.e., the Week 25 visit) or have discontinued treatment before Week 25. The first 12 subjects will be evaluated regardless of the length of treatment with acalabrutinib alone or in combination with pembrolizumab. If <2 subjects who received acalabrutinib monotherapy or the combination with pembrolizumab have achieved a response of "clinical improvement" or better (see Table 9), the MF group will not be expanded. The decision to expand the study is multifactorial and needs to take into consideration the nature and quality of response, safety, and evolving competitive landscape. If the safety and response data indicate that further evaluation is warranted, up to 18 additional subjects with MF (for a total of up to 30 subjects) will be treated on the same adaptive regimen as was given to the first 12 subjects.

Table 10 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of all possible values for the observed response rate in the initial group of 12 subjects.

Table 10 Two-Sided Exact 90% CIs for Response Rate in Initial Group in Part 3 (N=12)

Responses, n	Response Rate, %	90%CI	
		Lower Bound	Upper Bound
0	0%	0%	22%
1	8%	0%	34%
2	17%	3%	44%
3	25%	7%	53%
4	33%	12%	61%
5	42%	18%	68%
6	50%	25%	75%
7	58%	32%	82%
8	67%	39%	88%
9	75%	47%	93%
10	83%	56%	97%
11	92%	66%	100%
12	100%	78%	100%

CI=confidence interval.

If the MF group is expanded, enrollment of 30 subjects offers the opportunity to determine if there is sufficient antitumor activity to warrant further development in MF. A response rate

(clinical improvement, PR, or CR) of ≥25% within the sample size of 30 subjects with MF is considered the minimum value of potential interest in this highly unmet medical need population of MF patients with thrombocytopenia or anemia. To reject the null hypothesis of response rate ≤5% in favor of an alternative hypothesis that the response rate is ≥25%, 30 subjects will preserve approximately 90% power to detect the difference at a 0.05 level of significance by 1-sided exact test for single proportion.

Considering the planned expansion cohort size of 30 subjects, Table 11 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of all possible values for the observed response rate.

Table 11 Two-Sided Exact 90% CIs for Response Rate in Expansion Cohorts in Part 2 and Part 3 (N=30)

Responses, n	Response Rate, %	90%CI	
		Lower Bound	Upper Bound
0	0%	0%	10%
1	3%	0%	15%
2	7%	1%	20%
3	10%	3%	24%
4	13%	5%	28%
5	17%	7%	32%
6	20%	9%	36%
7	23%	11%	39%
8	27%	14%	43%
9	30%	17%	47%
10	33%	19%	50%
11	37%	22%	53%
12	40%	25%	57%
13	43%	28%	60%
14	47%	31%	63%
15	50%	34%	66%
16	53%	37%	69%
17	57%	40%	72%
18	60%	43%	75%
19	63%	47%	78%
20	67%	50%	81%
21	70%	53%	83%
22	73%	57%	86%
23	77%	61%	89%
24	80%	64%	91%
25	83%	68%	93%
26	87%	72%	95%
27	90%	76%	97%
28	93%	80%	99%
29	97%	85%	100%
30	100%	90%	100%

CI=confidence interval.

5.3 DEFINITION OF ANALYSIS POPULATIONS

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

- **All-**treated **population:** All enrolled subjects who receive ≥1 dose of any study drug (either acalabrutinib or pembrolizumab). The safety analyses and primary efficacy analyses will be performed on the All-treated population.

- **Efficacy-**evaluable **population**: All subjects in the All-treated population who have ≥1 evaluable response assessment after the first dose of study drug (either acalabrutinib or pembrolizumab). Sensitivity analyses for efficacy will be carried out on the Efficacy-evaluable population.
- **PD** analysis **population**: A subset of subjects from the All-treated population who have sufficient baseline measurements and undergo ≥1 PD assessment after treatment. This analysis set will be used for PD parameters.

5.4 MISSING DATA HANDLING

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

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Safety Endpoint

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

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

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

5.5.2 Demographics and Baseline Characteristics

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

5.5.3 Study Treatment Administration and Compliance

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

For each subject, acalabrutinib and pembrolizumab compliance will be described in terms of the relative dose intensity.

5.5.4 Analysis of Efficacy Parameters

Response Rate

The individual and composite endpoints of response and progression will be determined. Tumor control will be documented at each assessment by response category (see Section 4.2) as defined for each response parameter, date that response is first documented, and date of disease progression.

