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Clinical Protocol

A Phase 1, Open-Label, Single-Dose Study to Investigate the Influence of Severe Hepatic Impairment on the Pharmacokinetics of Acalabrutinib and its Metabolite (ACP-5862)

Celerion Project No.: CA24897

Sponsor Project No.: ACE-HI-102

US IND No.: 118717

SPONSOR: Acerta Pharma, BV
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SPONSOR'S REPRESENTATIVE: [redacted]
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GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1 PROTOCOL REVISION HISTORY

Date/Name	Description
04Jun2018 by [redacted]	Final Protocol

2 PRINCIPAL INVESTIGATOR – SIGNATORIES

I have carefully read Protocol CA24897 (ACE-HI-102) entitled “A Phase 1, Open-Label, Single-Dose Study to Investigate the Influence of Severe Hepatic Impairment on the Pharmacokinetics of Acalabrutinib and its Metabolite (ACP-5862)”.

I agree to conduct this study as outlined herein and in compliance with GCP, all applicable regulatory requirements, and with the ethical principles laid down in the Declaration of Helsinki. Furthermore, I understand that the Sponsor, Acerta Pharma, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must approve any changes to the protocol in writing before implementation.

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

_____

Signature

_____ _____

Print Name of Principal Investigator Date (DD Month YYYY)

3 ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Event Reporting	Acerta Medical Safety Fax: US: [redacted] or Outside of US: [redacted] E-mail: [redacted]
Sponsor's Medical Monitor:	[redacted] Acerta Pharma, BV Tel.: + [redacted] E-mail: [redacted]
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5 SYNOPSIS

Compound:	Acalabrutinib (ACP-196), a generic name for Calquence®, will be used in place of ACP-196 in this document.
Clinical Indication:	B cell lymphoid cancer
Study Phase and Type:	Phase 1 – Hepatic Impairment (HI) Study
Study Objectives:	**Primary:** To compare the plasma pharmacokinetics of acalabrutinib and ACP-5862 in subjects with severe HI with that in matched-control subjects following a single-dose administration of 50-mg acalabrutinib. **Secondary:** To evaluate the safety and tolerability of acalabrutinib in subjects with severe HI after a single-dose administration of 50-mg acalabrutinib. **Exploratory**: The exploratory objectives listed below may be investigated at the discretion of the Sponsor: • [redacted] • [redacted] • [redacted]
Summary of Study Design:	This is a Phase 1, non-randomized, open-label, single-dose study to evaluate the effect of severe HI on the pharmacokinetics of acalabrutinib and its major metabolite, ACP-5862. On Day 1, a single oral dose of acalabrutinib will be administered followed by pharmacokinetic (PK) blood sampling for 24 hours in matched-control subjects and for 72 hours in subject with HI. Urine samples will also be collected over a 24-hour collection interval. The Clinical Research Unit (CRU) will attempt to contact all subjects who received the study drug (including subjects who terminate the study early) using their standard procedures approximately 14 days after dosing to determine whether any adverse event (AE) has occurred since the last study visit.

Number of Subjects:	A total of 16 adult men and/or women will be enrolled. Subjects with Severe HI: Eight subjects with severe HI (a score of 10 to 15, on the Child-Pugh scale) to obtain at least 6 evaluable subjects. Not more than 25% of the hepatic-impaired subjects (eg, 2 of 8 subjects with HI) will be allowed to have a transjugular intrahepatic portosystemic shunt (TIPS). Matched-Control Subjects: Eight subjects with normal hepatic function to match all evaluable subjects with severe HI in a 1:1 ratio. Subjects will be matched for age [within age groups <45 years old or ≥45 years old], body weight [± 20 %], and sex [1:1] to the subjects with HI.
Inclusion Criteria:	**All Subjects:** 1. Continuous non-smokers or smokers (of fewer than 20 cigarettes/day or the equivalent). Subjects must agree to consume no more than 5 cigarettes or equivalent/day from 24 hours before dosing and throughout the period of sample collection. 2. Women must be of non-childbearing status (ie, subject is surgically sterile due to a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure with serum estradiol and follicle stimulating hormone [FSH] levels within the institutional postmenopausal range as per Principal Investigator [PI] judgment; or is menopausal [≥ 50 years of age with amenorrhea for ≥ 6 months]). 3. Understands the study procedures in the informed consent form (ICF) and be willing and able to comply with the protocol. 4. Willingness and ability to swallow study drug capsules. **Hepatic-Impaired Subjects Only:** 5. Adult men or women, 18 to 75 years of age, inclusive, at screening. 6. Body mass index (BMI) ≥ 19 and ≤ 40 kg/m^2, at screening. 7. Have medical history, physical examination, vital signs, 12-lead electrocardiograms (ECGs), and laboratory safety test results consistent with a diagnosis of HI, but is otherwise judged to be in good health as determined by the PI. 8. Subject has a diagnosis of chronic (> 3 months), stable (no acute episodes of illness within the previous 2 months due to deterioration in hepatic function) HI with features of cirrhosis due to any etiology. 9. Subject's score on the Child-Pugh scale must range from 10 to 15 at screening. Subjects who have compensated HI while on medical therapy should be classified by their pretreatment parameters. **Matched-Control Subjects Only:** 5. Adult men and women will be matched in a 1:1 ratio to a specific subject in the HI group based upon age, weight, and sex. The following criteria should be fulfilled:

Inclusion Criteria *(continued)*:	a. 18 to 75 years of age, inclusive, at screening. Age must be within the same age group (ie, <45 years old or ≥45 years old) of the matched subject's age in the HI group. b. BMI ≥ 19 and ≤ 40 kg/m^2 at screening. Weight must be within ± 20% of the matched subject's weight in the HI group. 6. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles (including serum amylase and lipase, hematology, and thyroid function), vital signs, or ECGs, as deemed by the PI. Liver function tests (eg, serum alanine aminotransferase [ALT], aspartate aminotransferase [AST]), and serum bilirubin (total), must be ≤ the upper limit of normal (ULN) at screening for inclusion.
Exclusion Criteria*:*	**All Subjects:** 1. History or presence of clinically significant or unstable medical or psychiatric condition or disease in the opinion of the PI. 2. Subject is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study. 3. History of any illness that, in the opinion of the PI, might confound the results of the study or poses an additional risk to the subject by their participation in the study. 4. Presence of any clinically significant, ongoing systemic bacterial, fungal, or viral infections (including upper respiratory tract infections, but excluding localized cutaneous fungal infections), in the opinion of the PI. 5. History of any major surgical procedure within 30 days before dosing. 6. History of stroke or intracranial hemorrhage within 6 months before the dosing. 7. History of a bleeding diathesis (eg, hemophilia, von Willebrand disease). 8. Any clinically significant condition that may affect acalabrutinib absorption in the opinion of the PI, including gastric restrictions and bariatric surgery (eg, gastric bypass). Subjects with cholecystectomy will be allowed. 9. Women with positive serum pregnancy test results or lactating. 10. Positive results for human immunodeficiency virus (HIV) at screening or using HIV protease inhibitors. 11. Have been on a diet incompatible with the on-study diet, in the opinion of the PI, within the 28 days before dosing, and throughout the study. 12. Donation of blood > 500 mL or significant blood loss within 56 days before the dose of study drug. 13. Plasma donation within 7 days before dosing. 14. Is working at or has an immediate family member (spouse or children) who works at the investigational site or is a Sponsor staff

Exclusion Criteria *(continued):*	directly involved with this trial. 15. Dosed in another clinical trial within 28 days before dosing of study drug and throughout the current study. The 28-day window will be derived from the date of dosing in the previous study to Day 1 of the current study. **Hepatic-Impaired Subjects Only:** 16. History or presence of drug abuse within 2 years before screening. 17. Positive results for the urine or breathalyzer alcohol test and/or urine drug screen at screening or check-in, unless the positive drug screen is due to prescription drug use and is approved by the PI and Acerta Pharma's medical monitor. 18. History of hepatitis B virus (HBV) infection or subjects with active hepatitis C virus (HCV) that have persistent elevations of transaminase levels > 6 times ULN. 19. Unable to refrain from or anticipates the use of: • Any medication (including prescription or over the counter, vitamins supplements, natural or herbal supplements) that cannot be discontinued ≥ 14 days before dosing and throughout the study. Note: hepatic-impaired subjects who are taking medications to treat stable diseases or to treat manifestations of hepatic disease and are on a stable dose, drug, and regimen for ~2 weeks before dosing will be allowed to participate in the study at the discretion of the PI. Consultation with Acerta Pharma's medical monitor may occur on a case-by-case basis, as described in Section 11.4.1. Ibuprofen (up to 1200 mg per 24-hour period) may be permitted during the study. See Section 11.4.1 for additional details on allowable and prohibited concomitant therapy. • Any drug known to be a strong or moderate inhibitor or inducer of cytochrome P450 enzymes (CYP) 3A and/or P-glycoprotein (P-gp), including St. John's Wort, should be restricted for 14 and 28 days, respectively, before dosing and throughout the study unless it was deemed acceptable following consultation with Acerta Pharma's medical monitor and the PI. Appropriate sources, such as those listed in Appendix 1, will be reviewed by the PI or designee to confirm lack of PK and / or pharmacodynamic (PD) interaction with study drug. **Matched-Control Subjects Only** 16. History or presence of alcoholism and/or drug abuse within 2 years before screening. 17. Positive results for the urine or breathalyzer alcohol test and/or urine drug screen at screening or check-in. 18. Positive results at screening for hepatitis B surface antigen (HBsAg) or HCV. 19. Seated blood pressure is < 90/40 mmHg or > 150/95 mmHg at screening. 20. Seated heart rate is < 40 bpm or > 99 bpm at screening.