ORR will be defined as the proportion of subjects who achieve a response of PR or CR (see Section 4.2). For Part 3 subjects with MF, ORR will be defined as the proportion of subjects who achieve a response of clinical improvement or better (clinical improvement, PR, or CR) as shown in Table 9. ORR will be calculated and the corresponding exact 2-sided 90% and 95% CIs will be derived.

In addition, for subjects with CLL/SLL in Parts 1 and 2, a response will be assessed according to Table 6, which reflects modified International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include PRL. For the purpose of this analysis, lymphocytosis at a given timepoint will be defined as absolute lymphocyte count which is above normal limits and is not ≥50% decreased from baseline.

For Part 3 subjects with MF, an additional analysis will evaluate response when defined as CR + PR only. A descriptive analysis will be done on the subgroups of subjects with MF who receive acalabrutinib alone or the combination of acalabrutinib and pembrolizumab.

Duration of Response

The duration of overall response defined as the interval from the first documentation of response to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects

will be censored and detailed censoring rules will be specified in the statistical analysis plan (SAP).

Progression-free Survival

Progression-free survival is defined as the interval from the first dose date of acalabrutinib or pembrolizumab to the earlier of the first documentation of objective disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quartiles (including the median). Data from surviving, non-progressing subjects will be censored, and detailed censoring rules will be specified in the SAP.

Time-to-Next Treatment

Time-to-next treatment defined as the time from the first dose date of acalabrutinib or pembrolizumab to the start of the next treatment other than the study treatment. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quartiles (including the median). Data from subjects who have not received subsequent therapy will be censored at the earliest of death or the last time that lack of administration of a new therapy was objectively documented.

Overall Survival

Overall survival is defined as the time from the first dose date of acalabrutinib or pembrolizumab until date of death due to any cause. Subjects who are known to be alive or whose survival status is unknown will be censored at the date last known to be alive. The analysis methods for overall survival will be similar to those described for progression-free survival.

5.5.5 PD or Biomarker Analyses

CCI [redacted]

6.0 ASSESSMENT OF SAFETY

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

6.1 DEFINITIONS

6.1.1 Adverse Events

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

This includes the following:

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

The following are NOT considered an AE:

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

measures (e.g., routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.

- **Abnormal** laboratory **results**: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example, a blood transfusion for low hemoglobin) or requires a change in study drug (e.g., lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Progression of underlying malignancy**: Progression of underlying malignancy will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying cancer. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as an SAE. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying malignancy, or if they do not fit the expected pattern of progression for the disease under study.

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

If there is any uncertainty about an AE being due only to the disease under study, it should be reported as an AE or SAE.

6.1.2 Serious Adverse Events

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

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

- It results in death (i.e., the AE actually causes or leads to death).
- It is life-threatening (i.e., the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.

- It results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of nonhematologic and hematologic AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

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

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the CRF. All SAEs must be reported on the SAE form or clinical database.

6.2.1 Adverse Event Reporting Period

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

For acalabrutinib, all AEs will be reported until 30 days after the last dose of acalabrutinib or the start of new anticancer therapy (whichever comes first). After this period, investigators should report SAEs or other AEs of concern that are believed to be related to prior treatment with acalabrutinib.

For pembrolizumab, all AEs must be reported through 30 days after the last dose of pembrolizumab; any SAEs, or follow-up to an SAE, including death due to any cause other than progression of the cancer under study, must be reported through 90 days after the last dose or 30 days after the last dose of pembrolizumab if the subject initiates a new anticancer therapy within the 90-day posttreatment timeframe.

SAEs considered related to study drug(s) or study procedures occurring after the end of the AE reporting period (as defined above) must be reported.

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

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, that occur to any subject from the time of first dose through 30 days following the cessation of study drug(s), and all SAEs that occur to any subject receiving pembrolizumab from the time of first dose through 90 days following cessation of pembrolizumab, or 30 days following cessation of pembrolizumab if the subject initiates new anticancer therapy (whichever is earlier) will be recorded in the subject's medical record and on the AE CRF.

Disease progression itself is not considered an AE unless it is considered to be drug-related by the investigator; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

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

See Appendix 3 for more detail on assessing causality.

6.2.3 Second Primary Malignancies

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

The above instruction applies only when the malignant tumor event in question is a new malignant tumor (i.e., it is not the tumor for which entry into the study is a criterion and that is being treated by the investigational product (IP) under study and is not the development of new or progression of existing metastasis to the tumor under study). Malignant tumors that—as part of normal, if rare, progression—undergo transformation (e.g., Richter's transformation of B-cell chronic lymphocytic leukemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumor.

6.2.4 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported to Acerta Pharma, according to the usual timelines and directions for SAE reporting (see Section 6.2.4).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 2 days after the last dose of acalabrutinib, or within 120 days after the last dose of pembrolizumab or 30 days after the last dose of pembrolizumab if the subject initiates a new anticancer therapy (whichever is earlier of the pembrolizumab dosing situations) will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner is willing to participate in follow-up.

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

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving study drug who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Upon completion of the pregnancy, additional information on the mother, pregnancy, and baby will be collected and sent to PPD

6.2.5 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. All initial SAE reports and follow-up information will be reported using the protocol-specific electronic data capture system. If electronic SAE reporting is not available, paper SAE forms must be emailed or faxed to Acerta Pharma Drug Safety (see Table 12), or designee. These must also be completed within 24 hours of the discovery of the SAE. Acerta Pharma may request follow-up and other additional information from the investigator (e.g., hospital admission/discharge notes and laboratory results).

Whenever possible, AEs/SAEs should be reported by diagnosis term, not as a constellation of symptoms.

Death due to disease progression should be recorded on the appropriate form in the electronic data capture system. If the primary cause of death is disease progression, the death due to

disease progression should not be reported as an SAE. If the primary cause of death is something other than disease progression, then the death should be reported as an SAE with the primary cause of death as the event term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

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

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product (or if a causality assessment is not provided for the SAE, in which case the default of 'related' must be used for expedited reporting purposes) and the SAE is not listed in the current acalabrutinib IB (i.e., an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the suspected unexpected serious adverse reaction (SUSAR) to all investigators. Each investigator must then notify his or her IRB/IEC of the SUSAR.

Table 12 Acerta Pharma Drug Safety Contact Information

Drug Safety Contact Information		
Fax	United States	PPD
	Outside United States	PPD
Email	PPD	

6.2.6 Reporting Events of Clinical Interest

Selected non-serious and serious AEs are also known as ECIs and must be reported to the sponsor.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to study drug

must be reported within 24 hours to the sponsor either by electronic media or paper as described in Section 6.2.5.

Events of Clinical Interest for this trial include:

1) An overdose of study drug (overdose is defined in Section 3.10.10) that is not associated with clinical symptoms or abnormal laboratory results.
2) An elevated AST or ALT lab value that is ≥3 times the ULN and an elevated total bilirubin value that is ≥2 times ULN and, at the same time, an alkaline phosphatase value that is <2 times the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing. [a]
3) Ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation).

a These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The guidance for assessment and follow-up of these criteria for potential drug-induced liver injury can be found in Appendix 7.

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

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

6.2.8 Other Safety Issues Requiring Expedited Reporting

For studies being conducted in Europe expedited reporting is required for safety issues that might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. For a detailed description of safety issues that may qualify for expedited reporting please refer to the European Commission guidance titled, “Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use – April 2006” available at http://ec.europa.eu/health/files/eudralex/vol-10/21_susar_rev2_2006_04_11_en.pdf.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

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

- Unsatisfactory subject enrollment with regard to quality or quantity

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

7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

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

7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent form. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and

its designees, regulatory agencies, and IRBs/IECs. As the study sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.3 SUBJECT SCREENING LOG

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

7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete CRFs designed for this study according to the completion guidelines that will be provided within the clinical database. The investigator will ensure that the CRFs are accurate, complete, legible, and completed promptly. The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the CRFs are never obliterated or destroyed. Refer to Section 7.7 for record retention requirements.

7.5 STUDY MONITORING REQUIREMENTS

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

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail

de-identified copies of radiology, pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.6 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

Acalabrutinib and pembrolizumab must be kept in a locked limited access cabinet or space. The study drug must not be used outside the context of the protocol.

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

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

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

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

1) Study identification number (ACE-LY-005)
2) Subject identification number
3) Lot number(s) of acalabrutinib and pembrolizumab dispensed for that subject
4) Date and quantity of drug dispensed
5) Any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its designee, for return of unused

investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor. Returned capsules must not be redispensed. Only a sufficient quantity of capsules will be dispensed to reach the next protocol-specified visit unless approved by the medical monitor.

7.7 RECORD RETENTION

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

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

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

7.8 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the

amendment may take effect. Additionally, under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.9 PUBLICATION OF STUDY RESULTS

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

7.10 CLINICAL TRIAL INSURANCE

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

7.11 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1) He or she will conduct or supervise the study.
2) His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3) The study is conducted according to the protocol and all applicable regulations.
4) The protection of each subject's rights and welfare is maintained.
5) Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6) The consent process is conducted in compliance with all applicable regulations and privacy acts.
7) The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8) Any amendment to the protocol is submitted promptly to the IRB/IEC.
9) Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10) CRF pages are completed promptly.