Exclusion Criteria *(continued):*	21. Hemoglobin level below the lower limit of normal at screening, and considered clinically significant by the PI. 22. Unable to refrain from or anticipates the use of: • Any medication (including prescription or over the counter, vitamins supplements, natural or herbal supplements) that cannot be discontinued ≥ 14 days before dosing and throughout the study. Ibuprofen (up to 1200 mg per 24-hour period) may be permitted during the study. See Section 11.4.1 for additional details on allowable and prohibited concomitant therapy. • Any drug known to be a strong or moderate inhibitor or inducer of CYP3A and/or P-gp, including St. John's Wort, should be restricted for 14 and 28 days, respectively, before dosing and throughout the study unless it was deemed acceptable following consultation with Acerta Pharma's medical monitor and the PI. Appropriate sources, such as those listed in Appendix 1, will be reviewed by the PI or designee to confirm lack of PK and / or PD interaction with study drug.
Dosage, Dosage Form, Route, and Dose Regimen:	Each subject will receive a single oral dose of 50-mg acalabrutinib (1 x 50-mg capsules). Study drug will be administered orally with approximately 240 mL of water.
Key Assessments:	**Pharmacokinetics** The following PK parameters will be calculated for acalabrutinib and its metabolite, ACP-5862, in plasma, as appropriate: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-24}}$, $AUC_{\%extrap}$, C_{max}, T_{max}, T_{last}, λ_z, $t_{½}$, CL/F (parent only), V_z/F (parent only), metabolite-to-parent ratio (MR)_C_{max}, MR_$AUC_{0\text{-last}}$, and MR_$AUC_{0\text{-inf}}$. An analysis of variance (ANOVA) will be performed on the natural log (ln)-transformed acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-24}}$, $AUC_{0\text{-inf}}$, and C_{max}. Similar analyses may be performed on ACP-5862 PK parameters. The relationship between plasma acalabrutinib and ACP-5862 pharmacokinetics and HI may be examined in an exploratory manner via a scatter plot of plasma acalabrutinib and ACP-5862 PK parameters versus the Child-Pugh score, including the data from subjects with severe HI, and matched-control subjects as reference. Relationships between plasma acalabrutinib and ACP-5862 PK parameters and the baseline laboratory components of the Child-Pugh score (ie, bilirubin and albumin levels) may be assessed graphically. [redacted] of acalabrutinib and ACP-5862 in plasma will be determined at specified timepoints from blood samples collected for this purpose as outlined in the Study Events Flow Chart (Section 6). Remaining PK blood samples may also be used to determine [redacted] of acalabrutinib and ACP-5862. Remaining PK blood samples following analyses and dedicated [redacted] samples may be used for potential future analysis of liver function biomarkers (eg, CP-I and CP-III [Lai 2016]).

Key Assessments *(continued)*:	Urine samples may be used for potential future analysis to estimate acalabrutinib and ACP-5862 [redacted] and [redacted] (eg, CP-I and CP-III [Lai 2016]). **Safety** Safety will be monitored through 12-lead ECGs, vital sign measurements, clinical laboratory tests, AEs, and physical examinations, as applicable. AEs will be tabulated and summary statistics for the 12-lead ECGs, vital signs, and clinical laboratory tests may be computed and provided, as deemed clinically appropriate.

6 STUDY EVENTS FLOW CHART

6.1.1 Subjects With Hepatic Impairment

Study Procedures [a]	Screen [b]	Study Days																									FU [c]
Days →	(-28 to -2)	-1	1																			2		3		4	
Hours →		C-I [d]	0	0.167	0.25	0.5	0.75	0.863	1	1.5	1.75	2	3	4	5	6	6.5	8	10	12	14	24	36	48	60	72	
Administrative Procedures																											
Informed Consent	X																										
Inclusion/Exclusion Criteria	X	X																									
Medical History	X																										
Safety Evaluations																											
Full Physical Examination [e]	X	X																								X [f]	
Height	X																										
Weight	X	X																								X [f]	
Child-Pugh Classification	X																										
12-lead Safety ECG	X		X [g]																							X [f]	
Vital Signs (HR, BP, RR, & T)	X		X [g]																							X [f]	
Hem, Serum Chem, and UA	X [h]	X [i]																				X [i]				X [i,f]	
PT/INR	X																										
Serum TSH	X																										
Serum Preg Test (♀ only)	X	X																								X [f]	
Serum FSH (PMP ♀ only)	X																										
Urine/Breathalyzer Alcohol, Urine Drug Screen	X	X																									
HIV/Hepatitis Screen	X																										
AE Monitoring		X																									X
Concomitant Medication Monitoring	X	X																									
Study Drug Administration / Pharmacokinetics																											
Acalabrutinib Administration			X																								
Blood for acalabrutinib and ACP-5862 Pharmacokinetics [j]			X [k]	X	X	X	X		X	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	
Urine for acalabrutinib and ACP-5862 Pharmacokinetics			X [l]																								
Blood for acalabrutinib and ACP-5862 PRT Binding [m]								X			X						X										

Study Procedures [a]	Screen [b]	Study Days																									FU [c]
Days →	(-28 to -2)	-1	1																			2		3		4	
Hours →		C-I [d]	0	0.167	0.25	0.5	0.75	0.863	1	1.5	1.75	2	3	4	5	6	6.5	8	10	12	14	24	36	48	60	72	
Other Procedures																											
Confinement in the CRU		X																									
Visit	X																										

a: For details on Procedures, refer to Section 13.

b: Within 28 days prior to study drug administration.

c: The CRU will attempt to contact all subjects who received the study drug (including subjects who terminate the study early) using their standard procedures approximately 14 days after dosing to determine whether any AE has occurred since the last study visit.

d: Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU.

e: Symptom-driven physical examination may be performed, at the PI's or designee's discretion.

f: To be performed on Day 4 or before early termination from the study.

g: To be performed within 24 hours prior to dosing.

h: Samples for serum chemistry at screening will be obtained after a fast of ≥ 12 hours. Samples for fasting cholesterol, triglycerides, amylase, and lipase will be collected only at screening

i: On-study samples for serum chemistry (including check-in) will be obtained after a fast of ≥ 8 hours; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

j: Remaining PK blood samples following analyses may also be used for potential future analysis to assess acalabrutinib and ACP-5862 [redacted] and [redacted] (eg, CP-I and CP-III).

k: To be performed before dosing.

l: Urine samples may be used for potential future analysis to estimate acalabrutinib and ACP-5862 [redacted] and [redacted] Urine collection will be collected at the following intervals: pre-dose, 0 to 4, 4 to 24 hours after dosing.

m: Blood sample collected for [redacted] will be assayed and may be reported separately from CSR, as appropriate. Remaining blood samples following analyses may also be used for potential future analysis to assess [redacted]

Abbreviations: ♀ = Women, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, CRU = Clinical research unit, CSR = Clinical Study Report, ECG = Electrocardiogram, FSH = Follicle stimulating hormone, FU = Follow-up, Hem = Hematology, HI = Hepatic Impairment, HIV = Human immunodeficiency virus, HR = Heart rate, INR = international normalized ratio, PI = Principal Investigator, PK = Pharmacokinetic, PMP = Postmenopausal, Preg = Pregnancy, PRT = Protein, PT = prothrombin time, RR = Respiratory rate, Screen = Screening, T = Temperature, TSH = Thyroid stimulating hormone, UA = Urinalysis.

6.1.2 Matched-Control Subjects

Study Procedures [n]	Screen [o] (-28 to -2)	Study Days																					FU [p]
Days →		-1	1																			2	
Hours →		C-I [q]	0	0.167	0.25	0.5	0.75	0.863	1	1.5	1.75	2	3	4	5	6	6.5	8	10	12	14	24	
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Safety Evaluations																							
Full Physical Examination [r]	X	X																				X [s]	
Height	X																						
Weight	X	X																				X [s]	
12-lead Safety ECG	X		X [t]																			X [s]	
Vital Signs (HR, BP, RR, & T)	X		X [t]																			X [s]	
Hem, Serum Chem, and UA	X [u]	X [v]																				X [v,s]	
PT/INR	X																						
Serum TSH	X																						
Serum Preg Test (♀ only)	X	X																				X [s]	
Serum FSH (PMP ♀ only)	X																						
Urine/Breathalyzer Alcohol, Urine Drug Screen	X	X																					
HIV/Hepatitis Screen	X																						
AE Monitoring		X																					X
Concomitant Medication Monitoring	X	X																					
Study Drug Administration / Pharmacokinetics																							
Acalabrutinib Administration			X																				
Blood for acalabrutinib and ACP-5862 Pharmacokinetics [w]			X [x]	X	X	X	X		X	X		X	X	X	X	X		X	X	X	X	X	
Urine for acalabrutinib and ACP-5862 Pharmacokinetics [y]			X																				
Blood for acalabrutinib and ACP-5862 PRT Binding [z]								X			X						X						
Other Procedures																							
Confinement in the CRU		X																					
Visit	X																						

n: For details on Procedures, refer to Section 13.

o: Within 28 days prior to study drug administration.

p: The CRU will attempt to contact all subjects who received the study drug (including subjects who terminate the study early) using their standard procedures approximately 14 days after dosing to determine whether any AE has occurred since the last study visit.

q: Subjects will be admitted to the CRU on Day -1, at the time indicated by the CRU.

r: Symptom-driven physical examination may be performed, at the PI's or designee's discretion.

s: To be performed on Day 2 or before early termination from the study.

t: To be performed within 24 hours prior to dosing.

u: Samples for serum chemistry at screening will be obtained after a fast of ≥ 12 hours. Samples for fasting cholesterol, triglycerides, amylase, and lipase will be collected only at screening

v: On-study samples for serum chemistry (including check-in) will be obtained after a fast of ≥ 8 hours; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

w: Remaining PK blood samples following analyses may also be used for potential future analysis to assess acalabrutinib and ACP-5862 [redacted] and [redacted]

x: To be performed before dosing.

y: Urine samples may be used for potential future analysis to estimate acalabrutinib and ACP-5862 [redacted] and analysis [redacted] Urine collection will be collected at the following intervals: pre-dose, 0 to 4, 4 to 24 hours after dosing.

z: Blood sample collected for [redacted] will be assayed and may be reported separately from CSR, as appropriate. Remaining blood samples following analyses may also be used for potential future analysis to assess [redacted]

Abbreviations: ♀ = Women, AE = Adverse events, BP = Blood pressure, C-I = Check-in, Chem = Chemistry, CRU = Clinical research unit, CSR = Clinical Study Report, ECG = Electrocardiogram, FSH = Follicle stimulating hormone, FU = Follow-up, Hem = Hematology, HIV = Human immunodeficiency virus, HR = Heart rate, INR = international normalized ratio, PI = Principal Investigator, PK = Pharmacokinetic, PMP = Postmenopausal, Preg = Pregnancy, PRT = Protein, PT = prothrombin time, RR = Respiratory rate, Screen = Screening, T = Temperature, TSH = Thyroid stimulating hormone, UA = Urinalysis.