11) All Investigational New Drug Safety Reports/SUSAR Reports are submitted promptly to the IRB/IEC.

12) All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge via the clinical database and to the IRB/IEC per their requirements.

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9.0 APPENDICES

Appendix 1 Performance Status Scores

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

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

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Appendix 2 Known Strong In Vivo Inhibitors or Inducers of CYP3A

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

Source: FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥5-fold.
b. In vivo inhibitor of P-glycoprotein (P-gp).
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

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

Appendix 3 Adverse Event Assessment of Causality

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

No___ Yes___

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

No=There is no reasonable possibility that the event may have been caused by study drugs. The adverse event:

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

Yes=There is a reasonable possibility that the event may have been caused by study drugs. The adverse event:

- Follows a temporal sequence from administration of study drug
- Is a known response to the study drug based on clinical or nonclinical data
- Could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- Disappears or decreases upon cessation or reduction of dose of study drug
- Reappears or worsens when study drug is re-administered

Appendix 4 Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score

Symptom	**1 to 10 (0 if absent) Ranking** 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms	
Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration - Compared to prior to my myeloproliferative disease (MPD)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100° F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Source: Scherber et al. The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS): prospective international assessment of an abbreviated symptom burden scoring system among 1408 MPN patients. Available at: http://jco.ascopubs.org/content/suppl/2012/10/15/JCO.2012.42.3863.DC1/data_supplement_JCO.2012.42.3863.pdf. Accessed on: 14 August 2015.

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Appendix 5 Schedule of Assessments – Parts 1 and 2

		Treatment Phase[b]											Safety Follow-up Visit[c]	Follow-up Phase[d]
		Weeks												
Study Weeks	**Screening[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Wks 10-103 (Q3W) [aa]**	**Wks >103 (Q24W/ Q52W)[aa]**	**ET**	**+30 days after last dose**	**Q12W**
Study Window	**-28 days**		**±3 days**							**±3 days**	**±10 days**	**+3 days**	**+7 days**	**±10 days**
Informed consent	x													
Confirm eligibility	x													
Medical history	x													
PE[e]/Vital signs[f]/Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG[g]	x													
Lab assessments:														
Urine or serum pregnancy test[h]	x	x[r,u]			x			x		x	x	x	x	
Hematology (w/smear)[i]	x	x[r]	x	x	x	x	x	x	x	x	x	x	x	
Serum chemistry[j]	x	x[r]	x	x	x	x	x	x	x	x	x	x	x	
Thyroid panel[k]	x	x[r]	x	x	x	x	x	x	x	x[k]	x[k]	x	x	
Hepatitis serology[v]	x													
HBV PCR[w]	x				x				x	Week 12 then Q4W	Q3M[w]			Q3M[w]
HCV PCR[x]	x									Week 13 and 25				
Urinalysis[l]	x													
T/B/NK cell count[m]		x[r]					x		x	Week 19 then Q12W	x[m]			
Serum Ig[n]		x[r]					x		x	Week 19 then Q12W	x[n]			
Disease markers[o,q] (MM and WM only)	x	x[r]		x			x		x	x	x			
CCI														
Tumor tissue[p]	x													
CCI														
Skeletal survey (MM only)[q]	x	As clinically indicated, and at Week 52												
Acalabrutinib 100 mg BID		x	x	x	x	x	x	x	x	x	x			
Pembrolizumab 200 mg Q3W		x			x			x		x	x			
Study drug compliance		x	x	x	x	x	x	x	x	x	x			
CCI														
Radiologic assessments[q]	x								x[q]	Week 19 then Q12W[q]	x[q]			

		Treatment Phase[b]											Safety Follow-up Visit[c]	Follow-up Phase[d]
		Weeks												
Study Weeks	**Screening[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**Wks 10-103 (Q3W) [aa]**	**Wks >103 (Q24W/ Q52W)[aa]**	**ET**	**+30 days after last dose**	**Q12W**
Study Window	**-28 days**		**±3 days**							**±3 days**	**±10 days**	**+3 days**	**+7 days**	**±10 days**
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events[z]		x	x	x	x	x	x	x	x	x	x	x	x	
Follow-up post-allogenic stem cell transplantation data collection[y]														x
Time-to-next treatment													x	x
Survival													x	x

AE=adverse event; anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; BID=twice per day; CLL=chronic lymphocytic leukemia; CR=complete remission; CT=computed tomography; ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, ET=early termination; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; Ig=immunoglobulin; IVIG =intravenous immunoglobulins; MM=multiple myeloma; PCR=polymerase chain reaction; CCI PE=physical examination; PET=positron-emission tomography; PR=partial response; Q12W=every 12 weeks; Q3W=every 3 weeks; Q4W=every 4 weeks; SAE=serious adverse event; SCT=stem cell transplantation; SLL=small lymphocytic lymphoma; WM=Waldenström macroglobulinemia.

Footnotes for Appendix 5 ACE-LY-005 Schedule of Study Activities – Parts 1 and 2

a Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.

b Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Treatment with pembrolizumab may continue for 24 months (103 weeks) from first dose of pembrolizumab, provided subject is tolerating the drug and not progressing. Treatment may be stopped earlier for confirmed CR as described in the protocol. Treatment with acalabrutinib can continue until the end of trial, defined as 48 months after the last subject is enrolled, for subjects who are tolerating therapy and not progressing.

c A 30-day (+7 days) safety follow-up visit is required when subjects discontinue study drug.

d Subjects who discontinue study therapy will continue on study to measure survival unless they withdraw consent, are lost to follow up, die, or the sponsor ends the study.

e The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Physical examinations are done thereafter. For all subjects except those with MM, the following B symptoms will be collected at each examination. Unintentional weight loss of normal body weight over a period of ≤6 months; disease associated intermittent fevers ≥38°C; drenching sweats especially at night.

f Vital signs (blood pressure, pulse and temperature) will be assessed after the subject has rested in the sitting position.

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

h Women of childbearing potential must have a negative urine or serum pregnancy testing within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.

i Hematology includes complete blood count with peripheral blood smear and differential, and platelet and reticulocyte counts. Week 1 hematology does not need to be repeated if screening hematology was done within 7 days.

j Serum chemistry: albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, bone-specific alkaline phosphatase, calcium, chloride, creatinine, c-terminal telopeptide, glucose, lactate dehydrogenase, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin, total protein, and uric acid. Week 1 serum chemistry does not need to be repeated if screening chemistry was within 7 days.

k Thyroid panel: total triiodothyronine, free thyroxine, and thyroid stimulating hormone. Week 1 thyroid panel does not need to be repeated if screening thyroid panel was within 7 days. Thyroid function tests will be performed once weekly for the first 8 weeks, followed by a Week 10 visit and then every 6 weeks until 6 months after the last dose of pembrolizumab. For subjects who permanently discontinue pembrolizumab, i.e., before completing 103 weeks, thyroid tests must be completed every 6 weeks after the last dose of pembrolizumab for 6 months until 1) testing that was performed at 6 months was normal, and 2) testing that was performed 6 weeks prior to the 6-month timepoint was normal (for a total of 2 consecutive normal test results). Otherwise, thyroid testing will continue as scheduled until 2 consecutive normal test results. Subjects who complete pembrolizumab through 103 weeks will have a thyroid panel collected at Week 106 and Week 109 only, and every 6 weeks thereafter. Thyroid testing may be discontinued at 6 months after pembrolizumab discontinuation if 1) testing that was performed at 6 months was normal and 2) testing that was performed 6 weeks prior to the 6-month timepoint was normal (for a total of 2 consecutive normal test results). Otherwise, thyroid testing will continue every 6 weeks until 2 consecutive normal test results.

l Urinalysis: pH, ketones, specific gravity, bilirubin, N-terminal telopeptide, protein, blood, and glucose.

m T/B/NK cell count (i.e., CD3, CD4, CD8, CD19, CD16/56), conducted at Week 1, Week 6, Week 8, and Week 19, and then every 12 weeks through Week 103, thereafter collected every 24 weeks starting at Week 127 through 3 years (for subjects with CLL/SLL histologies) or 5 years (for subjects with non-CLL/SLL histologies [i.e., DLBCL/Hodgkin lymphoma]), and then every 52 weeks thereafter (all histologies).

n Serum immunoglobulin: IgG, IgM, IgA, conducted at Week 1, Week 6, Week 8, and Week 19, and then every 12 weeks through Week 103, thereafter collected every 24 weeks starting at Week 127 through 3 years (for subjects with CLL/SLL histologies) or 5 years (for subjects with non-CLL/SLL histologies [i.e., DLBCL/ Hodgkin lymphoma]), and then every 52 weeks thereafter (all histologies).

o Refer to Section 4.1.18 for a list of MM and WM disease markers. For MM, serum samples should be drawn approximately 1 hour before or 1 hour after the end of the 24-hour urine collection.

p Provide tissue (if available) from either an archived or newly obtained tumor sample (most recent biopsy) for biomarker and correlative analysis.