7 ABBREVIATIONS

ACP-5862	Acalabrutinib active metabolite (M27)
AE	Adverse event
Ae	Amount recovered
Ae_{t1-t2}	Amount of unchanged drug excreted in t1 to t2 urine collection interval
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
$AUC_{\%extrap}$	Percent of AUC_{0-inf} extrapolated
AUC_{0-inf}	Area under the concentration-time curve, from time 0 extrapolated to infinity
AUC_{0-last}	The area under the concentration-time curve, from time 0 to the last observed non-zero concentration
AUC_{0-24}	The area under the concentration-time curve from time 0 to the 24-hour time point
BMI	Body mass index
bpm	Beats per minute
BTK	Bruton tyrosine kinase
CFR	Code of Federal Regulations
CI	Confidence interval
CL/F	Apparent total plasma clearance after oral (extravascular) administration
CLL	Chronic lymphocytic leukemia
CL_R	Renal clearance
C_{max}	Maximum observed concentration
CP-I	coproporphyrin-I
CP-III	coproporphyrin-III
CRU	Clinical research unit
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
Cys	Cysteine
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
Gly-Cys	Glycine-cysteine

GSH	Glutathione
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HI	Hepatic Impairment
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
λ_z	Apparent terminal elimination rate constant
MCL	Mantle cell lymphoma
MedDRA®	Medical Dictionary for Regulatory Activities®
MR	Metabolite-to-parent ratio
P-gp	P-glycoprotein
PD	Pharmacodynamics
PI	Principal Investigator
PK	Pharmacokinetic
PML	Progressive multifocal leukoencephalopathy
PT	Prothrombin time
QA	Quality assurance
SAE	Serious adverse event
SAP	Statistical analysis plan
SSRI	Selective serotonin reuptake inhibitors
TEAE	Treatment-emergent adverse event
T_{last}	Time of the last measurable concentration
T_{max}	Time to reach maximum observed concentration
TSH	Thyroid stimulating hormone
$t_{½}$	Apparent terminal elimination half-life
ULN	Upper limit of normal
US	United States
V_z/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration
WHO	World Health Organization

8 INTRODUCTION

8.1 Background

8.1.1 Lymphoid Cancers and the Role of Bruton Tyrosine Kinase

B cell lymphoid malignancies comprise the most common hematological malignancies (SEER 2014). These cancers arise from the accumulation of monoclonal B lymphocytes in lymph nodes and in organs such as blood, bone marrow, lymph nodes, spleen, and liver. Among the variants of these cancers are diffuse large B cell lymphoma, indolent non-Hodgkin lymphoma, mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and Hodgkin lymphoma. These disorders are characterized by lymphadenopathy that is frequently disturbing for patients and can sometimes induce life-threatening organ dysfunction; patients may also have constitutional symptoms (fevers, night-sweats, and/or weight loss) and fatigue (Diehl 2004, Salles 2007, Dighiero 2008).

The goal of therapy for these diseases is to induce tumor regression and delay tumor progression to control disease-related complications and potentially extend life. Patients who require treatment are commonly given chemotherapeutic and/or immunotherapeutic agents (Eichhorst 2011, Gribben 2011, Hoppe 2012, Zelenetz 2014). However, most treated patients will eventually experience disease relapse, and some will experience recurrent disease even with initial induction therapy and later salvage therapy. Despite use of agents with differing mechanisms of action, progressive resistance to treatment develops. Patients with progressive disease have a poor prognosis; median survival for these groups of patients is generally ≤ 2 years. Therefore, novel mechanisms of action are needed to offer additional treatment options for patients with lymphoid malignancies who are experiencing progressive lymphadenopathy or symptoms due to disease progression.

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

8.1.2 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 a potent, highly selective covalent inhibitor of BTK (Covey 2015). Acalabrutinib is orally bioavailable in humans and is formulated as a capsule. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices. Summaries of relevant nonclinical and ongoing clinical studies are provided below. For more detailed background information, refer to the Investigator Brochure and Calquence product label.

Acalabrutinib is an investigational product. On 31 October 2017, acalabrutinib (Calquence) was approved by United States Food and Drug Administration (FDA) under Accelerated Approval for New Drug Application 210259 for the treatment of adult patients with MCL who have received at least 1 prior therapy.

Nonclinical Studies

In vitro and in vivo safety pharmacology and in vivo toxicology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile. For more detailed information on nonclinical safety of acalabrutinib, refer to the IB and Calquence product label.

Metabolism and Transport

In vivo, glutathione (GSH), glycine-cysteine (Gly-Cys), cysteine (Cys) and oxidized GSH conjugates were the major biotransformation products observed in rats and dogs. In vitro studies using human liver microsomes and recombinant systems expressing individual P450 isoforms showed that CYP3A4/5 is mainly responsible for oxidative metabolism of acalabrutinib. Based on available nonclinical and clinical data, acalabrutinib is cleared by multiple P450 and non-P450 metabolic pathways and CYP3A-mediated oxidation appears to be a major route of metabolism in humans. In vitro studies showed that acalabrutinib is a substrate for P-gp.

The major circulating acalabrutinib metabolite, ACP-5862, is formed by CYP3A-mediated oxidation. ACP-5862 is the only human metabolite in plasma that accounted for > 10% of total acalabrutinib-related material. In vitro evaluation of acalabrutinib and ACP-5862 demonstrated that ACP-5862 is also a covalent inhibitor of BTK.

Please refer to the IB and Calquence product label for more details on the metabolism of acalabrutinib.

Clinical Experience

Summary of Acalabrutinib Clinical Pharmacology in Healthy Subjects

The clinical pharmacology of acalabrutinib has been characterized in 10 studies conducted in healthy subjects, one of which also included subjects with mild and moderate HI, and in 7 Phase 1 and 2 hematologic oncology studies. A list of clinical pharmacology studies which have been conducted with acalabrutinib is presented in Section 8 of the Investigator Brochure (Annex 4). Acalabrutinib has a short PK half-life with a long-lasting PD effect due to covalent binding to BTK. PK properties of acalabrutinib in healthy adult subjects were evaluated after oral administration of 2 daily divided doses of 2.5 to 50 mg and a single dose of 100 mg. Acalabrutinib plasma T_{max} values were between 0.5 and 1.0 hour for all dose cohorts, and were independent of dose level. Mean half-life values ranged from 0.97 hours to 2.1 hours.

Acalabrutinib has an absolute oral bioavailability of 25% and can be taken with or without food. Acalabrutinib does not accumulate in plasma upon repeat-dose administration. Based on population PK analysis, acalabrutinib PK was linear over the 75-mg to 250-mg dose range. At a dose of 100 mg twice daily, exposure and an elimination half-life of approximately 1 hour were relatively comparable across most individuals in healthy subject and patient studies. Based on a population PK analysis, acalabrutinib dose adjustment is not required based on a patient's age, sex, body weight, ethnicity, race (white versus black), mild or moderate renal impairment status, mild HI status and/or Eastern Cooperative Oncology Group performance status (0 versus 1). Variability in exposure to acalabrutinib is mainly due to a combination of pH-dependent dissolution and absorption and predominantly CYP3A-mediated metabolism. Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on in vitro studies. Co-administration with a strong CYP3A inhibitor (200-mg itraconazole once daily for 5 days) increased the acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold in healthy subjects. Co-administration with a strong CYP3A inducer (600-mg rifampin once daily for 9 days) decreased acalabrutinib C_{max} by 68% and AUC by 77% in healthy subjects. The most abundant circulating metabolite in human was ACP-5862 (denoted M27) which was formed by CYP3A and also circulated in nonclinical species. In a hepatic impairment study (HI-101), compared to subjects with normal liver

function (n=6), acalabrutinib exposure (AUC) was increased by less than 2-fold in subjects with mild (n=6) (Child-Pugh A) and moderate (n=6) (Child-Pugh B) HI, respectively. Therapeutic plasma acalabrutinib concentrations after a 100-mg dose or supra-therapeutic plasma acalabrutinib concentrations after a 400-mg dose in healthy subjects did not prolong the QTc interval in a thorough QT study.

Refer to the IB and Calquence product label for detailed background information on acalabrutinib.

8.2 Rationale

8.2.1 Rationale for this Study and Study Design

This study is designed to meet the objectives outlined in Section 9.

The liver is involved in the clearance of many drugs through a variety of oxidative and conjugative metabolic pathways and/or through biliary excretion of the unchanged drug or metabolites. Alterations of these excretory and metabolic activities by HI can lead to higher drug exposure. Hepatic disease can alter the absorption and disposition of drugs as well as their efficacy and safety.