CCI [redacted]

r The indicated samples at this timepoint must be drawn predose.

CCI [redacted]

t This peripheral blood sample will be collected if treatment termination is due to disease progression.

u This urine or serum pregnancy test is to be performed on Week 1 Day 1 (- 3 days) and at each visit for subjects with childbearing potential.

v Hepatitis serology must include HBsAg, anti-HBs, anti-HBc, and hepatitis C antibody. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #30).

w Subjects who are anti-HBc positive (or have a known history of HBV) should have a quantitative PCR test for HBV DNA performed during screening and while on study treatment. These subjects should have a quantitative PCR test performed monthly while on combination treatment and every 3 months while on acalabrutinib monotherapy. Following study drug discontinuation, monitoring should continue every 3 months until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. As IVIG may cause false positive serology, monthly PCR testing is not required in subjects who are currently receiving or received prophylactic IVIG within 3 months before study enrollment and have a documented negative anti-HBc test before the initiation of IVIG therapy. Additional PCR testing should be performed when clinically indicated (e.g., in the setting of rising transaminase levels).

x Subjects with a known history of hepatitis C or who are hepatitis C antibody-positive should have quantitative PCR testing for HCV DNA performed during screening and at Weeks 13 and 25. No further testing beyond Week 25 is necessary if PCR results are negative.

y For subjects who have an allogeneic SCT within 24 months of last dose of pembrolizumab, transplant parameters will be collected, and specific events will be collected for 18 months from the date of the allogeneic transplant, to include graft-versus-host-disease (acute and/or chronic), veno-occlusive disease, febrile syndrome (a steroid-requiring febrile illness without an infectious cause), and encephalitis, for all grades, and regardless of relationship to study drug. Additional medically important adverse events post-allogeneic SCT may be submitted at the investigator's discretion. If available and relevant to an event post-allogeneic SCT, concomitant medications and/or laboratory results may also be reported.

z After the end of the protocol-defined AE reporting period, only SAEs considered related to study drug(s) or study procedures are required to be collected.

aa All subjects continuing single-agent acalabrutinib treatment after Week 103 will have a Week 103 and Week 115 visit, and then every 24 weeks thereafter beginning at Week 127 through 3 years (for subjects with CLL/SLL histologies) or 5 years (for subjects with non-CLL/SLL histologies [i.e., DLBCL/Hodgkin lymphoma]), and then every 52 weeks thereafter (all histologies). Subjects who discontinue pembrolizumab at Week 103 must also have visits at Week 106 and Week 109. Subjects who discontinue pembrolizumab before Week 103 must continue visits every 3 weeks until Week 37, after which time visits are every 12 weeks through 104 weeks, and thereafter every 24 or 52 weeks as described above. However, it is noted that because the discontinuation timepoint of pembrolizumab (if applicable) is unique per subject, the first every 12-week visit for these subjects will be scheduled to align with the radiologic tumor assessment timepoint nearest to the 12-week interval.

Appendix 6 Schedule of Assessments – Part 3 (Myelofibrosis)

		Treatment Phase[b]														Safety Follow-up Visit[c]	Follow-up Phase[d]
		Weeks												Wks 13-52 (Q3W)	Wks >52 (Q3W)	ET	+30 days after last dose	Q12W
Study Weeks	**Screening[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**					
Study Window	**-28 days**		**±3 days**											**±3 d**	**±3 d**	**+3 d**	**+7 d**	**±10 d**
Informed consent	x																	
Confirm eligibility	x																	
Medical history	x																	
PE[e]/Vital signs[f]/Weight	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG[g]	x																	
Lab assessments:																		
Urine or serum pregnancy test[h]	x	x[r,y]			x			x			x			x	x			
Hematology (w/ smear)[i]	x	x[r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Serum chemistry[j]	x	x[r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Hepatitis serology[z]	x																	
HBV PCR[aa]					x				x				x	Q4W	Q4W			Q4W
Thyroid panel[k]	x	x[r]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Urinalysis[l]	x																	
CCI																		
Serum Ig[n]		x[r]					x							Wks 16 & 25, + Q9W	Q12W			
Disease markers[o]	x	As clinically indicated																
CCI																		
Acalabrutinib 100 mg BID		x	x	x	x	x	x	x	x	x	x	x	x	x				
Pembrolizumab 200 mg Q3W[t]								x[t]			x[t]			x[t]	x[t]			
Study drug compliance		x	x	x	x	x	x	x	x	x	x	x	x	x	x			
CCI																		
MRI/CT of spleen[w]	x							x						Wks 16 & 25, + Q9W	Q12W			
MPN-SAF TSS[u]	x							x						Wks 16 & 25, + Q9W	Q12W			

		Treatment Phase[b]														Safety Follow-up Visit[c]	Follow-up Phase[d]
		Weeks												Wks 13-52 (Q3W)	Wks >52 (Q3W)	ET	+30 days after last dose	Q12W
Study Weeks	**Screening[a]**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**					
Study Window	**-28 days**		**±3 days**											**±3 d**	**±3 d**	**+3 d**	**+7 d**	**±10 d**
Concomitant medications (including transfusions)[v]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Time-to-next treatment																	x	x
Survival																	x	x

Footnotes for Appendix 6 ACE-LY-005 Schedule of Study Activities – Part 3 (Myelofibrosis):

Anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody; BID=twice per day; CR=complete remission; CT=computed tomography; d=days; ECG=electrocardiogram, ECOG=Eastern Cooperative Oncology Group, ET=early termination; F/U=follow-up; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; Ig=immunoglobulin; IVIG =intravenous immunoglobulins; JAK=Janus kinase; MF=myelofibrosis; MPN-SAF TSS=Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; MRI=magnetic resonance imaging; PCR=polymerase chain reaction; CCI [redacted] PE=physical examination; PR=partial response; Q3W=every 3 weeks; Q4W=every 4 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; QM=every month

a Screening tests should be performed within 28 days before the first administration of study drug, unless otherwise indicated.

b Treatment with acalabrutinib may be continued until disease progression or an unacceptable drug-related toxicity occurs as defined in the protocol. Treatment with pembrolizumab may continue for 24 months (103 weeks) from first dose of pembrolizumab, provided subjects are tolerating the drug and not progressing. Treatment may be stopped earlier for confirmed CR as described in the protocol. Treatment with acalabrutinib can continue until the end of trial, defined as 48 months after the last subject is enrolled, for subjects who are tolerating therapy and not progressing.

c A 30-day (+7 days) safety follow-up visit is required when subjects discontinue study drug.

d Subjects who discontinue study therapy will continue on study until withdrawal of consent, loss to follow-up, death, or study termination by the sponsor.

e The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. As part of tumor assessment, Physical examinations, including presence and degree of splenomegaly and hepatomegaly (where appropriate) by palpation, are done thereafter.

f Vital signs (blood pressure, pulse, and temperature) will be assessed after the subject has rested in the sitting position.

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

h Women of childbearing potential must have a negative urine or serum pregnancy testing within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.

i Hematology includes complete blood count with peripheral blood smear and differential, and platelet and reticulocyte counts. Week 1 hematology does not need to be repeated if screening hematology was done within 7 days.

j Serum chemistry: albumin, alkaline phosphatase, alanine transaminase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, bone-specific alkaline phosphatase, calcium, chloride, creatinine, c-terminal telopeptide, glucose, lactate dehydrogenase, magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Week 1 serum chemistry does not need to be repeated if screening chemistry was within 7 days.

k Thyroid panel: total triiodothyronine, free thyroxine, and thyroid stimulating hormone. Week 1 thyroid panel does not need to be repeated if screening thyroid panel was within 7 days. Thyroid function tests will be performed once weekly for the first 8 weeks, followed by a Week 10 visit and then every 6 weeks thereafter until the 6-month timepoint. Thyroid testing may be discontinued at 6 months if 1) testing that was performed at 6 months was normal and 2) testing that was

performed 6 weeks prior to the 6-month timepoint was normal (for a total of 2 consecutive normal test results). Otherwise, thyroid testing will continue beyond the 6-month timepoint as scheduled until 2 consecutive normal test results.

l Urinalysis: pH, ketones, specific gravity, bilirubin, N-terminal telopeptide, protein, blood, and glucose.

CCI

n Serum immunoglobulin: IgG, IgM, IgA.

o Molecular disease markers to be done at baseline and repeated as clinically indicated (at the investigator's discretion) to assess molecular response (see Section 4.2)

p (Footnote not applicable for Part 3)

CCI

r The indicated samples at this timepoint must be drawn predose.