Study ACE-HI-001 already evaluated the effect of mild to moderate HI on the single-dose pharmacokinetics of acalabrutinib. The geometric mean AUC of acalabrutinib increased by [redacted]-fold and [redacted]-fold in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) HI, respectively, compared with subjects with normal liver function. Based on a population PK analysis, no clinically relevant PK difference was observed in subjects with mild and moderate HI relative to subjects with normal liver function.

The purpose of this study is to determine the effect of severe impaired hepatic function on the single-dose pharmacokinetics of acalabrutinib and its metabolite, ACP-5862. The data generated may provide guidance in developing dosage regimens for subjects with severe chronic hepatic dysfunction.

A group of matched-control subjects will be enrolled in the study as controls for the hepatic-impaired subjects to detect clinically relevant PK differences. These subjects will be matched in a 1:1 ratio to a subject with HI for age, weight, and sex variables.

8.2.2 Child-Pugh Classification of Hepatic Impairment

The Child-Pugh classification will be used to categorize HI due to its widespread use and acceptance by regulatory agencies (including the FDA). This study design is supported by FDA guidelines for drugs that undergo substantial hepatic metabolism and for which a dosage guideline is sought for subjects with HI.

In the current study, subjects with chronic, stable HI with features of cirrhosis due to any etiology will be enrolled, and the Child-Pugh scale will be used to classify the severity of liver disease. The scale employs 5 clinical measures of liver disease listed in Table 1. Each measure is scored 1 to 3, with 3 indicating most severe derangement. The bilirubin score in the table is dependent upon the type of cirrhosis (primary biliary cirrhosis versus all other causes). Subjects' scores of 10 to 15 on this scale are classified as having severe hepatic failure.

Table 1: Child-Pugh Classification of the Severity of Liver Disease

	Points Score for Increasing Abnormality		
Assessment	**1**	**2**	**3**
Encephalopathy[a]	None	Grade I or II (or suppressed by medication)	Grade III or IV or subject receiving medication(s) to prevent encephalopathy / or subject receiving medication(s) to treat grade III or IV encephalopathy
Ascites	Absent	Slight or on 1 medication to control ascites	Moderate or severe or on 2 medications to control ascites
Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (second prolonged) or International normalized ratio	<4 <1.7	4 to 6 1.7 to 2.2	>6 >2.2
Bilirubin (mg/dL)—not PBC[b] Bilirubin (mg/dL)—only for PBC[b]	<2 <4	2 to 3 4 to 10	>3 >10

[a] Portal-system encephalopathy is Staged 0 to 4.

[b] Select only 1 dependent on type of cirrhosis.

Abbreviation: PBC=Primary Biliary Cirrhosis.

8.2.3 Rationale for the Dose Selection

A 50-mg single oral dose of acalabrutinib has been selected for this study since this dose has been used in previous patient and healthy subject studies, and was well tolerated with no safety concerns. To date, single doses of up to 400 mg in healthy subjects and repeat doses of 100 to 400 mg QD for ≥ 28 days in subjects with relapsed/refractory CLL were tested and were well tolerated with no dose-limiting toxicity observed. In healthy subjects, the mean C_{max} and $AUC_{0\text{-last}}$ values were 1673 ng/mL and 3966 ng*h/mL, respectively, after a single 400-mg dose providing a clinical margin of safety for the 50-mg dose of approximately 7.5- and 16-fold for C_{max} and $AUC_{0\text{-last}}$, respectively. When a 50-mg dose was administered to subjects with moderate HI, the mean C_{max} and $AUC_{0\text{-last}}$ values were 288 ng/mL and 535 ng*h/mL, respectively, well within the clinical margin of safety. Two potential mechanism pathways may be affected in subjects with HI; 1) CYP3A4/5-mediated metabolism of acalabrutinib; and 2) the direct conjugation of acalabrutinib with glutathione through glutathione S-transferase. In the CYP3A inhibitor study (ACE-HV-001), the mean plasma acalabrutinib C_{max} and $AUC_{0\text{-last}}$ values increased 3.7-fold and 5.1-fold, respectively, in the presence of itraconazole, a strong inhibitor of CYP3A4/5, relative to no pretreatment. In this CYP3A interaction study in healthy subjects (n=17), no treatment-related AEs were reported.

8.2.4 Rationale for Endpoints

The primary objective of this study is to evaluate the plasma pharmacokinetics of acalabrutinib administered to subjects with severe HI. This study will be comparing the overall plasma PK profile (eg, AUC and C_{max}) of acalabrutinib in subjects with severe HI with that in matched-control subjects (ie, by age, weight, and sex).

8.3 Risks and/or Benefits to Subjects

The dose of acalabrutinib administered in this study is not anticipated to induce any potential risk or benefit to subjects participating in this study, because it is a single dose administered according to the recommendations listed in the IB.

The safety monitoring practices employed by this protocol (ie, 12-lead ECG, vital signs, clinical laboratory tests, AE questioning, and physical examinations, as applicable) are adequate to protect the subjects' safety and should detect all expected treatment-emergent AEs (TEAEs).

There will be no direct health benefit for study participants from receipt of study drug. An indirect health benefit to the matched-control subjects enrolled in this study is the free medical tests received at screening and during the study.

Risks Associated with Acalabrutinib Treatment

The following summarizes the experience with acalabrutinib in hematological cancer studies. For more detailed information on TEAEs and details regarding the clinical safety of acalabrutinib, refer to the current acalabrutinib IB.

Hemorrhage

Bleeding events, some fatal, including central nervous system, respiratory, and gastrointestinal hemorrhage, have been reported in subjects treated with acalabrutinib.

Subjects receiving antiplatelet or anticoagulant therapies may be at increased risk of hemorrhage and should be monitored for signs of bleeding. As a precaution, it is suggested per protocol that acalabrutinib be withheld for at least 3 days pre- and post-surgery.

Subjects with hemorrhage should be managed per institutional guidelines or as clinically indicated.

Infections

Serious infections, including fatal events, have been reported in subjects treated with acalabrutinib. Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate.

Hepatitis B Reactivation

Cases of HBV reactivation have been reported in subjects treated with acalabrutinib with 1 case resulting in liver failure and death.

Progressive Multifocal Leukoencephalopathy (PML)

Cases of PML have been reported in subjects treated 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
- Polymerase chain reaction analysis for JC virus DNA in cerebrospinal fluid

If PML is confirmed, permanently discontinue acalabrutinib.

Cytopenias

Grade 3 or 4 events of cytopenias, including neutropenia, anemia, and thrombocytopenia have occurred in subjects treated with acalabrutinib. Monitor blood counts as medically appropriate. Subjects with cytopenias should be managed according to institutional guidelines or as clinically indicated.

Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas, have been reported in subjects treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (squamous cell carcinoma of the skin). Subjects with a second primary malignancy should be managed according to institutional guidelines or as clinically indicated.

Atrial Fibrillation

Atrial fibrillation or flutter have been reported in subjects treated with acalabrutinib, Risk factors may include hypertension, diabetes mellitus, acute infections, or a previous history of atrial fibrillation. Subjects with atrial fibrillation should be managed per institutional guidelines or as clinically indicated.

9 OBJECTIVES AND ENDPOINTS

9.1 Objectives

Primary:

To compare the plasma pharmacokinetics of acalabrutinib and ACP-5862 in subjects with severe HI with that in matched-control subjects following a single-dose administration of 50-mg acalabrutinib.

Secondary:

To evaluate the safety and tolerability of acalabrutinib in subjects with severe HI after a single-dose administration of 50-mg acalabrutinib.

Exploratory:

The exploratory objectives listed below may be investigated at the discretion of the Sponsor:

- To determine the [redacted] of acalabrutinib and ACP-5862 in subjects with severe HI and matched-control subjects following a single 50-mg dose of acalabrutinib.
- To evaluate acalabrutinib and ACP-5862 [redacted] in subjects with severe HI and matched-control subjects following a single 50-mg dose of acalabrutinib.
- To assess the effect of acalabrutinib on plasma [redacted] in subjects with severe HI and matched-control subjects following a single 50-mg dose of acalabrutinib.

9.2 Endpoints

Pharmacokinetics

The following PK parameters will be calculated for acalabrutinib and its metabolite, ACP-5862, in plasma, as appropriate: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-}24}$, $AUC_{\%extrap}$, C_{max}, T_{max}, T_{last}, λ_z, $t_{½}$, CL/F (parent only), V_z/F (parent only), metabolite-to-parent ratio (MR)_C_{max}, MR_$AUC_{0\text{-last}}$, and MR_$AUC_{0\text{-inf}}$.

Relationship between plasma acalabrutinib and ACP-5862 PK parameters and hepatic function tests (prothrombin time, bilirubin levels, albumin levels, and Child-Pugh score) may be investigated.

[redacted] of acalabrutinib and ACP-5862 in plasma will be determined at specified timepoints from blood samples collected for this purpose as outlined in the Study Events Flow Chart (Section 6). Remaining PK blood samples may also be used to determine [redacted] of acalabrutinib and ACP-5862.

Remaining PK blood samples following analyses and dedicated [redacted] samples may be used for potential future analysis of [redacted] [Lai 2016]).

Urine samples may be used for potential future analysis to estimate acalabrutinib and ACP-5862 [redacted] and analysis of [redacted] [Lai 2016]).

Safety

Safety endpoints will include 12-lead ECGs, vital signs, clinical laboratory tests, AEs, and physical examinations, as applicable.

10 STUDY DESIGN

10.1 Overall Study Design and Plan

This is a Phase 1, non-randomized, open-label, single-dose study to evaluate the effect of severe HI on the pharmacokinetics of acalabrutinib and its major metabolite, ACP-5862. The study was designed in accordance with the FDA Guidance for Industry entitled, "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" (FDA 2003).

A total of 16 adult men and/or women will be enrolled. Eight subjects with severe HI (a score of 10 to 15, on the Child-Pugh scale) will be enrolled to obtain at least 6 evaluable subjects. Not more than 25% of the hepatic-impaired subjects (eg, 2 of 8 subjects with HI) will be allowed to have a TIPS. Eight subjects with normal hepatic function to match all evaluable subjects with severe HI in a 1:1 ratio. Subjects will be matched for age [within age groups <45 years old or ≥45 years old], body weight [± 20 %], and sex [1:1] to the subjects with HI.

Screening of subjects will occur within 28 days prior to dosing.

On Day 1, a single oral dose of acalabrutinib will be administered followed by PK blood sampling for 24 hours in matched-control subjects and for 72 hours in subject with HI. Urine samples will also be collected over a 24-hour collection interval.

Safety will be monitored throughout the study by repeated clinical and laboratory evaluations.

Discontinued subjects may be replaced at the discretion of the Sponsor.

10.1.1 Confinement, Return Visits, and Follow-Up

Subjects will be housed on Day -1, at the time indicated by the CRU, until after the 72-hour blood draw and/or study procedures for subjects with severe HI or until after the 24-hour blood draw and/or study procedures for matched-control subjects. At all times, a subject may be required to remain at the CRU for longer at the discretion of the PI or designee.

The CRU will attempt to contact all subjects who received the study drug (including subjects who terminate the study early) using their standard procedures approximately 14 days after dosing to determine whether any AE has occurred since the last study visit.

10.1.2 End of Study Definition

The end of study is defined as the date of the last scheduled study procedure as outlined in the Study Events Flow Chart (Section 6).

11 STUDY POPULATION

11.1 Inclusion Criteria

Subjects must fulfill all of the following inclusion criteria to be eligible for participation in the study:

All Subjects:

1. Continuous non-smokers or smokers (of fewer than 20 cigarettes/day or the equivalent). Subjects must agree to consume no more than 5 cigarettes or equivalent/day from 24 hours before dosing and throughout the period of sample collection.
2. Women must be of non-childbearing status (ie, subject is surgically sterile due to a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure with serum estradiol and FSH levels within the institutional postmenopausal range as per PI judgment; or is menopausal [≥ 50 years of age with amenorrhea for ≥ 6 months]).
3. Understands the study procedures in the ICF and be willing and able to comply with the protocol.
4. Willingness and ability to swallow study drug capsules.

Hepatic-Impaired Subjects Only:

5. Adult men or women, 18 to 75 years of age, inclusive, at screening.
6. BMI ≥ 19 and ≤ 40 kg/m^2, at screening.
7. Have medical history, physical examination, vital signs, 12-lead ECGs, and laboratory safety test results consistent with a diagnosis of HI, but is otherwise judged to be in good health as determined by the PI.
8. Subject has a diagnosis of chronic (> 3 months), stable (no acute episodes of illness within the previous 2 months due to deterioration in hepatic function) HI with features of cirrhosis due to any etiology.
9. Subject's score on the Child-Pugh scale must range from 10 to 15 at screening. Subjects who have compensated HI while on medical therapy should be classified by their pretreatment parameters.

Matched-Control Subjects Only:

5. Adult men and women will be matched in a 1:1 ratio to a specific subject in the HI group based upon age, weight, and sex. The following criteria should be fulfilled:
    a. 18 to 75 years of age, inclusive, at screening. Age must be within the same age group (ie, <45 years old or ≥45 years old) of the matched subject's age in the HI group.

b. BMI ≥ 19 and ≤ 40 kg/m^2 at screening. Weight must be within ± 20% of the matched subject's weight in the HI group.

6. Medically healthy with no clinically significant medical history, physical examination, laboratory profiles (including serum amylase and lipase, hematology, and thyroid function), vital signs, or ECGs, as deemed by the PI. Liver function tests (eg, serum ALT, AST), and serum bilirubin (total), must be ≤ the ULN at screening for inclusion.

11.2 Exclusion Criteria

Subjects must not be enrolled in the study if they meet any of the following criteria:

All Subjects:

1. History or presence of clinically significant or unstable medical or psychiatric condition or disease in the opinion of the PI.

2. Subject is mentally or legally incapacitated or has significant emotional problems at the time of the screening visit or expected during the conduct of the study.

3. History of any illness that, in the opinion of the PI, might confound the results of the study or poses an additional risk to the subject by their participation in the study.

4. Presence of any clinically significant, ongoing systemic bacterial, fungal, or viral infections (including upper respiratory tract infections, but excluding localized cutaneous fungal infections), in the opinion of the PI.

5. History of any major surgical procedure within 30 days before dosing.

6. History of stroke or intracranial hemorrhage within 6 months before the dosing.

7. History of a bleeding diathesis (eg, hemophilia, von Willebrand disease).

8. Any clinically significant condition that may affect acalabrutinib absorption in the opinion of the PI, including gastric restrictions and bariatric surgery (eg, gastric bypass). Subjects with cholecystectomy will be allowed.

9. Women with positive serum pregnancy test results or lactating.

10. Positive results for HIV at screening or using HIV protease inhibitors.

11. Have been on a diet incompatible with the on-study diet, in the opinion of the PI, within the 28 days before dosing, and throughout the study.

12. Donation of blood > 500 mL or significant blood loss within 56 days before the dose of study drug.

13. Plasma donation within 7 days before dosing.

14. Is working at or has an immediate family member (spouse or children) who works at the investigational site or is a Sponsor staff directly involved with this trial.

15. Dosed in another clinical trial within 28 days before dosing of study drug and throughout the current study. The 28-day window will be derived from the date of dosing in the previous study to Day 1 of the current study.

Hepatic-Impaired Subjects Only:

16. History or presence of drug abuse within 2 years before screening.

17. Positive results for the urine or breathalyzer alcohol test and/or urine drug screen at screening or check-in, unless the positive drug screen is due to prescription drug use and is approved by the PI and Acerta Pharma's medical monitor.

18. History of HBV infection or subjects with active HCV that have persistent elevations of transaminase levels > 6 times ULN.

19. Unable to refrain from or anticipates the use of:

    - Any medication (including prescription or over the counter, vitamins supplements, natural or herbal supplements) that cannot be discontinued ≥ 14 days before dosing and throughout the study. Note: hepatic-impaired subjects who are taking medications to treat stable diseases or to treat manifestations of hepatic disease and are on a stable dose, drug, and regimen for ~2 weeks before dosing will be allowed to participate in the study at the discretion of the PI. Consultation with Acerta Pharma's medical monitor may occur on a case-by-case basis, as described in Section 11.4.1. Ibuprofen (up to 1200 mg per 24-hour period) may be permitted during the study. See Section 11.4.1 for additional details on allowable and prohibited concomitant therapy.

    - Any drug known to be a strong or moderate inhibitor or inducer of CYP3A and/or P-gp, including St. John's Wort, should be restricted for 14 and 28 days, respectively, before dosing and throughout the study unless it was deemed acceptable following consultation with Acerta Pharma's medical monitor and the PI. Appropriate sources, such as those listed in Appendix 1, will be reviewed by the PI or designee to confirm lack of PK and / or PD interaction with study drug.

Matched-Control Subjects Only

16. History or presence of alcoholism and/or drug abuse within 2 years before screening.

17. Positive results for the urine or breathalyzer alcohol test and/or urine drug screen at screening or check-in.

18. Positive results at screening for HBsAg or HCV.

19. Seated blood pressure is < 90/40 mmHg or > 150/95 mmHg at screening.

20. Seated heart rate is < 40 bpm or > 99 bpm at screening.

21. Hemoglobin level below the lower limit of normal at screening, and considered clinically significant by the PI.

22. Unable to refrain from or anticipates the use of:

    - Any medication (including prescription or over the counter, vitamins supplements, natural or herbal supplements) that cannot be discontinued ≥ 14 days before dosing and throughout the study. Ibuprofen (up to 1200 mg per 24-hour period) may be permitted during the study. See Section 11.4.1 for additional details on allowable and prohibited concomitant therapy.

- Any drug known to be a strong or moderate inhibitor or inducer of CYP3A and/or P-gp, including St. John's Wort, should be restricted for 14 and 28 days, respectively, before dosing and throughout the study unless it was deemed acceptable following consultation with Acerta Pharma's medical monitor and the PI. Appropriate sources, such as those listed in Appendix 1, will be reviewed by the PI or designee to confirm lack of PK and / or PD interaction with study drug.

11.3 Early Termination of Subjects from the Study

Subjects are free to withdraw from the study at any time for any reason.

In addition, subjects may be withdrawn from the study by the PI or designee for the following reasons:

- AEs.
- Difficulties in blood collection.
- Positive pregnancy test result.

A subject may be withdrawn by the PI (or designee) or the Sponsor if enrollment into the study is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

The clinical report will include reasons for subject withdrawals as well as details relevant to the subject withdrawal.

11.4 Study Restrictions

11.4.1 Concomitant Therapy

All prescription or non-prescription medications (including St. John's Wort) that are strong or moderate inhibitors or inducers of CYP3A or P-gp transporters should be restricted. These inhibitors and inducers should not be allowed for 14 days and 28 days, respectively, before dosing and throughout the study. Appropriate sources, such as Appendix 1, will be consulted by the PI or designee to confirm lack of PK/PD interaction with study drug.

Subjects with Severe HI:

If a hepatic-impaired subject is taking a restricted medication, following discussion with Acerta Pharma's medical monitor, the PI may switch the hepatic-impaired subject to an alternate non-restricted medication. The hepatic-impaired subject can be screened for the study after a sufficient time period has elapsed to allow stabilization on the new medication (~2 weeks). This switch will be done after the hepatic-impaired subject signs the consent form.

Any medications (including prescription or over the counter, vitamins supplements, natural or herbal supplements) will be prohibited. They will not be allowed for ≥ 14 days before dosing and throughout the study, with the following exceptions:

- Ethacrynic acid will be prohibited for ≥ 24 hours before dosing and throughout the study.
- Proton pump inhibitors (eg, omeprazole) will be prohibited for ≥ 5 days before dosing and until 12 hours after dosing.
- Calcium carbonate containing drugs or supplements will be prohibited ≥ 2 hours before and after dosing.

- Lactulose and H2 receptor blockers (eg, ranitidine) will be prohibited ≥ 16 hours before and until 6 hours after dosing.

- Diuretics, neomycin, beta-blockers - prescription medications used to treat manifestations of hepatic disease in hepatic-impaired subjects: restricted ≥ 4 hours before and after dosing on Day 1. Subjects must be on a stable dose, drug, and regimen for ~2 weeks before dosing.

  Note: Any diuretics or beta-blockers that are strong or moderate CYP3A inhibitors or inducers (eg, conivaptan) are not permitted. The PI should switch subjects to a weak CYP3A inhibitor or inducer and subjects should be on a stable dose and regimen as noted above (~2 weeks for subjects before dosing).

- Other required prescribed concomitant medications needed to treat stable hepatic diseases: restricted ≥ 2 hours before and after dosing.

- Selective serotonin reuptake inhibitors (SSRI): restricted ≥ 4 hours before and after dosing on Day 1. Subjects must be on a stable dose, drug, and regimen for ~2 weeks before dosing. Note: Any SSRI that are strong or moderate CYP3A inhibitors or inducers are not permitted.

- Any prescribed concomitant medications needed to treat stable diabetes will be allowed on a case-by-case basis following discussion with Acerta Pharma's medical monitor. Allowed diabetes concomitant medications will be restricted ≥ 4 hours before and after dosing on Day 1. Subjects must be on a stable dose, drug, and regimen for ~2 weeks before dosing.

- Hormonal Replacement Therapy: postmenopausal subjects will be allowed to continue to take hormonal replacement therapy if they have started 1 month before dosing.

- Acetaminophen will be prohibited ≥ 2 hours before and after dosing.

- Ibuprofen (up to 1200 mg per 24 hours): may be administered at the discretion of the PI.

Matched-Control Subjects:

Any medications (including prescription or over the counter, vitamins supplements, natural or herbal supplements) will be prohibited. They will not be allowed for ≥ 14 days before dosing and throughout the study, with the following exceptions:

- Ethacrynic acid will be prohibited for ≥ 24 hours before dosing and throughout the study.

- Proton pump inhibitors (eg, omeprazole) will be prohibited for ≥ 5 days before dosing and until 6 hours after dosing.

- Calcium carbonate containing drugs or supplements will be prohibited ≥ 2 hours before and after dosing.

- H2 receptor blockers (eg, ranitidine) will be prohibited ≥ 16 hours before and until 6 hours after dosing.

- Hormonal Replacement Therapy: postmenopausal subjects will be allowed to continue to take hormonal replacement therapy if they have started 1 month before dosing.

- Acetaminophen will be prohibited ≥ 2 hours before and after dosing.

- Ibuprofen (up to 1200 mg per 24 hours): may be administered at the discretion of the PI.

The PI will review and approve all concurrent therapy with any medication during the course of the study including both prescription and non-prescription drugs in accordance with the restrictions listed above. However, if questions arise concerning the use of any medications, these must first be discussed between the PI and Acerta Pharma's medical monitor before administration, unless appropriate medical care necessitates that therapy should begin before Acerta Pharma's medical monitor can be consulted.

Should there be a clinical indication for any additional medication during the course of the study, the name of the drug, dosage, date of administration, and reason for use must be recorded on the appropriate case report form. All medications taken by subjects during the course of the study will be recorded. The use of any non-study medication during this study may require discontinuation of the subject following discussion between the PI and the Sponsor.

11.4.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/Caffeine: 24 hours prior to dosing and throughout the period of PK sample collection (small amounts of caffeine derived from normal foodstuffs eg, 250 mL/8 oz./1 cup decaffeinated coffee or other decaffeinated beverage, per day, with the exception of espresso; 45 g/1.5 oz. chocolate bar, per day, would not be considered a deviation to this restriction);
- Alcohol: 48 hours prior to dosing and throughout the period of PK sample collection;
- Grapefruit/Seville orange: 14 days prior to dosing and throughout the period of PK sample collection.

If deviations occur, the PI or designee in consultation with the Sponsor if needed will decide on a case-by-case basis whether the subject may continue participation in the study.

11.4.3 Meals

Water (except water provided with dosing) will be restricted 1 hour prior to and 1 hour after study drug administration, but will be allowed ad libitum at all other times. Other fluids may be given as part of meals and snacks but will be restricted at all other times throughout the confinement period.

Subjects will fast overnight ≥ 10 hours before study drug administration and will continue the fast for ≥ 2 hours after dosing. A low–fat snack (eg, 2 slices of toast with jelly) will be given 2 hours after dosing and should be consumed in its entirety.

When confined, standard meals and snacks will be provided at appropriate times, except when they are required to fast. When confined in the CRU, subjects will be required to fast from all food and drink except water between meals and snacks.

Each meal and/or snacks served at the CRU will be standardized and will be similar in caloric content and composition.

11.4.4 Activity

Subjects will remain ambulatory or seated upright for the first 4 hours after dosing, except when they are supine or semi-reclined for study procedures. However, should AEs occur at any time, subjects may be placed in an appropriate position or will be permitted to lie down on their right side.

Specific measures will be taken to prevent the subject from missing a urine collection by strictly controlling and providing access to designated restrooms only. Subjects will be asked to void prior to entering the shower.

Subjects will be instructed to refrain from strenuous physical activity that could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

Depending on the CRU rules and regulations, subjects may be prohibited from smoking during their confinement or during portions of their confinement.

12 TREATMENTS

12.1 Treatments Administered

Acalabrutinib will be supplied as 50-mg hard gelatin capsules.

Each subject will receive a single 50-mg acalabrutinib (1 x 50-mg capsules) to be administered orally with approximately 240 mL of water at Hour 0 on the morning of Day 1, after an overnight fast.

Subjects will be instructed not to crush, split, or chew the study drug.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each subject.

The exact clock time of dosing will be recorded.

12.2 Dose Modification

The dose and administration of the study drug to any subject may not be modified. If necessary a subject must be discontinued for the reasons described in Section 11.3.

12.3 Method of Treatment Assignment

Each subject will be assigned a unique identification number upon screening. Subjects who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique identification number at the time of dosing, different from the screening number, and will receive acalabrutinib on 1 occasion.

If replacement subjects are used, the replacement subject number will be 100 more than the original (eg, Subject No. 101 will replace Subject No. 1).

12.4 Blinding

This is an open-label study.

12.5 Treatment Compliance

A qualified designee will be responsible for monitoring the administration of the timed oral dose. A mouth check will be performed by the qualified designee to ensure that the subjects have swallowed the study drug. Once a subject has finished the dosing water, the qualified designee will use a flashlight and a tongue depressor to check the subject's mouth. Subjects' hands will also be verified to ensure that the study drug was ingested.

13 STUDY ASSESSMENTS AND PROCEDURES

The Study Events Flow Chart (Section 6) summarizes the clinical procedures to be performed at each visit. Individual clinical procedures are described in detail below. Additional evaluations/testing may be deemed necessary by the PI or designee and/or the Sponsor for reasons related to subject safety.

For this study, the blood collection for acalabrutinib and its metabolite ACP-5862 is the critical parameter and needs to be collected as close to the exact time point as possible. All other procedures should be completed as close to the prescribed/scheduled time as possible, but can be performed prior or after the prescribed/scheduled time.

Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

13.1 Screening

Within 28 days prior to dosing, medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI (kg/m^2) and tobacco use (including number of cigarettes smoked per day) will be reported. Each subject will have a physical examination, vital sign measurements (heart rate, blood pressure, temperature, and respiratory rate), 12-lead ECG, and the laboratory tests of hematological, coagulation, hepatic and renal function and additional tests as noted in Section 13.2.4.

Re-evaluation of the following procedures may be performed for the purpose indicated below:

1. For inclusion and Child-Pugh categorization laboratories that are deemed inconsistent with the usual stage of hepatic impairment of the subject may be repeated.
2. For eligibility purposes, abnormal vital signs, laboratory, or ECG results may be repeated if an abnormal result is observed at the initial reading.
3. In the event that the participation of a subject in the study is delayed and some screening procedures had been performed outside the prescribed screening window, outdated screening procedures can be repeated.
4. Subjects who do not qualify based on a reversible medical condition or mild inter-current illness may be re-evaluated after further testing/examination or re-screened after the condition is resolved.

13.2 Safety Assessments

13.2.1 Physical Examination

A full physical examination will be performed as outlined in the Study Events Flow Chart (Section 6). Symptom-driven physical examinations may be performed at other times, if deemed necessary by the PI or designee.

13.2.2 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure and heart rate, will be measured as outlined in the Study Events Flow Chart (Section 6). Additional vital signs may be taken at any other times, if deemed necessary.

Blood pressure and heart rate measurements will be performed with subjects in a seated position, except when they are supine or semi-reclined because of study procedures and/or AEs (eg, nausea, dizziness) or if deemed necessary by the PI or designee.

Vital signs will be measured within 24 hours prior to Day 1 dosing for the pre-dose time point. When scheduled after dosing, vital signs will be performed within approximately 15 minutes of the scheduled time point.

13.2.3 ECG Monitoring

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Additional ECGs may be taken at any other times, if deemed necessary by the PI or designee.

ECGs will be performed with subjects in a supine position for ≥ 5 minutes. All ECG tracings will be reviewed by the PI or designee.

ECGs will be measured within 24 hours prior to Day 1 dosing for the pre-dose time point. When scheduled after dosing, ECGs will be performed within approximately 20 minutes of the scheduled time point.

13.2.4 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the PI or designee. Laboratory results that are deemed inconsistent with the usual stage of HI of the subject may be repeated.

Hematology

- Hemoglobin
- Hematocrit
- Total and differential leukocyte count
- Red blood cell count
- Platelet count

Coagulation

- prothrombin time (PT)/ international normalized ratio (INR)

Serum Chemistry[a]

- Blood Urea Nitrogen
- Bilirubin (total and direct)
- Alkaline phosphatase
- AST
- ALT
- Albumin
- Protein (total)
- Sodium
- Potassium
- Chloride
- Calcium
- Phosphorus
- Glucose (fasting)
- Gamma-glutamyl transferase
- Lactate dehydrogenase
- Uric acid
- Cholesterol
- Triglycerides
- Amylase
- Lipase
- Creatinine[b]

Urinalysis
- pH
- Specific gravity
- Protein[c]
- Glucose
- Ketones
- Bilirubin
- Blood[c]
- Nitrite[c]
- Urobilinogen
- Leukocyte esterase[c]

Additional Tests
- HIV test
- HBsAg
- HCV
- Thyroid stimulating hormone (TSH)
- Urine drug screen
  - Opiates
  - Amphetamines
  - Barbiturates
  - Benzodiazepines
  - Cocaine
  - Cannabinoids
  - Tricyclic antidepressants
  - Methadone
- Urine/breathalyzer alcohol screen
- Serum pregnancy test (for women only)
- FSH (for postmenopausal women only)

a Serum chemistry tests at screening will be performed after a fast of ≥ 12 hours. Samples for fasting cholesterol, triglycerides, amylase, and lipase will be collected only at screening. On-study samples (including check-in and before check-out) will be obtained after a fast of ≥ 8 hours; however, in case of dropouts or rechecks, subjects may not have fasted for 8 hours before the serum chemistry sample is taken.

b At screening, creatinine clearance will be calculated using the Cockcroft-Gault formula.

c If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination (for red blood cells, white blood cells, bacteria, casts, and epithelial cells) will be performed.

13.2.5 Adverse Events

13.2.5.1 Adverse Event Definition

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

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period (see Section 13.2.6.1)

- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)

- Pre-existing medical conditions (other than the condition being studied) judged by the PI 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: A pre-existing condition (documented on the medical history case report form) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.

- Pre-planned hospitalization: A hospitalization planned before signing the ICF is not considered a serious adverse event (SAE), but rather a therapeutic intervention. However, if during the pre-planned 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 (eg, routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.

Abnormal laboratory results that the Investigator considers to not be clinically significant: Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low hemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).

13.2.5.2 Serious Adverse Event

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

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

- It results in death (ie, the AE actually causes or leads to death).

- It is life-threatening (ie, the AE, in the view of the PI, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).

- It requires or prolongs in-patient hospitalization.

- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject’s ability to conduct normal life functions).

- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.

- It is considered a significant medical event by the PI based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

13.2.5.3 Severity

Definitions found in the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (CTCAE 2017) will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

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

13.2.5.4 Adverse Events of Special Interest

This protocol will record, on a specific electronic case report form (eCRF), any AEs related to risk of serious bleeding. The AEs of interest on this protocol are as follows:

- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome
- Bleeding causing a fall in hemoglobin level of ≥ 20 g/L or leading to transfusion of ≥ 2 units of whole blood or red cells
- Bleeding resulting in a serious adverse drug experience (as defined in Section 13.2.5.2)

13.2.6 Documenting and Reporting of Adverse and Serious Adverse Events

The PI is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the previous sections, are recorded on the SAE report form.. All SAEs also must be reported on the SAE report form (see Section 13.2.6.4).

13.2.6.1 Adverse Events Reporting Period

The AE reporting period for this study begins when the subject receives the dose of study drug and ends, irrespective of seriousness, 30 days after the last dose of study drug. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. SAEs occurring 30 days after the reporting period ***AND*** assessed by the PI as related to acalabrutinib must be reported.

If an SAE is present at the last study visit, the SAE should be followed to resolution or until the PI assesses the subject as stable or the subject is lost to follow-up or withdraws consent. Resolution/stable means the subject has returned to baseline state of health or the PI does not expect any further improvement or worsening of the event.

13.2.6.2 Assessment of Adverse Events

The PI and/or designee will assess the occurrence of AEs and SAEs at all subjects' evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means, will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE report form.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' Answer: Yes or No.

See Appendix 2 for more detail on assessing relationship.

13.2.6.3 Pregnancy

The PI 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 (see personnel listed in Section 3). Any pregnancy-associated SAE must be reported using the SAE report form, according to the usual timelines and directions for SAE reporting (see Section 13.2.6.4).

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 30 days after dosing study medication will be reported, followed to conclusion, and the outcome reported.

Monitoring of the pregnancy should continue until conclusion of the pregnancy at which point the Pregnancy Report Form must be completed and submitted to Acerta Pharma Drug Safety (see personnel listed in Section 3). If a viable baby is born, then 2 months postpartum the Pregnancy Report Form must be completed and submitted.

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

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

13.2.6.4 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discovery. Initial SAE reports and follow-up information will be reported using the SAE report form. The paper SAE report form must be emailed or faxed to Acerta Pharma Drug Safety (see personnel listed in Section 3). Acerta Pharma Drug Safety may request follow-up and other additional information from the PI (eg, hospital admission/discharge notes and laboratory results).

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

All deaths should be reported with the primary cause of death as the AE term, 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 (see personnel listed in Section 3) or designee, as outlined above.

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

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

13.2.6.5 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 PI assesses the subject as stable, or the subject is lost to follow-up or withdraws consent.

13.3 Pharmacokinetic Assessments

13.3.1 Blood Sampling and Processing

For all subjects, blood samples for the determination of acalabrutinib and ACP-5862 plasma concentrations and blood samples collected for determination of acalabrutinib and ACP-5862 [redacted] only, will be collected in lithium heparin tubes, at scheduled time points as delineated in the Study Events Flow Chart (Section 6).

Remaining PK blood samples following analyses may be used for potential future analysis of acalabrutinib and ACP-5862 [redacted] and [redacted] [Lai 2016]). Remaining dedicated [redacted] samples may also be used for potential future analysis of [redacted]

The allowable deviation window is as follows:

Sample time	Allowed deviation
0 < sampling ≤ 8 hours	± 2 minutes
8 hours < sampling ≤ 24 hours	± 5 minutes
Sampling > 24 hours	± 10 minutes

A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

13.3.2 Plasma Pharmacokinetic Parameters

PK parameters for plasma acalabrutinib and ACP-5862 will be calculated as follows, as appropriate:

$AUC_{0\text{-last}}$: The area under the concentration-time curve, from time 0 to the last observed non-zero concentration, as calculated by the linear trapezoidal method.

$AUC_{0\text{-}24}$: The area under the concentration-time curve from time 0 to the 24-hour time point, as calculated by the linear trapezoidal method. If the 24-hour plasma concentration is missing, below the limit of quantification or not reportable, then this parameter cannot be calculated.

$AUC_{0\text{-}inf}$:	The area under the concentration-time curve from time 0 extrapolated to infinity. $AUC_{0\text{-}inf}$ is calculated as the sum of $AUC_{0\text{-}last}$ plus the ratio of the last measurable plasma concentration to the elimination rate constant.
$AUC_{\%extrap}$:	Percent of $AUC_{0\text{-}inf}$ extrapolated, represented as (1 - $AUC_{0\text{-}last}$/$AUC_{0\text{-}inf}$)*100.
CL/F:	Apparent total plasma clearance after oral (extravascular) administration, calculated as Dose/$AUC_{0\text{-}inf}$ (parent only).
C_{max}:	Maximum observed concentration.
T_{max}:	Time to reach C_{max}. If the maximum value occurs at > 1 time point, T_{max} is defined as the first time point with this value.
T_{last}:	Time of the last measurable concentration.
λ_z:	Apparent terminal elimination rate constant; represents the fraction of drug eliminated per unit time.
$t_{½}$:	Apparent first-order terminal elimination half-life will be calculated as 0.693/ λ_z.
V_z/F:	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration, calculated as (Dose/$AUC_{0\text{-}inf}$) x λ_z (parent only).
f_u	Fraction of unbound drug in plasma (if evaluated).

The following MR PK parameters will also be calculated after molar conversion: MR_C_{max}, MR_$AUC_{0\text{-}last}$, and MR_$AUC_{0\text{-}inf}$.

No value for λ_z, $AUC_{0\text{-}inf}$, CL/F, V_z/F, or $t_{½}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile.

No PK parameters will be calculated for subjects with 2 or fewer consecutive time points with detectable concentrations.

Individual and mean plasma concentration-time curves (both linear and log-linear) will be included in the final report.

PK parameters may also be expressed in terms of unbound concentrations (eg, C_{maxu}, AUC_u, and CL_u/F) and may be reported separately from the clinical study report (CSR), as appropriate.

13.3.3 Urine Sampling and Processing

For all subjects, urine samples for the possible future analyses to estimate acalabrutinib and ACP-5862 [redacted], as well as [redacted] will be collected at scheduled intervals as delineated in the Study Events Flow Chart (Section 6).

Prior to the pre-dose sample, each subject will be instructed as to urine collection methods. All urine during an interval is to be collected.

On Day 1, a spot collection will be obtained prior to dosing for the pre-dose sample. Subjects will be asked again to empty their bladder within approximately 15 minutes prior to dosing, and no urine will be collected at this time unless it is needed for the pre-dose sample. Only 1 pre-dose urine sample will be collected on Day 1.

Subjects will be encouraged to void at the end of each collection interval. If they do void at any time during the collection interval, the time should be documented. Should this be the case, subjects need

to void again at the end of the collection period, as scheduled. However, should subjects be unable to void, this will be documented as well.

Urine will be refrigerated during the collection intervals. At the end of each interval, urine will be pooled and thoroughly mixed. Total urine volume will be weighed and recorded.

Instructions for urine sampling, collection, processing, and sample shipment will be provided separately document.

13.3.4 Urine Pharmacokinetic Parameters

PK parameters for urine acalabrutinib and ACP-5862 may be calculated if urine analysis is performed, as follows:

Ae_{t1-t2}	Amount of unchanged drug excreted in the urine collection interval from t_1 to t_2.
Ae:	Total amount of drug excreted unchanged in the urine over the entire period of sample collection (0-X h), obtained by adding the amounts excreted over each collection interval.
CL_R:	Renal clearance calculated as $Ae_{(t'-t")}/AUC_{(t'-t")}$ where t'-t" is the longest interval of time during which Ae and AUC are both obtained.

13.3.5 Analytical Method

Samples will be analyzed for plasma acalabrutinib and ACP-5862 and [redacted] of acalabrutinib and ACP-5862 using validated bioanalytical methods. Possible future analyses of urine samples may be performed for acalabrutinib and ACP-5862 concentrations and [redacted] using validated bioanalytical methods. Samples from subjects to be assayed are specified in Section 14.2.

Remaining plasma samples may be analyzed for [redacted] (ie. PK blood samples) and [redacted] (ie, PK and [redacted] blood samples), if deemed appropriate.

13.4 Blood Volume Drawn for Study Assessments

Table 2: Blood Volume during the Study

Sample Type	Number of Time Points	Approximate Volume per Time Point [a] (mL)	Approximate Sample Volume Over Course of Study (mL)
Screening laboratory safety tests (including hematology, serum chemistry, serology, TSH, and PT/INR), FSH (for postmenopausal women only) and serum pregnancy (for women only).	1	16	16
On-study hematology and serum chemistry (this includes serum pregnancy for women only when scheduled at the same time) for subject with HI	3	12.5	37.5
On-study hematology and serum chemistry (this includes serum pregnancy for women only when scheduled at the same time) for matched-control subject	2	12.5	25
Blood for acalabrutinib and ACP-5862 pharmacokinetics / [redacted] for subject with HI	21	4	84
Blood for acalabrutinib and ACP-5862 pharmacokinetics / [redacted] for matched-control subject	17	4	68
Blood for acalabrutinib and ACP-5862 [redacted]	3	4	12
Total Blood Volume for subject with HI (mL)→			149.5 [b]
Total Blood Volume for matched-control subject (mL)→			121 [b]

a Represents the largest collection tube that may be used for this (a smaller tube may be used).

b A temporary intravenous device type catheter may be used for blood collection and a heparin flush may be used as per CRU's standard practices. At least 0.5 mL of blood must be withdrawn from the temporary intravenous device type catheter before PK samples are collected. If additional safety, PK, or PD analysis is necessary, if larger collection tubes are required to obtain sufficient plasma/serum for analysis, or if a temporary intravenous device type catheter is used, additional blood (up to 50 mL) may be drawn.

Abbreviations: CRU = Clinical research unit, FSH = Follicle stimulating hormone, HI = Hepatic Impairment, HIV = Human immunodeficiency virus, INR = international normalized ratio, PK = Pharmacokinetic, PT = prothrombin time, TSH = Thyroid stimulating hormone.

14 STATISTICAL CONSIDERATIONS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCP.

14.1 Sample Size Determination

The sample size chosen for this study was selected without statistical considerations and was based on FDA guidance for Industry (FDA 2003). It has been determined adequate to meet the study objectives.

14.2 Population for Analyses

Safety Population: All subjects who received the study drug will be included in the safety evaluations.

PK Population: All subjects who received the study drug and displayed evaluable PK profiles will be included in the PK evaluations and the statistical analyses. If subjects show unusual findings (e.g., vomiting at/or before 2 times median Tmax, incomplete dosing, non-compliance), these subjects may be excluded from PK evaluations and statistical analyses..

14.3 Statistical Analyses

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

14.3.1 Pharmacokinetic Analyses

14.3.1.1 Descriptive Statistics

Values will be calculated for the plasma concentrations and the PK parameters listed in Section 13.3.2 using appropriate summary statistics to be fully outlined in the SAP. If urine samples are analyzed, similar descriptive statistic for the urine concentrations and renal clearance may be calculated as appropriate.

14.3.1.2 Analysis of Variance

Individual $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, $AUC_{0\text{-}24}$, and C_{max} values of acalabrutinib after a single-dose administration of 50-mg acalabrutinib to subjects with severe HI and matched-control subjects (matched by age, weight, and sex to subjects with severe HI) will be ln-transformed and evaluated with an ANOVA. The ANOVA model will include population as fixed effects. The 90% confidence interval of the difference will be calculated. The estimates from the ANOVA will be back transformed to the original scale and presented.

The unbound AUC and C_{max} (ie, AUC_u and C_{maxu}) for [redacted] of acalabrutinib may be examined in an exploratory fashion and may be reported separately from CSR, as appropriate.

Similar analyses may be performed for plasma ACP-5862 PK parameters.

14.3.2 Other analysis

The relationship between plasma acalabrutinib and ACP-5862 pharmacokinetics and HI may be examined in an exploratory manner via a scatter plot of plasma acalabrutinib and ACP-5862 PK

parameters versus the Child-Pugh score, including the data from subjects with HI, and matched-control subjects as reference.

Relationships between plasma acalabrutinib and ACP-5862 PK parameters and the baseline laboratory components of the Child-Pugh score (ie, bilirubin and albumin levels) may be assessed graphically.

14.3.3 Safety Analyses

All safety data will be populated in the individual eCRFs. All safety data will be listed by subject.

Dosing dates and times will be listed by subject.

AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion and summarized by population for the number of subjects reporting the TEAE and the number of TEAEs reported. A by-subject AE data listing including verbatim term, coded term, population, severity, and relationship to treatment will be provided.

Safety data including ECGs, vital signs assessments, and clinical laboratory results will be summarized by population and time point of collection.

Descriptive statistics using appropriate summary statistics will be calculated for quantitative safety data as well as for the difference to baseline, when appropriate.

Concomitant medications will be listed by subject and coded using the most current version of WHO drug dictionary available at Celerion. Medical history will be listed by subject.

15 STUDY ADMINISTRATION

15.1 Ethics

15.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the IRB has approved the protocol or a modification thereof. The IRB is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The IRB is ICH compliant.

15.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, 21 CFR Parts 50, 56, and 312, the ethical principles set forth in the Declaration of Helsinki, GCP, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

15.1.3 Subject Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date an ICF summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Subjects will be given a copy of their signed ICF.

15.2 Termination of the Study

Celerion/clinical site reserves the right to terminate the study in the interest of subject welfare.

Sponsor reserves the right to suspend or terminate the study at any time.

15.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion/clinical site relevant to the quality of this study. Designated personnel of Celerion will be responsible for implementing and maintaining quality assurance (QA) and quality control systems to ensure that the study is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements and local laws, rules and regulations relating to the conduct of the clinical study.

The Clinical Study Report will be audited by the QA department and the QA audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® or comparable statistical program to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to database lock.

15.4 Direct Access to Source Data/Documents

Celerion/clinical site will ensure that the Sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other study-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

15.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of acalabrutinib capsules to allow completion of this study. The lot numbers and expiration dates (where available) of the study drug supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the study drugs supplied. At the conclusion of the study, any unused study drugs will be retained by the site, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

15.6 Data Handling and Record Keeping

Celerion standard eCRFs will be supplied. eCRFs are printed off directly from the database. Each eCRF is reviewed and signed by the PI.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained by Celerion until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the PI/Institution as to when these documents no longer need to be retained.

15.7 Report Format

According to the ICH Harmonized Tripartite Guideline (Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use M4 and the ICH M2 Expert Working Group), the final report will be written according to the ICH E3 Guideline (Structure and Content of Clinical Study Reports).

15.8 Publication Policy

All unpublished information given to Celerion/clinical site by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

16 REFERENCES

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Appendix 1 – Known Strong and Moderate In Vivo Inhibitors or Inducers of CYP3A and P-gp

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[d]
boceprevir	carbamazepine
clarithromycin	phenytoin
cobicistat	mitotane
conivaptin	rifampin
indinavir	St John's wort
itraconazole	enzalutamide
ketoconazole	
lopinavir/ritonavir (combination drug)	
danoprevir/ritonavir (combination drug)	
elvitegravir/ritonavir (combination drug)	
Indinavir/ritonavir (combination drug)	
paritaprevir/ritonavir and (ombitasvir and/or dasabuvir)	
tipranavir/ritonavir (combination drug)	
Mibefradil[b]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir	
saquinavir	
telaprevir	
telithromycin	
troleandomycin	
voriconazole	

Moderate Inhibitors of CYP3A	Moderate Inducers of CYP3A
aprepitant	bosentan
cimetidine	efavirenz
ciprofloxacin	etravirine
clotrimazole	modafinil
crizotinib	
cyclosporine	
dronedarone	
erythromycin	
fluconazole	
fluvoxamine	
imatinib	
tofisopam	
verapamil	

Inhibitors of P-gp[c]

amiodarone
carvedilol
clarithromycin
dronedarone
itraconazole
lapatinib
lopinavir/ritonavir
propafenone
quinidine
ranolazine
ritonavir

saquinavir/ritonavir telaprevir tipranavir/ritonavir verapamil

a. A strong inh bitor is defined as able to increases the AUC of a substrate by ≥ 5-fold.
b. Withdrawn from the United States market because of safety reasons.
c. Defined as able to increase the AUC of digoxin ≥ 2-fold with co-administration.
d. A strong inducer is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate.

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.

Based:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers . Web link https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Abbreviation: CYP = cytochrome P450 enzymes

Appendix 2 - Adverse Event Assessment Causality

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

No___ Yes___

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

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

The adverse event:

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

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

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or 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