CCI

t Subjects with MF will receive a run-in of 6 weeks of acalabrutinib alone. Subjects who are demonstrating a clinically meaningful response, in the opinion of the investigator, may continue on acalabrutinib monotherapy; those who are not will receive combination therapy thereafter.

u MPN-SAF TSS will be assessed at the end of Week 6 (±7 days), end of Week 15 (±7 days), end of Week 24 (±7 days), every 9 weeks (±10 days) through Week 52, and every 12 weeks (±14 days) thereafter, or more frequently at investigator discretion.

v Document all concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug. For subjects with MF, record all transfusions of blood products (e.g., red blood cells or platelets) within 12 weeks before the first study dose and throughout the study period.

w A pretreatment MRI or CT scan to measure spleen volume is required within 30 days of the first dose; this baseline MRI/CT scan must be done at least 2 weeks after the last dose of any JAK inhibitors. MRI is the preferred modality; the same modality (either MRI or CT) should be used for all timepoints for a given subject. On-treatment MRIs or CT scans will be done for spleen measurements at the end of Week 6 (±7 days), end of Week 15 (±7 days), end of Week 24 (±7 days), every 9 weeks (±10 days) through Week 52, and every 12 weeks (±14 days) thereafter, or more frequently at investigator discretion.

x This peripheral blood sample will be collected if treatment termination is due to disease progression.

y This urine or serum pregnancy test is to be performed on Cycle 1 Day 1 (- 3 days).

z Hepatitis serology must include HBsAg, anti-HBs, anti-HBc, and hepatitis C antibody. Subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #30).

aa Subjects who are anti-HBc positive (or have a known history of HBV) should be monitored every 3 months with a quantitative PCR test for HBV DNA and this testing is recommended to continue until 12 months after last dose of study drug(s). Any subject with a rising viral load (above lower limit of detection) should discontinue study drug(s) and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.

Appendix 7 Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

INTRODUCTION

This Appendix describes the process to be followed in order to identify and appropriately report potential Hy's law (PHL) cases and Hy's law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

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

The investigator participates with the sponsor in the review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product (IMP). The investigator is responsible for recording data pertaining to PHL/HL cases and for reporting AEs and SAEs according to the outcome of the review and assessment in line with standard safety reporting processes.

DEFINITIONS

Potential Hy's Law

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

Hy's Law

AST or ALT ≥3× ULN together with total bilirubin ≥2× ULN, where no other reason other than the IMP can be found to explain the combination of increases (e.g., elevated alkaline phosphatase indicating cholestasis, viral hepatitis, or another drug).

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

IDENTIFICATION OF POTENTIAL HY'S LAW CASES

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

- ALT ≥3× ULN
- AST ≥3× ULN
- Total bilirubin ≥2× ULN

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

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

REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

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

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

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

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

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

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

- Send updated SAE (report term "Hy's law") according to the sponsor's standard processes:
    - The "Medically Important" serious criterion should be used if no other serious criteria apply.
    - Because there is no alternative explanation for the HL case, a causality assessment of "related" should be assigned.

If there is an unavoidable delay of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until an informed decision can be made:

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

ACTIONS REQUIRED FOR REPEAT EPISODES OF POTENTIAL HY'S LAW

This section is applicable when a subject meets PHL criteria while receiving study treatment and has already met PHL criteria at a previous on-study treatment visit. The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL and answer the following question:

Was the alternative cause for the previous occurrence of PHL determined to be the disease under study (e.g., chronic or progressing malignant disease, severe infection, or liver disease)?

If the answer is **No**:

Follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.

If the answer is **Yes**:

Determine whether there has been a significant change in the subject's condition compared with the previous occurrence of PHL. Note: A "significant" change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or total bilirubin) in isolation or in combination or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the study medical monitor if there is any uncertainty.

- If there is no significant change, no action is required.
- If there is a significant change, follow the process described in "Potential Hy's Law Criteria Met" in this Appendix for reporting PHL as an SAE.

LABORATORY TESTS

Table 13 represents the standard comprehensive list of follow-up tests that may aid in assessing PHL/HL.

Test results used to assess PHL/HL should be recorded on the appropriate eCRF.

Table 13 Laboratory Tests to Aid in Assessing Potential Hy's Law / Hy's Law

Additional standard chemistry and coagulation tests	GGT
	LDH
	Prothrombin time
	INR
Viral hepatitis	IgM anti-HAV
	IgM and IgG anti-HBc
	HBsAg
	HBV DNA
	IgM and IgG anti-HCV
	HCV RNA
	IgM anti-HEV
	HEV RNA
Other viral infections	IgM and IgG anti-CMV
	IgM and IgG anti-HSV
	IgM and IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)
Autoimmune hepatitis	Antinuclear antibody (ANA)
	Anti-Liver/Kidney Microsomal Ab (Anti-LKM)
	Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin
	Ceruloplasmin
	Iron
	Ferritin
	Transferrin
	Transferrin saturation

Reference

FDA Guidance for Industry (issued July 2009). Drug-induced liver injury: premarketing clinical evaluation. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf