Clinical Study Protocol	
Drug Substance	Acalabrutinib
Study Code	D822FC00003
Version	5.0
Date	24Jul2020

A Phase 2, Open Label, Randomized Study of the Efficacy and Safety of Acalabrutinib with Best Supportive Care Versus Best Supportive Care in Subjects Hospitalized with COVID-19

Sponsor:

Acerta Pharma B.V., a Dutch limited liability company, whose registered office is at Kloosterstraat 9, 5349 AB, Oss, The Netherlands, a member of the AstraZeneca group ("Company")

IND Number 149513

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 4 (Version 5.0)	24Jul2020
Amendment 3 (Version 4.0)	23Jun2020
Amendment 2 (Version 3.0)	13May2020
Amendment 1 (Version 2.0)	08May2020
Original Protocol (Version 1.0)	01May2020

Amendment 4 (24Jul2020)

The overall rationale for this amendment was to address feedback from study sites that are managing patient care during the COVID-19 pandemic.

In addition to the amendment changes summarized below, a few minor errors and typos were corrected.

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
1.1 Schedule of Activities (Table 1 and Table 2)	Removed Day 1 column from both Tables 1 and 2. Made changes to "Daily until hospital discharge" column to adjust for this change.	Clarification	Non-substantial
1.1 Schedule of Activities (Table 1)	CCI		Substantial
1.1 Schedule of Activities (Table 2)			Substantial
1.1 Schedule of Activities (Table 1 and Table 2), 8.3 On-study Procedures	Added nasal swab sample collection for SARS-CoV-2 viral load/viral shedding	To clarify method of sample collection for SARS-CoV-2 viral load/viral shedding	Substantial

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
1.1 Schedule of Activities (Table 1), 9.6.3 Pharmacokinetic and Pharmacodynamic Analyses	Added footnote t to Table 1 and text to Section 9.6.3 to indicate that PK assessments will be conducted in up to 15 evaluable subjects and PD assessments in up to 15 evaluable subjects randomized to Arm 1 (acalabrutinib + BSC)	Assessment in up to 15 evaluable subjects each are considered adequate to characterize the PK/active metabolite and PD, respectively, of acalabrutinib in the COVID-19 population	Non-substantial
1.2 Synopsis, 6.1.1 Dosing and Duration of Treatment, 6.1.3.1 Drug-drug Interactions, 6.5.4 Acalabrutinib Drug-drug Interaction Guidance in the Presence of Life-threatening COVID-19 Infection, 6.5.4.2 Active Substances That May Decrease Acalabrutinib Plasma Concentrations	For subjects not on PPIs, removed volume (240 mL) of water and just stated that it should be taken with water. For subjects who are on PPIs, changed volume of COCA-COLA from 240 mL to "at least 100 mL".	Based on in-vitro data, administering acalabrutinib 100 mg oral capsules (in the presence of PPIs) with at least a 100 mL of COCA-COLA is considered to be adequate for mitigating the effect of PPIs on acalabrutinib PK/PD	Non-substantial
1.2 Synopsis, 4.4 Internal DMC	Added text to indicate that the iDMC will review safety and efficacy data. In addition, the iDMC may support any health authority interactions or internal discussions based on their review, and the study team will remain blinded to the data that the iDMC will review.	For transparency and to preserve the trial integrity	Substantial
5.2 Exclusion Criteria	Removed the cutoffs for oxygen flow rates from Exclusion Criterion 1 and indicated that subjects should be considered for eligibility in part based on their ability to swallow pills	Clarified which patients with respiratory failure are eligible for enrollment	Substantial

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
	Added an exception to Exclusion Criterion 8 to indicate that AST and/or ALT can be up to 5 × ULN if considered due to underlying COVID-19, but cannot be associated with concurrent elevated bilirubin (up to 2 × ULN)	Hepatotoxicity and ALT/AST are not currently adverse drug reactions for acalabrutinib and there is evidence for ALT/AST increases associated with COVID-19 (Cai et al 2020, Guan et al 2020)	Substantial
8.1 Screening Assessments, 8.1.1 Informed Consent	Moved second paragraph under Section 8.1.1 to Section 8.1	Paragraph relates to all screening visits	Non-substantial
9.6. Statistical Analyses	Added a description of the timing of the primary analysis of the study and the updated analysis	For clarity	Non-substantial

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BSC = best supportive care; COVID-19 = coronavirus disease 2019; iDMC = internal Data Monitoring Committee; PD = pharmacodynamics; PK = pharmacokinetics; PPI = proton-pump inhibitor; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; ULN = upper limit of normal.

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1. PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

The SoAs for Arm 1 (acalabrutinib + best supportive care [BSC]) and Arm 2 (BSC only) are presented in Table 1 and Table 2, respectively.

Table 1 Schedule of Activities - Arm 1 (Acalabrutinib + BSC)

Assessments	Screening (Day -3 to Day -1 [l])	Daily until hospital discharge	Day 10 or discharge [h]	Day 14 (±2 days) after randomi-zation	Day 28 (±3 days) after randomi-zation	Safety FU 28 (±3) days after last dose of acala-brutinib [i]	Long-term FU 90 (±7) days after randomi-zation [i,j]	CSP section
Informed consent	X							8.1.1
Demography	X							8.1.2
Determine eligibility	X							5.1, 5.2
Medical history and COVID-19 epidemiology	X							8.1.4
Physical examination (symptom driven, including lung auscultation, height, weight)	X							8.1.5
Chest imaging	X [r]	As clinically indicated						8.1.5, 8.3
Electrocardiogram	X [l]	As clinically indicated	X					8.1.5, 8.3
Echocardiogram	As clinically indicated	As clinically indicated						8.1.5, 8.3
Vital signs (blood pressure, respiratory rate, oximetry, pulse and body temperature)	X [s]	X	X	X	X			8.1.6, 8.3
Local laboratory assessments:								
Urine or serum pregnancy test (for WOCBP only)	X			X		X		8.1.7, 8.3
Hematology [b]	X	X	X	X	X	X		8.1.8, 8.3
Serum or plasma chemistry [c]	X	X	X	X	X	X		8.1.8, 8.3
Arterial blood gases (if available) [n]	X	X		X	X			8.1.6, 8.1.8, 8.3, 8.4.1
Hepatitis B and C testing [d]	X	As clinically indicated				As clinically indicated		6.6.3, 8.1.8, 8.3
Serum ferritin [m]	X	qod (starting from Day 1)	X	X	X			8.1.8, 8.3
Fibrinogen [m]	X	qod						8.1.8, 8.3
PT, aPTT, and INR [m]	X	qod						8.1.8, 8.3

Table 1 Schedule of Activities - Arm 1 (Acalabrutinib + BSC)

Assessments	Screening (Day -3 to Day -1 [l])	Daily until hospital discharge	Day 10 or discharge [h]	Day 14 (±2 days) after randomi-zation	Day 28 (±3 days) after randomi-zation	Safety FU 28 (±3) days after last dose of acala-brutinib [i]	Long-term FU 90 (±7) days after randomi-zation [i,j]	CSP section
D-dimer [m]	X	qod		X	X			8.1.8, 8.3
CRP	X	X	X	X	X			8.1.8, 8.3
Procalcitonin (if available) [m]	X	qod		X	X			8.1.8, 8.3
Cardiac troponin I [m]	X	Day 5	X					8.1.8, 8.3
SARS-CoV-2 RT-PCR virus testing for eligibility [e]	Within 7 days prior to randomi-zation							8.1.8, 5.1
Clinical assessments		**As applicable until hospital discharge**						8.4
9-point ordinal scale	X	X		X	X			8.8.1
Central laboratory assessments [q]								
Correlative samples [a,o]		Days 1 [a], 3, and 7	X	X	X		-	8.3
Immunophenotyping [a,g]		Days 1 [a], 3, and 7	X	X	X			8.3
Serum and nasal swab samples for SARS-CoV-2 viral load/viral shedding [a]		Days 1 [a], 3, and 7	X	X	X			8.3
CCI [redacted]								
Acalabrutinib PK [p,t]		0.5 and 2 hours postdose on Day 3; 1 and 4 hours postdose on Day 7						8.3

Table 1 Schedule of Activities - Arm 1 (Acalabrutinib + BSC)

Assessments	Screening (Day -3 to Day -1 [l])	Daily until hospital discharge	Day 10 or discharge [h]	Day 14 (±2 days) after randomi-zation	Day 28 (±3 days) after randomi-zation	Safety FU 28 (±3) days after last dose of acala-brutinib [i]	Long-term FU 90 (±7) days after randomi-zation [i,j]	CSP section
Acalabrutinib administration		**The first dose of acalabrutinib should be administered within 6 hours of randomization** 100 mg bid (q12h) × 10 days (maximum)						6.1
Adverse events	X [k]	X	X	X	X	X[j]		8.6
Concomitant medications	X	X	X	X	X	X[j]		8.2
Survival status				X	X	X[j]	X[j]	4.5

anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time, bid = twice daily; BSC = best supportive care; CD = cluster of differentiation; CRP = C-reactive protein; CT = computed tomography; ECG = electrocardiogram; FU = follow-up; COVID-19 = coronavirus disease 2019; CSP = Clinical Study Protocol; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = Informed Consent Form; ICU = intensive care unit; INR = international normalized ratio; PBMC = peripheral blood mononuclear cell; PD = pharmacodynamics; PK = pharmacokinetics; PT = prothrombin time; q12h = every 12 hours; qod = every other day; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] Predose.

[b] Hematology: complete blood count with differential includes, but not limited to white blood cell count, hemoglobin, platelet count, absolute neutrophil count (ANC) or percentage, red blood cell count, absolute monocyte count or percentage, and absolute lymphocyte count (ALC) or percentage.

[c] Serum or plasma chemistry: albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin (direct and indirect bilirubin, if available), total protein and uric acid.

[d] Hepatitis serology must include, at a minimum, HBsAg, anti-HBc, and HCV antibody. If additional hepatitis serology is collected per institutional guidelines, it should be recorded in the database. Additional testing information is provided in Section 6.6.3 and Section 8.1.8.

[e] COVID-19 infection must be confirmed according to the World Health Organization criteria (including positive nucleic acid test of any specimen [eg, respiratory, blood, urine, stool, or other bodily fluid]) within 7 days prior to randomization. If test has already been documented within 7 days prior to randomization, no need to repeat the testing again.

[f] CCI [redacted]

[g] Flow cytometry testing of peripheral blood will include, but is not limited to, CD3+, CD4+, CD8+, CD14+, CD19+, and CD16+/56+ cells.

[h] If a subject is discharged prior to Day 7, he/she needs to visit the site for an assessment 2 to 4 days after discharge. Assessments should match those for Day 10.

[i] Telemedicine is recommended for capturing adverse events concomitant medications, and survival. Safety laboratory tests can be done at the hospital or a local laboratory provided the results are ultimately captured in the clinical database for the study.

[j] All subjects will be followed for survival for 90 (± 7) days.

Table 1 Schedule of Activities - Arm 1 (Acalabrutinib + BSC)

Assessments	Screening (Day -3 to Day -1 [l])	Daily until hospital discharge	Day 10 or discharge [h]	Day 14 (±2 days) after randomi-zation	Day 28 (±3 days) after randomi-zation	Safety FU 28 (±3) days after last dose of acala-brutinib [i]	Long-term FU 90 (±7) days after randomi-zation [i,j]	CSP section

[k] After signing the ICF, but prior to randomization, only SAEs should be reported (see Section 8.6.2).

[l] Screening can be performed within 1 to 3 days prior to dosing, depending on the local requirements for laboratory turn-around times; ECG can be collected at any time during this screening window.

[m] Serum ferritin, fibrinogen, PT, aPTT, INR, D-dimer, procalcitonin, and cardiac troponin I should be performed more frequently if clinically indicated.

[n] Arterial gases should be collected from subjects if the sample is easily accessible and the procedure will not be painful to subjects (ie, subject is in ICU or has arterial port). All available data from the arterial gases should be entered into the database. If the collection of arterial gases is not clinically indicated, the test should not be performed.

[o] CCI [redacted]

[p] All blood samples for PK assessment (ie, 0.5, 1, 2, and 4 hours postdose) can also be collected during a single visit on Day 3 or after.

[q] For all central laboratory assessments, sample collection windows of ± 1 day will be allowed for each of Days 3 and 7.

[r] Per standard of care, chest imaging can be done by chest x-ray or CT scan with contrast, or any other appropriate means to confirm pneumonia prior to or upon hospitalization (within 7 days of randomization).

[s] During screening, vital signs should be collected as close as possible to randomization on Day 1. If more than one value is obtained for vital signs during screening, the value closest to randomization should be used.

[t] PK assessments will be conducted in up to 15 evaluable subjects and PD assessments in up to 15 evaluable subjects randomized to Arm 1 (acalabrutinib + BSC).

Table 2 Schedule of Activities - Arm 2 (BSC Only)

Assessments	Screening (Day -3 to Day -1 [l])	Daily until hospital discharge	Day 10 or discharge [h]	Day 14 (±2 days) after randomi-zation	Day 28 (±3 days) after randomi-zation	Safety FU 38 (±3) days after randomi-zation [i]	Long-term FU 90 (±7) days after randomi-zation [i,j]	CSP section
Informed consent	X							8.1.1
Demography	X							8.1.2
Determine eligibility	X							5.1, 5.2
Medical history and COVID-19 epidemiology	X							8.1.4
Physical examination (symptom driven, including lung auscultation, height, weight)	X							8.1.5
Chest imaging	X [q]	As clinically indicated						8.1.5, 8.3
Electrocardiogram	X [l]	As clinically indicated	X					8.1.5, 8.3
Echocardiogram	As clinically indicated	As clinically indicated						8.1.5, 8.3
Vital signs (blood pressure, respiratory rate, oximetry, pulse and body temperature)	X [r]	X	X	X	X			8.1.6, 8.3
Local laboratory assessments:								
Urine or serum pregnancy test (for WOCBP only)	X			X		X		8.1.7, 8.3
Hematology [b]	X	X	X	X	X	X		8.1.8, 8.3
Serum or plasma chemistry [c]	X	X	X	X	X	X		8.1.8, 8.3
Arterial blood gases (if available) [n]	X	X		X	X			8.1.6, 8.1.8, 8.3, 8.4.1
Hepatitis B and C testing [d]	X	As clinically indicated				As clinically indicated		6.6.3, 8.1.8, 8.3
Serum ferritin [m]	X	qod (starting from Day 1)	X	X	X			8.1.8, 8.3
Fibrinogen [m]	X	qod						8.1.8, 8.3

Table 2 Schedule of Activities - Arm 2 (BSC Only)

Assessments	Screening (Day -3 to Day -1 [l])	Daily until hospital discharge	Day 10 or discharge [h]	Day 14 (±2 days) after randomi-zation	Day 28 (±3 days) after randomi-zation	Safety FU 38 (±3) days after randomi-zation [i]	Long-term FU 90 (±7) days after randomi-zation [i,j]	CSP section
PT, aPTT, and INR [m]	X	qod						8.1.8, 8.3
D-dimer [m]	X	qod		X	X			8.1.8, 8.3
CRP	X	X	X	X	X			8.1.8, 8.3
Procalcitonin (if available) [m]	X	qod		X	X			8.1.8, 8.3
Cardiac troponin I [m]	X	Day 5	X					8.1.8, 8.3
SARS-CoV-2 RT-PCR virus testing for eligibility [e]	Within 7 days prior to randomi-zation							8.1.8, 5.1
Clinical assessments		**As applicable until hospital discharge**						8.4
9-point ordinal scale	X	X		X	X			8.8.1
Central laboratory assessments [p]								
Correlative samples [a,o]		Days 1 [a], 3, and 7	X	X	X		-	8.3
Immunophenotyping [a,g]		Days 1 [a], 3, and 7	X	X	X			8.3
Serum and nasal swab samples for SARS-CoV-2 viral load/viral shedding [a]		Days 1 [a], 3, and 7	X	X	X			8.3
CCI [redacted]								
Adverse events	X [k]	X	X	X	X	X[j]		8.6
Concomitant medications	X	X	X	X	X	X[j]		8.2
Survival status				X	X	X[j]	X[j]	4.5

anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time, BSC = best supportive care; CD = cluster of differentiation; CT = computed tomography; ECG = electrocardiogram; FU = follow-up; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CSP = Clinical Study Protocol; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICF = Informed Consent Form; ICU = intensive care unit; INR = international normalized ratio; PBMC = peripheral blood mononuclear cell; PT = prothrombin time; qod = every other day; RT-PCR = reverse transcriptase-polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WOCBP = women of childbearing potential.

[a] Predose.

Table 2 Schedule of Activities - Arm 2 (BSC Only)

Assessments	Screening (Day -3 to Day -1 [l])	Daily until hospital discharge	Day 10 or discharge [h]	Day 14 (±2 days) after randomi-zation	Day 28 (±3 days) after randomi-zation	Safety FU 38 (±3) days after randomi-zation [i]	Long-term FU 90 (±7) days after randomi-zation [i,j]	CSP section

[b] Hematology: complete blood count with differential includes, but not limited to white blood cell count, hemoglobin, platelet count, absolute neutrophil count (ANC) or percentage, red blood cell count, absolute monocyte count or percentage, and absolute lymphocyte count (ALC) or percentage.

[c] Serum or plasma chemistry: albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin (direct and indirect bilirubin, if available), total protein and uric acid.

[d] Hepatitis serology must include, at a minimum, HBsAg, anti-HBc, and HCV antibody. If additional hepatitis serology is collected per institutional guidelines, it should be recorded in the database. Additional testing information is provided in Section 6.6.3 and Section 8.1.8.

[e] COVID-19 infection must be confirmed according to the World Health Organization criteria (including positive nucleic acid test of any specimen [eg, respiratory, blood, urine, stool, or other bodily fluid]) within 7 days prior to randomization. If test has already been documented within 7 days prior to randomization, no need to repeat the testing again.

[f] CCI [redacted]

[g] Flow cytometry testing of peripheral blood will include, but is not limited to, CD3+, CD4+, CD8+, CD14+, CD19+, and CD16+/56+ cells.

[h] If a subject is discharged prior to Day 7, he/she needs to visit the site for an assessment 2 to 4 days after discharge. Assessments should match those for Day 10.

[i] Telemedicine is recommended for capturing adverse events concomitant medications, and survival. Safety laboratory tests can be done at the hospital or a local laboratory provided the results are ultimately captured in the clinical database for the study.

[j] All subjects will be followed for survival for 90 (± 7) days.

[k] After signing the ICF, but prior to randomization, only SAEs should be reported (see Section 8.6.2).

[l] Screening can be performed within 1 to 3 days prior to dosing, depending on the local requirements for laboratory turn-around times; ECG can be collected at any time during this screening window.

[m] Serum ferritin, fibrinogen, PT, aPTT, INR, D-dimer, procalcitonin, and cardiac troponin I should be performed more frequently if clinically indicated.

[n] Arterial gases should be collected from subjects if the sample is easily accessible and the procedure will not be painful to subjects (ie, subject is in ICU or has arterial port). All available data from the arterial gases should be entered into the database. If the collection of arterial gases is not clinically indicated, the test should not be performed.

[o] CCI [redacted]

[p] For all central laboratory assessments, sample collection windows of ± 1 day will be allowed for each of Days 3 and 7.

[q] Per standard of care, chest imaging can be done by chest x-ray or CT scan with contrast, or any other appropriate means to confirm pneumonia prior to or upon hospitalization (within 7 days of randomization).

[r] During screening, vital signs should be collected as close as possible to randomization on Day 1. If more than one value is obtained for vital signs during screening, the value closest to randomization should be used.

1.2 Synopsis

International Co-ordinating Investigators:

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Protocol Title:

A Phase 2, Open-Label, Randomized Study of the Efficacy and Safety of Acalabrutinib with Best Supportive Care Versus Best Supportive Care in Subjects Hospitalized with COVID-19

Rationale:

Coronavirus disease 2019 (COVID-19) is a new pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Most COVID-19 cases (~80%) are mild respiratory illnesses. However, the some require hospitalization (mostly due to pneumonia) and can progress quickly to severe acute lung injury and acute respiratory distress syndrome (ARDS) (Huang et al 2020, Wu and McGoogan 2020, Zhou et al 2020), which is associated with high mortality. A viral-induced cytokine storm or "hyperimmune response" is hypothesized to be a major pathogenic mechanism of ARDS in these patients through modulation of pulmonary macrophages and dendritic cells (Channappanavar et al 2016, Huang et al 2005, Wong et al 2004, Yoshikawa et al 2009) and/or neutrophils (Herold et al 2015). Putative inflammatory mediators include interleukin (IL)-1β, IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNFα), and monocyte chemoattractant protein-1 (MCP-1) (Chen et al 2020, Herold et al 2015, Yoshikawa et al 2009).

Bruton's tyrosine kinase (Btk) is a Tec family non-receptor protein kinase, expressed in B cells, myeloid cells, osteoclasts, mast cells and platelets. The function of Btk in signaling pathways activated by the engagement of the B-cell receptor has been well established (Buggy and Elias 2012). Btk is also involved in the following biologic processes: Fc gamma receptor signaling in myeloid cells, mast cell degranulation, osteoclast differentiation, and signaling through Toll-like receptors (TLRs) in macrophages and neutrophils. Btk inhibition is associated with a decrease in proinflammatory cytokines in patients with hematologic malignancies.

Acalabrutinib is a covalent Btk inhibitor with greater selectivity and better physiochemical properties than ibrutinib and other Btk inhibitors currently in development. Acalabrutinib is currently approved in the United States for the treatment of patients with mantle cell lymphoma or chronic lymphocytic leukemia/small lymphocytic lymphoma [Calquence® prescribing information]. Patients with hematologic malignancies treated with acalabrutinib

have shown statistically significant decreases in the following cytokines: TNFα ($p<0.001$), IL-10 ($p<0.001$), and MCP-1 ($p<0.01$) (Byrd et al 2016) and IL-6 ($p<0.05$) (data on file). Decreasing these immunomodulating cytokines in patients with COVID-19 may mitigate the pathophysiologic response that leads to the most severe morbidity and mortality associated with viral infection. Recently, encouraging results were reported in a case series of patients hospitalized with severe COVID-19 and treated with acalabrutinib led by investigators at the National Institutes of Health (Roschewski 2020). Similarly, other BTK inhibitors have shown promise in COVID-19 patients with hematologic malignancies (Thibaud et al 2020, Treon et al 2020).

The purpose of this Phase 2 study is to evaluate the safety and preliminary efficacy of adding acalabrutinib to best supportive care (BSC) for subjects with life-threatening COVID-19 symptoms.

Objectives and Endpoints:

Primary Objectives	**Primary Endpoints/Variables**
• To evaluate the safety of acalabrutinib in subjects with COVID-19 when administered with BSC • To evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	Safety • Type, frequency, severity, and relationship to study treatment of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious adverse events (SAEs), or adverse events (AEs) leading to discontinuation of study treatment. Efficacy • Proportion of subjects alive and free of respiratory failure at Day 28 For the purpose of this study, **respiratory failure** is defined based on resource utilization of any of the following modalities: ○ Endotracheal intubation and mechanical ventilation ○ Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) ○ Noninvasive positive pressure ventilation or continuous positive airway pressure ○ Extracorporeal membrane oxygenation
Secondary Efficacy Objectives	**Secondary Efficacy Endpoints/Variables**
To evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	• Proportion of subjects alive and free of respiratory failure (defined above) at Day 14

	• Percent change from baseline in C-reactive protein (CRP; time frame: baseline, Days 3, 5, 7, 10, 14, 28) • Change from baseline in ferritin (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • Change from baseline in absolute lymphocyte counts (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • All-cause mortality at Day 90 • Proportion of subjects alive and discharged from the intensive care unit (ICU) at Days 14 and 28 • Time from randomization to first occurrence of respiratory failure or death on study (up to 28 days after randomization) due to any cause • Number of days alive and free of respiratory failure from randomization to 28 days after randomization • Number of days with respiratory failure from randomization to 28 days after randomization • Number of days hospitalized from randomization to 28 days after randomization • Number of days in ICU (length of stay) from randomization to 90 days after randomization • Number of days alive outside of hospital from randomization to 28 days after randomization • Number of days alive outside of hospital from randomization to 90 days after randomization • Relative change from baseline in oxygenation index (SpO_2/FiO_2) to Days 3, 5, 7, and 10 • Time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale through Day 28 (see Section 8.8.1) • Time to $SpO_2 > 94\%$ on room air

Pharmacokinetic (PK) Objective	PK Endpoint/Variable
To assess PK of acalabrutinib and its active metabolite in subjects with COVID-19 when administered with BSC	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points. PK parameters (eg, area under the concentration-time curve [AUC] and maximum observed concentration [C_{max}]) estimated, as appropriate.
Exploratory Objectives	**Exploratory Endpoints/Variables**
CCI [redacted]	

Overall Design:

This is a multicenter, randomized, open-label, Phase 2 study that will evaluate acalabrutinib plus BSC versus BSC in subjects with COVID-19 who are hospitalized.

Subjects will be randomly assigned (1:1) to receive one of the following 2 treatments:

- Arm 1: Acalabrutinib 100 mg twice daily (bid) × 10 days + BSC (n=30)
- Arm 2: BSC alone (n=30)

For the purpose of this study, BSC is per discretion of the Investigator and institutional guidelines. However, refer to Section 5.2 and Section 6.5.3 for prohibited or restricted concomitant therapy. Subjects will be randomized based on the following stratification factors, which are considered prognostic factors for poor outcome:

- Age (≥ 65 vs < 65 years)
- Comorbidities (present vs absent). "Present" is defined as having at least 1 of the following comorbidities:
  - Cardiovascular disease, as defined by either heart failure New York Heart Association class ≥2 or hypertension requiring treatment
  - Diabetes mellitus requiring treatment
  - Chronic obstructive pulmonary disease or asthma requiring treatment
  - Current active solid tumor or hematologic malignancy

Inclusion/exclusion criteria are provided in Section 5. Assessments are provided in Section 1.1.

Study Period:

Estimated date of first subject enrolled Q2 2020.

Estimated date of last subject completed is Q3 2020.

Number of Subjects:

The total number of subjects to be randomized in this study is 60.

Treatments and Treatment Duration:

Acalabrutinib treatment should be administered **within 6 hours of randomization** on Day 1.

Subjects will take acalabrutinib 100 mg capsules by mouth bid for 10 days (a maximum of 20 doses). Capsules will be taken with water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

Subjects on concomitant proton-pump inhibitors (PPIs) must take acalabrutinib with at least 100 mL of COCA-COLA® at room temperature. Other cola beverages (eg, Diet Coke®, COCA-COLA Zero Sugar) or juices are not permitted. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in COCA-COLA. **NOTE:** COCA-COLA contains glucose (5 g per 100 mL). Blood glucose levels of diabetic subjects must be monitored as clinically indicated and blood glucose-lowering medications adjusted accordingly.

Acalabrutinib can be taken with or without food.

Retreatment with acalabrutinib is not allowed.

BSC will be administered in both arms per Investigator's discretion and institutional guidelines.

Refer to Section 6.1 for additional information on treatments administered.

Internal Data Monitoring Committee:

This study will have an internal Data Monitoring Committee (iDMC), independent from the Sponsor's study team. Details of the roles and responsibilities of the iDMC and the safety and efficacy review will be provided in a separate iDMC charter. The iDMC will be responsible for reviewing the safety data periodically, enable early identification of safety signals in the study, minimize risk to subjects during the study, and make recommendations according to

prespecified stopping rules for safety, and as to the future conduct of this study in accordance with the iDMC charter (refer to Section 4.4 for details).

Statistical Methods:

In general, continuous data will be summarized using descriptive statistics (number of observations, mean, standard deviation, median, minimum, and maximum). Frequencies and percentages will be used for summarizing categorical (discrete) data.

Safety will be summarized for the treated population (Safety population) and will be based on the treatment they actually received. In this study, treatment is either acalabrutinib + BSC or BSC only. If a subject receives at least 1 dose of acalabrutinib, the subject is considered as acalabrutinib-treated, regardless to which arm the subject was randomized. Safety assessments will consist of monitoring and recording AEs, SAEs, and AEs leading to discontinuation of study treatment; measurements of protocol-specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study treatment.

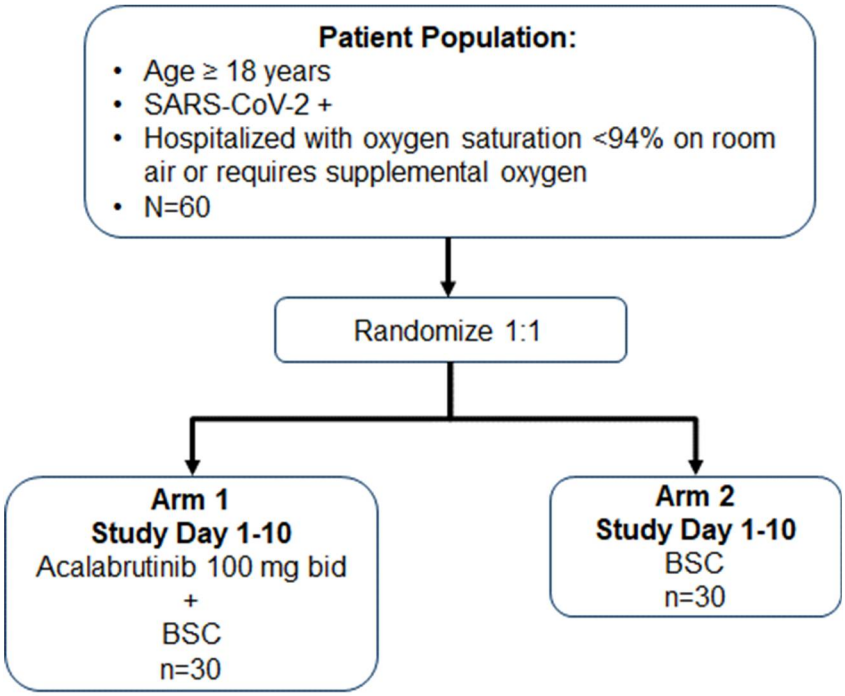
For subjects randomized to Arms 1 or 2, efficacy will be summarized for the intent-to-treat (ITT) population, which is defined as all subjects who were randomized, to be analyzed according to the arm to which they are randomly assigned, following "intent-to-treat" principle. An estimate of the primary endpoint, the proportion of subjects who are alive and free of respiratory failure at Day 28 and its 90% confidence interval (CI; using Wald method with continuity correction) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel $\chi 2$ test stratified by age (≥ 65 vs < 65 years) and comorbidities (present vs absent) will be used to compare the proportion of subjects who are alive and free of respiratory failure at Day 28 between the two treatment arms. An unstratified analysis will also be performed. Finally, the difference in the proportion of subjects who are alive and free of respiratory failure at Day 28 will also be provided with 90% CIs. The treatment difference will be also estimated using a logistic regression (Ge 2011) with indicators for treatment and the randomization stratification factors (2×2) as well as baseline respiratory failure (with vs without).

Refer to Section 9 for additional details.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study Design



bid = twice per day; BSC = best supportive care (for COVID-19 symptoms); SARS-CoV-2+ = severe acute respiratory syndrome coronavirus 2 positive.

2. INTRODUCTION

2.1 Background and Study Rationale

Coronavirus disease 2019 (COVID-19) is a new pandemic disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In a retrospective study of 191 patients with COVID-19, sepsis was the most frequently observed complication, followed by respiratory failure, acute respiratory distress syndrome (ARDS), heart failure, and septic shock. While sepsis might be directly caused by SARS-CoV-2 infection, further research is needed to investigate the pathogenesis of COVID-19 illness. Most COVID-19 cases (~80%) are mild respiratory illnesses. 5% to 15% of these respiratory illnesses require hospitalization (mostly due to pneumonia) and can progress quickly to severe acute lung injury and ARDS (Huang et al 2020, Wu and McGoogan 2020, Zhou et al 2020), which is associated with high mortality.

Normally, human coronaviruses are detected and cleared by the immune system, but a subset of patients experience increased severity of symptoms (Channappanavar and Perlman 2017, Zhou et al 2020). These symptoms have been associated with the loss of control of the virally induced immune response (Li et al 2020). In these cases, the inflammatory response is hypothesized to be a major pathogenic mechanism of ARDS through modulation of pulmonary macrophages and dendritic cells (Channappanavar et al 2016, Huang et al 2005, Wong et al 2004, Yoshikawa et al 2009) and/or neutrophils (Herold et al 2015). Putative inflammatory mediators include interleukin (IL)-1β, IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNFα), and monocyte chemoattractant protein-1 (MCP-1) (Chen et al 2020, Herold et al 2015, Yoshikawa et al 2009). During the acute phase of coronavirus infection, T cells are the critical mediators of clearance of infection, while B cells generate a protective humoral response (Zhao et al 2009, Zhao et al 2014). Generation of antibodies against coronaviruses is not always protective. In a mouse model, an anti-spike immunoglobulins (specific to SARS-COV) could skew the inflammation-resolving response which lead to severe acute lung injury in mice (Liu et al 2019).

Bruton's tyrosine kinase (Btk) is a Tec family nonreceptor protein kinase, expressed in B cells, myeloid cells, osteoclasts, mast cells, and platelets. The function of Btk in signaling pathways activated by the engagement of the B-cell receptor has been well established (Buggy and Elias 2012). Btk is also involved in the following biologic processes: Fc gamma receptor signaling in myeloid cells, mast cell degranulation, and signaling through Toll-like receptors (TLRs) in macrophages and neutrophils. Specifically, Btk is required for TLR 7/8 signaling, which recognize single strand RNA viruses such as coronaviruses, signal through Btk in macrophages (Page et al 2018).

Recently, Btk inhibition has shown to rescue mice from lethal influenza A-virus induced acute lung injury by significantly decreasing lung inflammation and macrophage/monocyte mediated cytokines/chemokines (TNFα, IL-1β, IL-6, MCP-1, etc) in the lung homogenates. These results suggest that Btk inhibition may represent a new immunomodulatory treatment for virally induced lung damage driven by excessive inflammation (Florence et al 2018). Additionally, in a murine model of sepsis, acalabrutinib has shown to ameliorate the cardiac dysfunction by suppressing pro-inflammatory cytokines/chemokines associated with sepsis (O'Riordan et al 2019). Patients with hematologic malignancies treated with acalabrutinib (Calquence®) have shown significant reduction of several cytokines/chemokines including pro-inflammatory markers such as: TNFα ($p<0.001$), IL-10 ($p<0.001$), MCP-1 ($p<0.01$), MIP-1β ($p<0.001$), MIP-1α ($p<0.001$), IL-16 ($p<0.001$), TARC ($p<0.001$), CXCL13 ($p<0.001$), Granzyme A ($p<0.001$) (Byrd et al 2016, Covey 2017), and IL-6 ($p<0.05$) (data on file). Several of these cytokines/chemokines have been shown to be associated with more severe illness in COVID-19 patients. We hypothesize that acalabrutinib treatment will inhibit cells that produce pro-inflammatory cytokines/chemokines, will lead to reduced inflammation of the lungs in patients with COVID-19, and mitigate the pathophysiologic response that leads to the most severe morbidity and mortality associated with viral infection. Recently, encouraging results were reported in a case series of patients hospitalized with severe COVID-19 and treated with acalabrutinib led by investigators at the National Institutes of Health (Roschewski 2020). Similarly, other BTK inhibitors have shown promise in COVID-19 patients with hematologic malignancies (Thibaud et al 2020, Treon et al 2020).

Together, strong scientific evidence justifies a clinical trial in this patient population. The purpose of this study is to evaluate the safety and preliminary efficacy of adding acalabrutinib to best supportive care (BSC) for subjects hospitalized due to COVID-19 symptoms.

2.2 Benefit/Risk Assessment

The lack of established treatments and vaccines for the novel SARS-CoV-2 virus has driven major medical centers to an unprecedented overload, which has undoubtedly contributed to the mortality observed with this disease. While vaccines and antiviral therapies are urgently needed, drugs that can address the pathophysiology of the disease to decrease the morbidity and mortality and reduce hospital admissions and intensive care unit (ICU) use are also needed without delay.

Btk inhibition may serve as an important addition to the COVID-19 armamentarium by reducing the viral-induced hyperimmune response, which leads to lung destruction. Acalabrutinib is currently approved in the United States for the treatment of patients with mantle cell lymphoma or chronic lymphocytic leukemia/small lymphocytic lymphoma. As of 30Oct2019, acalabrutinib has been administered to over 3300 participants in clinical studies, including subjects with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy subjects or those with mild to moderate hepatic impairment. No

serious adverse events (SAEs) have been reported in the hepatic impairment trial or in the healthy volunteer trials. Some subjects with chronic lymphocytic leukemia have been receiving acalabrutinib therapy for more than 5 years. Acalabrutinib has been administered alone and in combination with other kinase inhibitors, anti-CD20 antibodies, chemoimmunotherapy (eg, bendamustine/rituximab), and an anti-programmed cell death 1 (PD-1) receptor antibody. No dose-limiting toxicities (DLTs) have been identified for acalabrutinib monotherapy or when administered in combination with the aforementioned agents. Current clinical safety data supports combining acalabrutinib with other agents.

Refer to the acalabrutinib Investigator's Brochure for the most up to date safety and efficacy information. Identified risks for acalabrutinib are summarized in Section 6.6 and are based on events observed in subjects with cancer who have been on long-term treatment with acalabrutinib 100 mg twice daily (bid).

Based on the safety profile of acalabrutinib to date, no overt toxicities have been identified that would preclude acute treatment for subjects with moderate to severe COVID-19 symptoms.

Precautionary safety measures, in addition to regular monitoring of safety by an internal Data Monitoring Committee (iDMC) and the Sponsor, are included in the study design to enable early identification of safety signals in the study and minimize the risk to subjects.

3. OBJECTIVES AND ENDPOINTS

Table 3 Protocol Objectives and Endpoints

Primary Objectives	Primary Endpoints/Variables
• To evaluate the safety of acalabrutinib in subjects with COVID-19 when administered with BSC • To evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	Safety • Type, frequency, severity, and relationship to study treatment of any TEAEs or abnormalities of laboratory tests, SAEs, or AEs leading to discontinuation of study treatment. Efficacy • Proportion of subjects alive and free of respiratory failure at Day 28 For the purpose of this study, **respiratory failure**, is defined based on resource utilization of any of the following modalities: (a) Endotracheal intubation and mechanical ventilation (b) Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen

	delivered via reinforced nasal cannula at flow rates >20 L/min with fraction of delivered oxygen ≥0.5) (c) Noninvasive positive pressure ventilation or continuous positive airway pressure (d) Extracorporeal membrane oxygenation
Secondary Efficacy Objective	**Secondary Efficacy Endpoints/Variables:**
To evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	• Proportion of subjects alive and free of respiratory failure (as defined above) at Day 14 • Percent change from baseline in CRP (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • Change from baseline in ferritin (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • Change from baseline in absolute lymphocyte counts (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • All-cause mortality at Day 90 • Proportion of subjects alive and discharged from the ICU at Days 14 and 28 • Time from randomization to first occurrence of respiratory failure or death on study (up to 28 days after randomization) due to any cause • Number of days alive and free of respiratory failure from randomization to 28 days after randomization • Number of days with respiratory failure from randomization to 28 days after randomization • Number of days hospitalized from randomization to 28 days after randomization • Number of days in ICU (length of stay) from randomization to 90 days after randomization • Number of days alive outside of hospital from randomization to 28 days after randomization • Number of days alive outside of hospital from randomization to 90 days after randomization • Relative change from baseline in oxygenation index (SpO_2/FiO_2) to Days 3, 5, 7, and 10 • Time to clinical improvement of at least 2 points (from randomization) on a 9-point

	category ordinal scale through Day 28 (see Section 8.8.1) • Time to SpO_2 > 94% on room air
PK Objective	**PK Endpoints/Variables**
To assess PK of acalabrutinib and its active metabolite in subjects with COVID-19 when administered with BSC	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points. PK parameters (eg, AUC and C_{max}) estimated, as appropriate.
Exploratory Objectives	**Exploratory Endpoints/Variables**
CCI [redacted]	

AE = adverse event; AUC = area under the concentration-time curve; BSC = best supportive care; CCI [redacted] CL/F = apparent clearance; C_{max} = maximum observed concentration; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; FiO_2 = fraction of inspired oxygen; ICU = intensive care unit; CCI [redacted] PK = pharmacokinetics; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SpO_2 = oxygen saturation; $t_{1/2}$ = half-life; TEAE = treatment-emergent adverse event; t_{max} = time to maximum observed concentration; CCI [redacted] Vd_{ss}/F = apparent volume of distribution at steady-state.

4. STUDY DESIGN

4.1 Overall Design

This is a multicenter, randomized, open-label, Phase 2 study that will evaluate acalabrutinib plus BSC versus BSC in subjects with COVID-19 who are hospitalized.

Subjects will be randomly assigned (1:1) to receive one of the following 2 treatments:

- Arm 1: Acalabrutinib 100 mg bid × 10 days + BSC (n=30)
- Arm 2: BSC alone (n=30)

For the purpose of this study, BSC is per discretion of the Investigator and institutional guidelines. However, refer to Section 5.2 and Section 6.5.3 for prohibited or restricted concomitant therapy. Subjects will be randomized based on the following stratification factors, which are considered prognostic factors for poor outcome:

- Age (≥ 65 vs < 65 years)
- Comorbidities (present vs absent). "Present" is defined as having at least 1 of the following comorbidities:
  - Cardiovascular disease, as defined by either heart failure New York Heart Association (NYHA) class ≥2 or hypertension requiring treatment
  - Diabetes mellitus requiring treatment
  - Chronic obstructive pulmonary disease or asthma requiring treatment
  - Current active solid tumor or hematologic malignancy

Inclusion/exclusion criteria are provided in Section 5. Assessments are provided in Section 1.1.

4.2 Scientific Rationale for Study Design

The immune system is required to clear viral infections and generate protective immunity from viral pathogens like SARS-CoV-2. There is significant evidence that in patients with severe respiratory problems, the immune system and inflammation contribute to the severity of the disease. Macrophages and neutrophils are key to producing cytokines driving this inflammation. The hypothesis being evaluated in this trial is whether Btk inhibition of the viral-induced macrophage and neutrophil immune response can decrease inflammation and reduce respiratory failure or death. Given the various covariates that contribute to these outcomes (eg, lack of consensus on standard of care, actively changing local treatment practices, and patients' comorbid conditions), a single-arm study will likely not be informative as data from historical controls are changing almost daily. Hence, this will be a randomized study. Subjects who are hospitalized for COVID-19 disease and meet the eligibility criteria will be randomized 1:1 to receive acalabrutinib plus BSC (n=30) versus BSC (n=30).

Stratification by age and comorbidities will be applied to randomization as these are expected to be important covariates.

4.3 Justification for Dose

Acalabrutinib 100 mg bid has been evaluated in various indications (ie, B-cell malignancies and solid tumours) alone and in combination with anti-CD20 antibodies, chemotherapy, a phosphatidylinositol-3-kinase (PI3K) inhibitor, and an anti-PD-1 antibody. No DLTs have been identified for acalabrutinib alone or when given in combination with these agents. For all of these indications, acalabrutinib was administered daily until disease progression; some subjects have been receiving acalabrutinib for > 5 years. The long-term safety experience of chronic administration of acalabrutinib 100 mg bid monotherapy and in combination with other agents, supports the proposed dosage of acalabrutinib is 100 mg bid for acute treatment. In addition, correlative studies—in subjects with chronic lymphocytic leukemia treated with acalabrutinib 200 mg once daily (qd) or 100 mg bid—show bid dosing maintained higher Btk

occupancy and achieved more potent NF-kappaB pathway inhibition compared with qd dosing (Sun et al 2020). Activation of NF-kappaB occurs in the lungs of patients with ARDS and may contribute to the increased expression of proinflammatory mediators (Moine et al 2000). Therefore, 100 mg bid dosing is proposed for this study to ensure maximum target engagement.

4.4 Internal DMC

This study will have an iDMC. Details of the roles and responsibilities of the iDMC and the safety and efficacy review will be provided in a separate iDMC charter. The iDMC will be responsible for reviewing the safety data periodically.

The iDMC will review the cumulative safety data approximately 28 days after the first 30 subjects (approximately 15 subjects per arm) are randomized.

In addition, if at any time during the conduct of the study either of the criteria below are met, enrollment of additional subjects will be paused such that the iDMC would convene and conduct a full safety review.

- Any death due to acalabrutinib (per Investigator)
- ≥20% treatment discontinuation rate due to toxicity attributed to acalabrutinib (per Investigator), when 10 or more acalabrutinib subjects have been treated
- Any Grade 4 hemorrhage due to acalabrutinib (per Investigator)

During the safety review, the iDMC with compare the known adverse event (AE) profile associated with acalabrutinib with comprehensive safety data from the current study. The iDMC will determine if an unacceptable increase in Grade 3 or higher AEs known to be associated with acalabrutinib occurred in the study. After the review, the iDMC will make a recommendation regarding study continuation, hold, or termination.

At the time of the safety review the iDMC will also review all available efficacy data and will support any health authority interactions or internal discussions based on their review. The study team will remain blinded to the data that the iDMC will review.

4.5 End of Study Definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed his/her last scheduled procedure shown in the Schedule of Activities (SoA; Section 1.1). All randomized subjects will be followed for survival through 90 (± 7) days after randomization.

All subjects who discontinue the investigational study treatment for any reason other than withdrawal of consent, loss to follow-up, or death will have a safety follow up assessment 28 (± 3) days after the last dose of acalabrutinib (Arm 1), or 38 (± 3 days) after randomization for those subjects randomized to the BSC arm (Arm 2), as outlined in Section 1.1.

The study may be stopped if, in the judgment of the Sponsor, study subjects are placed at undue risk because of clinically significant findings.

See Appendix A 6 for guidelines for the dissemination of study results.

5. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all the inclusion criteria and none of the exclusion criteria for this study to be assigned to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to Section 5.3.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if **all** of the criteria below apply.

1. Ability to understand the purpose and risks of the study and provide signed and dated informed consent or have a legal representative provide consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).
2. Men and women ≥18 years of age at the time of signing the Informed Consent Form (ICF).
3. SARS-CoV-2 confirmed per World Health Organization criteria (including positive nucleic acid test of any specimen [eg, respiratory, blood, urine, stool, or other bodily fluid]) within 7 days of randomization.
4. COVID-19 pneumonia (documented radiographically) requiring hospitalization and oxygen saturation <94% on room air or requires supplemental oxygen.
5. Able to swallow pills.
6. Willing to follow contraception guidelines (refer to Appendix F).

5.2 Exclusion Criteria

Subjects are excluded from the study if **any** of the criteria below apply.

COVID-19 Related Medical Conditions

1. Respiratory failure at the time of screening (see Section 3 for definition of respiratory failure) due to COVID-19 pneumonia that impedes the ability to swallow pills, or in the opinion of the treating physician, the subject is likely to require mechanical ventilation within the immediate 24 hours and therefore unable to swallow pills.
2. Known medical resuscitation within 14 days of randomization.
3. Any serious medical condition or abnormality of clinical laboratory tests that, in the Investigator's judgment, precludes the subject's safe participation in and completion of the study.
4. Suspected uncontrolled active bacterial, fungal, viral, or other infection (besides infection with SARS-CoV-2).
5. In the opinion of the Investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments.

Medical Conditions

6. Not expected to survive 28 days given their preexisting, uncorrectable medical condition, for example, subjects with, or suspected to have, the following conditions: multiorgan failure, poorly controlled neoplasms; endstage cardiac disease; cardiac arrest requiring cardiopulmonary resuscitation or with pulseless electrical activity or asystole within past 30 days; endstage lung disease; endstage liver disease; or human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome with known endstage process.
7. Pregnant or breast feeding.
8. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and/or bilirubin $\geq 3 \times$ upper limit of normal (ULN) and/or severe hepatic impairment (Child-Pugh class C; see Appendix G) detected during the screening period (per local laboratory).

   Exception: AST and/or ALT can be up to $5 \times$ ULN if considered due to underlying COVID-19 disease, but cannot be associated with concurrent elevated bilirubin (up to $2 \times$ ULN).
9. Absolute neutrophil count (ANC) < 500/µL at screening (per local laboratory).
10. Platelet count < 50,000/µL at screening (per local laboratory).
11. Estimated creatinine clearance of <30 mL/min calculated using the Cockcroft-Gault formula [(140age) × mass (kg)/(72 × creatinine mg/dL) multiply by 0.85 if female].
12. Uncontrolled or untreated symptomatic arrhythmias, myocardial infarction within the last 6 weeks, or congestive heart failure (NYHA Grade 3 or 4).

    Exception: Subjects with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study.
13. History of chronic hypercarbia, respiratory failure in past 6 months, or use of home oxygen in the setting of severe chronic respiratory disease.

14. Quadriplegia.
15. History of primary immunodeficiency, tuberculosis, progressive multifocal leukoencephalopathy (PML), aspergillus or other invasive mold/fungal infection, or received organ or bone marrow transplantation within 6 months of randomization.
16. Serology status reflecting active hepatitis B or C infection.
    a) Subjects who are hepatitis B core antibody (anti-HBc) positive and who are hepatitis B surface antigen (HBsAg) negative will need to have a negative or undetectable hepatitis B viral load by quantitative polymerase chain reaction (PCR) result before randomization. Those who are HBsAg positive or have detectable hepatitis B viral load by PCR will be excluded.
    b) Subjects who are hepatitis C virus (HCV) antibody positive will need to have a negative PCR result before randomization. Those who are hepatitis C PCR positive will be excluded.
17. Known active HIV with detectable viral load or CD4 counts < 500 cells/mm^3.

Prior/Concomitant Therapy

18. Treatment with a strong cytochrome P450 (CYP)3A inhibitor (within 7 days before first dose of study drug) or inducer (within 14 days before first dose of study drug).
19. Subjects are excluded who have already received prior immunomodulatory/ immunosuppressive treatment intended as specific treatment for COVID-19 (after randomization these agents may be permitted – see Section 6.5.2). Note: Steroids are permitted prior to randomization and on study..
20. Active participation in other drug clinical trials or received treatment with an investigational drug within 5 half-lives or 30 days (whichever is longer) of randomization/enrollment.

    Exception: Subjects may receive COVID-19-specific antiviral drugs (eg, remdesivir, hydroxychloroquine).
21. Requires or is receiving specific anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days prior to randomization. Other anticoagulants are permitted.
22. Subjects on dual antiplatelet **and** therapeutic anticoagulant therapy (eg, aspirin and therapeutic doses of low molecular weight heparin).
23. History of hypersensitivity (ie, allergic response) to active or inactive excipients of acalabrutinib or other Btk inhibitors.
24. Known cytoreductive chemotherapy treatment within 14 days of randomization.
25. Major surgery (as defined by the Investigator) within 4 weeks prior to randomization or still recovering from prior surgery.

5.3 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE unrelated to the disease under investigation.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened subjects should be assigned the same subject number as for the initial screening.

6. STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study subject according to the study protocol. Study treatment in this study refers to acalabrutinib.

6.1 Treatments Administered

6.1.1 Dosing and Duration of Treatment

Acalabrutinib treatment should be administered **within 6 hours of randomization** on Day 1.

Subjects will take acalabrutinib 100 mg capsules by mouth bid for 10 days (a maximum of 20 doses). Capsules will be taken with water. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. For subjects requiring a proton-pump inhibitor (PPI), acalabrutinib must be administered as described in Section 6.1.3.1.

Acalabrutinib can be taken with or without food.

Retreatment with acalabrutinib is not allowed.

BSC will be administered in both arms per Investigator's discretion and institutional guidelines.

6.1.2 Missed Dosing Windows and Doses

The bid doses should be scheduled approximately 12 hours apart. It is recommended that acalabrutinib be taken as close to the scheduled time as possible (within ±1 hour). However, if the scheduled time is missed, it can be taken up to 3 hours after the scheduled time, with a return to the normal schedule upon the following dose for 10 days (a maximum of 20 doses).

If the 3-hour dosing window is missed, the dose must be skipped on that day. Study drug may be held for a maximum of 3 consecutive days (6 consecutive doses) from expected dose due to toxicity. If a dose is missed due to an adverse event (AE) or for any other reason, missed doses should be completed so the subject receives a maximum of 20 doses of study drug, even if this is beyond the 10-day dosing period.

6.1.3 Special Considerations

6.1.3.1 Drug-drug Interactions

Drug-drug interactions may occur with some of the drugs being used as BSC (eg, drugs that are moderate inhibitor of CYP3A, gastric acid reducing agents), and dosing of acalabrutinib may need to be adjusted. Please refer to Section 6.5.4 for detailed information and guidance.

Subjects on concomitant PPIs must take acalabrutinib with at least 100 mL of COCA-COLA® at room temperature. Other cola beverages (eg, Diet Coke®, COCA-COLA Zero Sugar) or juices are not permitted. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in COCA-COLA. **NOTE:** COCA-COLA contains glucose (5 g per 100 mL). Blood glucose levels of diabetic subjects must be monitored as clinically indicated and blood glucose-lowering medications adjusted accordingly.

Administration of acalabrutinib with COCA-COLA mitigates the effect of PPIs. Several acidic beverages with pH similar to COCA-COLA were assessed (eg, orange drink, lemonade, COCA-COLA Zero Sugar, cranberry juice, and grapefruit juice) but not found to be optimal. In healthy subjects, pharmacokinetic (PK) exposure following 100-mg acalabrutinib suspension in COCA-COLA (nasogastric delivery) is similar in the presence or absence of PPIs, and comparable to that of the 100-mg acalabrutinib capsule. In addition, based on a verified physiologically-based biopharmaceutics model (Pepin et al 2019), acalabrutinib exposure is predicted to be similar between the administration of 100-mg acalabrutinib capsule with 100 mL COCA-COLA in the presence of PPIs and the 100-mg acalabrutinib capsule taken with water. Overall, these data support the use of acalabrutinib in subjects who need to take PPIs for the management of various acid-related disorders.

6.1.3.2 Subjects With Respiratory Failure and Who Can Still Swallow Pills

Subjects who have respiratory failure before completing the maximum of 20 doses and who are still able to swallow pills, will be permitted to continue treatment with acalabrutinib for the maximum of 20 doses, according to the Investigator's clinical judgment.

6.1.3.3 Subjects No Longer Able to Swallow Pills

Subjects who can no longer swallow pills will not be eligible to continue acalabrutinib treatment.

6.1.3.4 Vomiting After Acalabrutinib Treatment

If vomiting occurs after taking acalabrutinib, the subject should not retake acalabrutinib until the next scheduled dose.

6.1.3.5 Discharged From Hospital Before Treatment Completion

Subjects who are discharged from the hospital before they have completed 10 days (20 doses) of acalabrutinib therapy will be required to complete the remaining dosing at home. They should adhere to their established dosing schedule and treatment guidelines, including in cases where subjects remain on PPIs. These subjects must complete a drug dosing diary to be faxed or mailed back to the study site.

6.2 Acalabrutinib Preparation/Handling/Storage/Accountability

Acalabrutinib should be stored according to the instructions on the label affixed to the package of the drug product.

If a drug shipment arrives damaged or if there are any other drug complaints, a Product Complaint Form should be completed and emailed to the Sponsor or the Sponsor's representative. Refer to the pharmacy manual and the Investigator's Brochure for additional information regarding the drug product to be used in this study.

The Investigator or designee (eg, pharmacist) must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Clinical Study Agreement.

6.3 Measures to Minimise Bias: Randomisation and Blinding

Given the urgent nature of the COVID-19 pandemic, this will be an open-label study. However, the study is randomized and include stratification factors as outlined in Section 4.1.

6.3.1 Subject Enrollment and Randomization

All eligible subjects will be centrally randomized using an interactive response technology (IRT) that will assign the subjects to either acalabrutinib plus BSC versus BSC, stratified by the stratification factors defined in Section 4.1. Before the study is initiated, log-in information and directions for the IRT will be provided to each site.

Investigators should keep a record (ie, the subject screening log) of subjects who entered screening.

At screening, the Investigators or suitably trained delegate will:

- Obtain informed consent before any study specific procedures are performed.
- Obtain a unique 7-digit enrollment number (E-code), through the IRT the following format (ECCNNXXX: CC being the country code, NN being the center number, and XXX being the subject enrollment code at the center). This number is the subject's unique identifier and is used to identify the subject on the electronic case report forms (eCRFs).
- Determine subject eligibility (see Section 5.1 and Section 5.2).

At randomization, once the subject is confirmed to be eligible, the Investigator or suitably trained delegate will:

- Log the E-code and stratification factors (age [≥ 65 vs < 65 years] and comorbidities [present vs absent]) in the IRT system and the system will sequentially randomize the eligible subject to 1 of the 2 treatment arms.
- If the subject is ineligible and not randomized, the IRT should be contacted to terminate the subject in the system.
- Subjects will begin treatment on Day 1. Treatment should start no more than 6 hours after being randomized. Subjects must not be randomized and treated unless all eligibility criteria have been met.

If a subject withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused. A withdrawn subject will not be replaced.

6.3.1.1 Procedures for Handling Incorrectly Enrolled or Randomized Subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform the study physician immediately, and a discussion should occur between the study physician and the Investigator

regarding whether to continue or discontinue the subject from treatment. The study physician must ensure all decisions are appropriately documented and that the potential benefit:risk profile remains positive for the subject.

6.3.1.2 Methods for Assigning Treatment Groups

The actual treatment assigned to subjects will be determined by the randomization scheme in the IRT. A stratified permuted block randomization scheme will be used, with the stratification factors defined in Section 4.1. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers.

Randomization codes will be assigned strictly sequentially, within each stratum, as subjects become eligible for randomization.

6.3.1.3 Methods for Ensuring Blinding

This is an open-label study for the personnel at study sites. Specific treatment to be taken by a subject will be assigned using an IRT. The site will contact the IRT prior to the start of study treatment administration for each subject. The site will record the treatment assignment on the applicable case report form, if required. To maintain the integrity of the study, the Sponsor's personnel directly involved in the study conduct will, under no circumstances, view data aggregated by treatment arm during the course of the study.

6.4 Treatment Compliance

The study treatment should only be used as directed in this protocol. Details of treatment with the study treatment, including change from the dosing schedule, dose interruptions, dose reductions, and dose discontinuations, should be recorded in the eCRF. The investigational product will not be distributed to the study site until the contract is concluded between the study site and the Sponsor. The Investigator or designee is responsible for managing the investigational product from time of receipt by the study site until the destruction of all unused investigational product at that site. The Investigator(s) is responsible for ensuring that all unused investigational product is returned to the site by the subject(s).

6.5 Concomitant Therapy

6.5.1 Premedications

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

6.5.2 Permitted Concomitant Therapy

BSC for COVID-19 is required for all subjects in this study except as listed in Section 5.2 and Section 6.5.3. Given the rapid emergence of new data related to COVID-19, BSC could

change during the duration of the study. The use of therapies such as remdesivir, therapeutic plasma, corticosteroids, or other immunomodulatory agents (eg, tocilizumab) is permitted if recommended by local authorities and part of institutional policies or guidelines. The concomitant administration of immunosuppressive agents with acalabrutinib may require additional safety monitoring as determined by the treating clinician. Investigators should maintain prohibitions of certain concurrent medications for other reasons as listed in Section 6.5.3.

6.5.3 Prohibited or Restricted Concomitant Therapy

The medications listed below are prohibited for all randomized subjects.

Medications Prohibited for All Subjects in Both Treatment Arms Through Day 28

Immunomodulatory drugs, intended as treatment for COVID-19 but not considered standard of care according to local institutional guidelines, are prohibited for all randomized subjects in the study through Day 28. Subjects who are taking immunomodulatory drugs for other medical conditions (eg, tocilizumab for rheumatoid arthritis) may continue with treatment upon discussion with the Medical Monitor.

Medications Prohibited for All Subjects in Both Treatment Arms Through Day 10

Strong CYP3A inhibitors or inducers: Drug-drug interactions may occur with some of the drugs being used as BSC (eg, drugs that are strong inducers or strong inhibitors of CYP3A). The concomitant use of strong inhibitors of CYP3A (see Appendix E) should be avoided by all subjects on the study. If a subject requires a strong CYP3A inhibitor while on treatment with acalabrutinib, discontinue acalabrutinib treatment. Conversely, concomitant administration of a strong inducer of CYP3A has the potential to decrease exposure of acalabrutinib and could reduce efficacy. Therefore, the concomitant use of strong CYP3A inducers should be avoided by all subjects in the study. If a subject requires a strong CYP3A inducer while on treatment with acalabrutinib, discontinue acalabrutinib. For additional information on drugs with potential drug-drug interactions, refer to Section 6.5.4.

Certain anticoagulants: Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited for all subjects in the study. Subjects who require prophylaxis or therapeutic anticoagulation for thrombosis (deep vein thrombosis or pulmonary embolism) will be allowed to receive therapeutic anticoagulation with a non-vitamin K inhibitor class of anticoagulants (eg, heparin or low-molecular-weight heparin).

Refer to Section 5.2 for additional restrictions on concomitant therapy.

6.5.4 Acalabrutinib Drug-drug Interaction Guidance in the Presence of Life-threatening COVID-19 Infection

Drug-drug interaction recommendations provided for acalabrutinib in this protocol are made with respect to the presence of life-threatening COVID-19 infection and ability to achieve pharmacodynamic (PD) Btk receptor occupancy steady-state in target B-cell and monocytic populations. Therefore, the Sponsor recommends that all eligible subjects with COVID-19 begin dosing with acalabrutinib 100 mg bid. The duration of acalabrutinib therapy will be limited to 10 days (a maximum of 20 doses). Table 4 provides moderate CYP3A inhibitors and acid reducing agent guidance for subjects with COVID-19. Refer to Appendix E for a list of common CYP3A inhibitors/inducers and gastric acid reducing medicines.

Table 4 Acalabrutinib Use with Moderate CYP3A Inhibitors and Gastric Acid Reducing Agents

	Co-administered Medicines	**Recommended Acalabrutinib Use**
CYP3A Inhibitor	Moderate CYP3A inhibitor	Monitor subjects closely for adverse reactions if taking moderate CYP3A inhibitors. For subjects who experience an intolerable adverse event (ie, Grade 3-4) attributed to acalabrutinib therapy, reduce the dose to 100 mg once daily.
Gastric Acid Reducing Medicines	Proton-pump inhibitors (PPIs)	Avoid concomitant use. If PPI concomitant use cannot be avoided, dose modification of acalabrutinib is not necessary; however, acalabrutinib must be administered with at least 100 mL of COCA-COLA to improve acalabrutinib absorption (refer to Section 6.1.3.1). Other cola beverages are not permitted.
	H2-receptor antagonists	Take acalabrutinib 2 hours before taking a H2-receptor antagonist.
	Antacids	Separate dosing by at least 2 hours.

6.5.4.1 Active Substances That May Increase Acalabrutinib Plasma Concentrations

CYP3A Inhibitors

Co-administration with a strong CYP3A inhibitor (200 mg itraconazole qd for 5 days) increased acalabrutinib maximum observed concentration (C_{max}) and area under the concentration-time curve (AUC) by 3.7- and 5.1-fold in healthy subjects (N=17), respectively.

Consider alternative therapies that do not strongly inhibit CYP3A activity. In subjects requiring strong CYP3A inhibitors (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, ritonavir, telaprevir, posaconazole, voriconazole), discontinue acalabrutinib treatment.

6.5.4.2 Active Substances That May Decrease Acalabrutinib Plasma Concentrations

CYP3A Inducers

Co-administration of a strong CYP3A inducer (600 mg rifampin qd for 9 days) decreased acalabrutinib C_{max} and AUC by 68% and 77% in healthy subjects (N=24), respectively.

Consider alternative therapies to strong inducers of CYP3A activity (eg, phenytoin, rifampin, carbamazepine). Avoid St. John's wort which may unpredictably decrease acalabrutinib plasma concentrations. If these inducers cannot be avoided, discontinue acalabrutinib treatment.

Gastric Acid Reducing Medications

Acalabrutinib solubility decreases with increasing pH. Co-administration of acalabrutinib with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy subjects. Co-administration with a PPI (40 mg omeprazole for 5 days), decreased acalabrutinib AUC by 43%.

If treatment with an acid reducing agent is required, consider using an antacid (eg, calcium carbonate), or an H2-receptor antagonist (eg, famotidine). For use with antacids, separate dosing by at least 2 hours. For H2-receptor antagonists, take acalabrutinib 2 hours before taking the H2-receptor antagonist.

Due to the long-lasting effect of PPIs, separation of doses with PPIs may not eliminate the interaction with acalabrutinib. In subjects requiring treatment with PPIs (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) during the study, acalabrutinib must be administered with at least 100 mL COCA-COLA at room temperature to improve acalabrutinib absorption (see Section 6.1.3.1). Other cola beverages are not permitted.

Dose modification of acalabrutinib is not necessary when co-administered with gastric acid reducing medications.

6.6 Risks Associated with Acalabrutinib

The safety profile of acalabrutinib in patients with COVID-19 is not yet established. The COVID-19 population is distinct from patients with hematologic malignancies, the population for which acalabrutinib is indicated, and the duration of acalabrutinib treatment for COVID-19 is much shorter than for the indicated population with hematologic malignancies. Therefore,

the safety profile of acalabrutinib in the COVID-19 population may differ from that established in the cancer population.

The experience with chronic administration of acalabrutinib in hematologic cancer studies is described below. Table 5 summarizes the risks associated with acalabrutinib (any grade, ≥ Grade 3, and mean time to first onset) based on 1040 subjects with hematologic malignancies who received acalabrutinib monotherapy (data on file).

For more detailed information on treatment-emergent adverse events (TEAEs), refer to the acalabrutinib Investigator's Brochure. Full details regarding the clinical safety of acalabrutinib are presented in Sections 5 and 6 of the acalabrutinib Investigator's Brochure.

Table 5 Risks Associated with Acalabrutinib Monotherapy in Subjects With Hematologic Malignancies (N = 1040)

Event category	Number (%) of subjects		Median (min, max), months
	Any grade	≥Grade 3	Time to first onset
Hemorrhage	482 (46.3)	28 (2.7)	1.2 (0, 53)
Major hemorrhage	37 (3.6)	28 (2.7)	9.8 (0, 44)
Infections	694 (66.7)	183 (17.6)	3.2 (0, 45)
Anemia	144 (13.8)	81 (7.8)	0.7 (0, 41)
Neutropenia	163 (15.7)	148 (14.2)	3.1 (0, 44)
Thrombocytopenia	93 (8.9)	50 (4.8)	1.7 (0, 39)
Second primary malignancy	127 (12.2)	43 (4.1)	9.5 (0, 50)
Atrial fibrillation	46 (4.4)	13 (1.3)	17.4 (0, 43)

max = maximum; min = minimum.

6.6.1 Hemorrhage

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

Please refer to Section 6.7 for study drug modification guidance.

6.6.2 Infections

Serious infections, including fatal events, have been reported in subjects treated with acalabrutinib (eg, aspergillosis). Subjects should be monitored for signs and symptoms of infection and treated as medically appropriate. Please refer to Section 6.7 for study drug modification guidance.

6.6.3 Hepatitis B Reactivation

Across the acalabrutinib clinical development program, 9 subjects had hepatitis B virus (HBV) reactivation. Seven of the 9 subjects developed HBV reactivation after receiving acalabrutinib, and 2 subjects had HBV reactivation prior to receiving (crossover) acalabrutinib. One subject experienced a serious Grade 4 event that subsequently resulted in liver failure and death. Subjects who are anti-HBc positive or have a known history of HBV infection may be monitored monthly with a quantitative PCR test for HBV DNA, when clinically indicated. Any subject with a rising viral load (above lower limit of detection) should discontinue study treatment and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming acalabrutinib in subjects who develop HBV reactivation.

6.6.4 Progressive Multifocal Leukoencephalopathy

Across the acalabrutinib clinical development program, 2 subjects had events of PML (both serious) after receiving acalabrutinib. Signs and symptoms of PML may include cognitive and behavioral changes, language disturbances, visual disturbances, sensory deficits, weakness, and coordination and gait difficulties. Please refer to Section 6.7 for study drug modification guidance.

6.6.5 Cytopenias

Grade 3 or 4 events of cytopenias, including anemia, neutropenia, and thrombocytopenia have occurred in subjects treated with acalabrutinib. Monitor blood counts as specified in the SoA and as medically appropriate. Please refer to Section 6.7 for study drug modification guidance.

6.6.6 Second Primary Malignancies

Second primary malignancies, including non-skin carcinomas solid tumors and skin cancers, have been reported in subjects with B-cell malignancies treated with acalabrutinib. The most frequent second primary malignancy was skin cancer (squamous basal cell carcinoma of the skin). Subjects should be monitored for signs and symptoms of malignancy. Subjects who develop a malignancy should be managed according to institutional guidelines with diagnostic evaluations or as clinically indicated, and it may be necessary for subjects to permanently discontinue study treatment. Continuation of acalabrutinib treatment should be discussed with the Medical Monitor.

6.6.7 Atrial Fibrillation

Monitor for symptoms of atrial fibrillation and atrial flutter (eg, palpitations, dizziness, syncope, chest pain, dyspnea), and obtain an electrocardiogram (ECG) as clinically indicated. Subjects with atrial fibrillation should be managed per institutional guidelines with supportive care and diagnostic evaluations or as clinically indicated. Please refer to Section 6.7 for study drug modification guidance.

6.6.8 Reference Safety Information

See the Reference Safety Information in the acalabrutinib Investigator's Brochure for assessment of expectedness of serious adverse reactions.

6.7 Dose Modification and Toxicity Management

In general, no acalabrutinib dose modification is required if a subject experiences a Grade 1 or Grade 2 AE. Acalabrutinib therapy should be modified or discontinued, however, for the following AEs:

Event	Acalabrutinib Dose Modification/Discontinuation
Hematological	
Grade 4 neutrophil count decrease (ANC < 500/μL)	• Hold acalabrutinib, and consider introducing growth factors (eg, G-CSF) and continue to monitor ANC • If neutropenia has improved to Grade 1 or baseline within 3 days of event onset, restart acalabrutinib • If neutropenia has *not* improved to Grade 1 or baseline within 3 days of event onset, discontinue acalabrutinib
Any grade febrile neutropenia lasting more than 2 days	• Discontinue acalabrutinib • Consider introducing growth factors (eg, G-CSF), evaluate subject for infection, and begin antibiotic treatment per institutional guidelines
Presence of significant bleeding events with or without thrombocytopenia, such as: • Grade 3 or 4 hemorrhage • Any grade serious hemorrhage event • Any grade intracranial hemorrhage or hematoma	Discontinue acalabrutinib
Grade 4 platelet count decrease (< 25,000/mm3)	• Hold acalabrutinib and consider platelet transfusions, as clinically indicated • If thrombocytopenia has improved to ≤Grade 2 within 3 days of event onset, restart acalabrutinib • If thrombocytopenia has *not* improved to ≤Grade 2 within 3 days of event onset, discontinue acalabrutinib
Gastrointestinal/hepatic	
Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or antidiarrheal therapy	Discontinue acalabrutinib

Event	Acalabrutinib Dose Modification/Discontinuation
Acute hepatic toxicity or hepatic failure, which is of such severity that after evaluation by a hepatologist, would consider appropriate to stop all non-essential medications	Discontinue acalabrutinib
Cardiovascular	
Grade 3 or 4 hypertension, if persistent despite optimal antihypertensive therapy	Discontinue acalabrutinib
Grade 3 or 4 arrhythmias that are sustained or associated with cardiovascular instability	Discontinue acalabrutinib
Infections	
Severe opportunistic infection (such as *Pneumocystis jirovecii* pneumonia, toxoplasmosis, disseminated *Mycobacterium avium* complex, PML)	Discontinue acalabrutinib
Grade 3 confirmed bacterial infections	• Hold acalabrutinib • If infection does not respond to appropriate antimicrobial therapy within 48-72 hours, discontinue acalabrutinib
Grade 4 confirmed bacterial infections	Discontinue acalabrutinib
Other	
Any non-COVID-19-related Grade 4 AE	Discontinue acalabrutinib
Any other Grade 3 or Grade 4 toxicity that persists despite optimal medical management	Discontinue acalabrutinib

AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; ALP = alkaline phosphatase; AST = aspartate aminotransferase; G-CSF = granulocyte colony-stimulating factor; PML = progressive multifocal leukoencephalopathy.

Clinical judgment should be used to determine appropriate management of the subject during any AE.

Acalabrutinib may be held for a maximum of 3 consecutive days (6 consecutive doses) from expected dose due to toxicity. Any other clinically important events where dose delays may be considered appropriate by the Investigator, as well as continuation of therapy after a dose is held beyond 3 days, must be discussed with the Medical Monitor. If a dose is missed due to an AE or for any other reason, missed doses should be completed so the subject receives a maximum of 20 doses of study drug, even if this is beyond the 10-day dosing period.

6.7.1 Renal Impairment

After administration of a single 100 mg radiolabeled acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces and 12% of the dose was recovered in the urine (2% acalabrutinib). No clinically relevant PK difference was observed in subjects with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 mL/min/1.73 m^2, as estimated by Modification of Diet in Renal Disease [MDRD] equation). Acalabrutinib PK and clinical safety has not been evaluated in subjects with severe renal impairment (eGFR <29 mL/min/1.73 m^2, MDRD) or renal impairment requiring dialysis.

The effect of dialysis on acalabrutinib plasma concentrations has not been studied. Acalabrutinib is rapidly absorbed, metabolised and distributed. The plasma protein binding is 97.5% and is noncovalent (potentially dialyzable). CCI [redacted] If subjects with COVID-19 enrolled in this study require acute hemodialysis, it is recommended to dose acalabrutinib 100 mg and pause hemodialysis for 2 to 4 hours after acalabrutinib administration to allow for absorption and distribution to target cell populations.

6.7.2 Hepatic Impairment

Acalabrutinib clinical safety has not been evaluated in patients with severe hepatic impairment. If acalabrutinib is administered to subjects with hepatic impairment, monitor subjects carefully for AEs and follow recommendation dose modifications in Section 6.7.

The PK acalabrutinib in subjects with hepatic impairment has been studied. Briefly, the AUC of acalabrutinib increased 1.9-fold in subjects with mild hepatic impairment (Child-Pugh class A), 1.5-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 5.3-fold in subjects with severe hepatic impairment (Child-Pugh class C) compared with subjects with normal liver function. No clinically relevant PK difference in ACP-5862 was observed in subjects with severe hepatic impairment (Child-Pugh class C) compared with subjects with normal liver function. No clinically relevant PK differences in acalabrutinib and ACP-5862 were observed in subjects with mild or moderate hepatic impairment (total bilirubin less and equal to ULN and AST greater than ULN, or total bilirubin greater than ULN and any AST) relative to subjects with normal hepatic function (total bilirubin and AST within ULN).

6.8 Treatment After the End of Study

Not applicable.

7. DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects may discontinue study treatment for the following reasons:

- Unable to swallow pills
- Completed treatment
- Pregnancy
- AE
- Investigator's decision
- Subject's withdrawal of consent from study
- Decision by the Sponsor to terminate the study
- Lost to follow-up
- Death
- Other

The Investigator should instruct the subject to contact the site before or at the time if study treatment is stopped. A subject that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the eCRF. Refer to the guidance in Section 6.5.3.

All subjects will be followed through 90 (± 7) days after randomization.

Subjects who receive acalabrutinib should have follow up assessments for safety 28 (± 3) days after the last dose of acalabrutinib (whether due to discontinuation or completion of dosing). Subjects who have been randomized to the BSC arm should have a follow up assessment for safety 38 (± 3) days after randomization.

For the safety and survival follow-up visits, telemedicine is recommended for capturing AEs and concomitant medications. Safety laboratory tests can be done at the hospital or a local laboratory provided the results are ultimately captured in the clinical database for the study.

7.2 Subject Withdrawal from the Study

A subject may withdraw from the study (eg, withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment.

A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any AE. The Investigator will follow up subjects as medically indicated.

7.3 Lost to Follow-Up

A subject will be considered lost to follow-up if he/she fails to return for scheduled visits or is unable to be contacted by the study site.

In the case a subject is lost to follow-up, every possible effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation. Site personnel should check hospital records and a publicly available death registry (if available), as well as checking with the subject's current physician, to obtain a current survival status. The measures taken to follow up must be documented (the applicable eCRF modules will be updated).

When a subject withdraws before completing the study, the reason for withdrawal must be documented in the eCRF and in the source documents. Subjects who withdraw consent should still be encouraged to complete the SFU assessments before withdrawing consent, but these assessments cannot be mandated once consent is withdrawn.

Subjects who are withdrawn or removed from study treatment will not be replaced.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA in Section 1.1.

The Investigator will ensure that data are recorded on the eCRF.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries per the Clinical Study Agreement. The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

Immediate safety concerns should be discussed with the Medical Monitor upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1 Screening Assessments

Procedures conducted as part of the subject's clinical management of COVID-19 symptoms and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within 24 hours of signing the informed consent.

8.1.1 Informed Consent

The informed consent process must be followed per local and institutional guidelines (Appendix A 3).

8.1.2 Demographics

The following subject demographics will be collected: age, sex, race, ethnicity, and history of substance abuse (cigarettes [yes/no; if yes, specify packs per day], vaping [yes/no], recreational drugs [yes/no; if yes, specify name], alcohol [yes/no; if yes, specify amount]).

8.1.3 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 5.

8.1.4 Medical History

Collect and record the subject's relevant medical history through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. Information on COVID-19 epidemiology will also be collected.

8.1.5 Physical Examinations and Chest Imaging, Electrocardiogram, and Echocardiogram

The screening physical examination will be symptom-directed and include height, weight and lung auscultation.

Per standard of care, chest imaging can be done by chest x-ray or CT scan with contrast, or any other appropriate means to confirm pneumonia prior to or upon hospitalization (within 7 days of randomization). Post treatment assessment will continue as clinically indicated.

A single 12-lead ECG and will be done during the screening period and at Day 10 or upon discharge from the hospital. ECG should be collected during the treatment period, as clinically

indicated. For all ECGs, details of rhythm, ECG intervals, and an overall evaluation will be recorded.

An echocardiogram should be collected at baseline or during the treatment period, as clinically indicated per SoA. Percentage left ventricular ejection fraction should be recorded.

If the Investigator considers an abnormal ECG or echocardiogram finding at screening or baseline to be clinically significant, that finding should be reported as a concurrent condition.

Any clinically significant abnormal ECG or echocardiogram findings during the treatment period should be recorded in the source document and the AE section of eCRF, according to standard AE collection and reporting processes.

8.1.6 Vital Signs

The vital signs to be collected are blood pressure, respiratory rate, oximetry, pulse, and body temperature.

During screening, vital signs should be collected as close as possible to randomization on Day 1. If more than one value is obtained for vital signs during screening, the value closest to randomization should be used. The oxygen-haemoglobin saturation of the blood will be assessed using standard pulse oximetry or by arterial blood gas for those subjects who have an arterial blood gas obtained.

8.1.7 Urine or Serum Pregnancy

Screening pregnancy testing will be done on women of childbearing potential only (refer to Appendix F).

8.1.8 Laboratory Tests

The screening period should occur immediately prior to randomization and dosing. Screening can be performed within 1 to 3 days prior to dosing, depending on the local requirements for laboratory turn-around times. The following laboratory tests will be done during screening as specified in the SoA (Section 1.1) using the sites local laboratories:

- Urine or serum pregnancy test (women of childbearing potential only)
- Hematology studies must include complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, platelet count, ANC or percentage, red blood cell count, absolute monocyte count or percentage, and absolute lymphocyte count (ALC) or percentage.
- Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin (direct and indirect bilirubin, if available), total protein, and uric acid.

- Arterial blood gases (if available; see Section 8.4.1)
- C-reactive protein (CRP)
- Serum ferritin, fibrinogen, D-dimer, procalcitonin
- Prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR)
- Cardiac troponin I
- Hepatitis serology must include, at a minimum, HBsAg, anti-HBc, and HCV antibody (if additional hepatitis serology is collected per institutional guidelines, it should be collected in the database)
- SARS-CoV-2 reverse transcriptase-polymerase chain reaction viral test. Sites should report this as positive/negative.

Refer to the laboratory manual for instructions on processing and shipping. Additional handling information provided in Appendix C.

8.2 Concomitant Medications

Document all concomitant medications and procedures from the start of screening procedures through the end of participation on the study (refer to Section 1.1). Reason for treatment should be captured as “disease under study”.

Medications used as BSC should be captured as concomitant medications.

8.3 On-study Procedures

Planned time points for all on-study procedures are provided in the SoA (Section 1.1). While the subject remains hospitalized, assessments should be performed per SoA until discharge. The date of admission and discharge will be collected for all subjects. If a subject is discharged prior to Day 10, the subject should continue to take acalabrutinib at home. If the subject was discharged prior to Day 7, the subject should return to the clinic 2 to 4 days after discharge and complete the Day 10 assessment as outlined in the SoA.

The following laboratory evaluations will be done at the local laboratories while on study:

- Urine or serum pregnancy test (women of childbearing potential only)
- Hematology studies must include complete blood count (CBC) with differential including, but not limited to white blood cell count, hemoglobin, platelet count, ANC or percentage, red blood cell count, absolute monocyte count or percentage, and absolute lymphocyte count (ALC) or percentage.
- Chemistry will include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, magnesium, phosphate/phosphorus, potassium, sodium, total bilirubin (direct and indirect bilirubin, if available), total protein, and uric acid.

- Arterial blood gases (if available; see Section 8.4.1)
- CRP
- Serum ferritin, fibrinogen, D-dimer, procalcitonin*
- PT, aPTT, INR*
- Cardiac troponin I*
- Hepatitis B serology will be collected as clinically indicated for subjects with a known history of hepatitis B exposure (see Section 6.6.3)

*These laboratory tests should be performed more frequently than described in the SoA (Section 1.1) if clinically indicated.

Samples (peripheral blood samples for mononuclear cells, serum/plasma, and RNA) will be collected per the timepoints delineated in the SoA (Section 1.1) and sent to respective central laboratories for the following tests:

- CCI [redacted]
- CCI [redacted]
- Immunophenotyping: Flow cytometry testing of peripheral blood will include, but is not limited to, CD3+, CD4+, CD8+, CD14+, CD19+ and CD16+/56+ cells
- Serum and nasal swab samples for SARS-CoV-2 viral load/viral shedding
- CCI [redacted]
- Plasma samples for acalabrutinib/ACP-5862 PK (subjects on acalabrutinib arm only)
- CCI [redacted]

NOTE: Safety, CRP, PK, PD, and correlative laboratory tests are considered Tier 1 and should not be missed. The site must follow the SoA.

Refer to the laboratory manual for instructions on processing and shipping. Additional handling information provided in Appendix C.

Other procedures to be performed while on study include:

- Chest imaging
- ECG
- Echocardiogram
- Vital signs

8.4 Clinical Assessments During Hospitalization

8.4.1 Oxygen Treatments and Ventilator Use

If a subject requires oxygen supplementation, data will be recorded, including method of oxygen supplementation, maximum daily flow rate and fraction of inspired oxygen (FiO_2).

If a subject requires mechanical ventilation, data will be recorded regarding whether ventilator weaning was attempted.

For subjects on mechanical ventilation the following ventilator settings will be recorded: tidal volume, FiO2, peak airway pressure over the last 24 hours, plateau pressure, positive end expiratory pressure, and respiratory rate. The data will be recorded qd, and the worst value of the day will be entered

For subjects on mechanical ventilation, an arterial blood gas (pH, partial pressure of oxygen [PaO_2], partial pressure of carbon dioxide [$PaCO_2$], and FiO_2 at the time the sample was obtained), will be recorded qd. If more than one value is obtained for the arterial blood gases, the value closest to 08:00 will be used.

Arterial gasses should be collected from subjects if the sample is easily accessible and the procedure will not be painful to subjects (ie, subject is in the ICU or has arterial port). All available data from the arterial gases should be entered into the database. If the collection of arterial gases is not clinically indicated, the test should not be performed.

Predicted body weight will be recorded on the ventilator eCRF for assessment of tidal volume.

8.4.2 Modified Sequential Organ Failure Assessment (SOFA) Scores

A modified SOFA score will be calculated. For each of the following routine assessments, the worst value of the day will be recorded in the eCRF: PaO_2/FiO_2 (mmHg) or oxygen saturation by pulse oximetry (SpO_2)/FiO_2 (mmHg), platelet count, bilirubin, vasopressor use (µg/kg/min, mmHg), and creatinine ([or urine output]). For laboratory values, use last available (if within 48 hours). On days when laboratory results are unavailable, values will be extrapolated from the previously available values.

8.4.3 Assessment of Number of Days in ICU

Assessment of ICU length of stay will be obtained by asking the Investigator to determine if the subject is receiving ICU standard care (or equivalent) on each day during hospitalization up to Day 90. In the event of an affirmative response, a further question will be asked to determine if this ICU care is considered necessary (rather than being due to logistical reasons).

Only days in the ICU (or equivalent), which the Investigator considers necessary, will be regarded as ICU days.

8.5 Follow Up Procedures

Follow up procedures are outlined in Section 1.1

8.6 Collection of Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

The following are NOT considered an AE:

- **Pre-existing condition that has not worsened:** A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **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:** 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 haemoglobin) or requires a change in study drug (eg, lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).
- **Progression of underlying disease:** Progression of underlying disease unequivocally related to COVID-19 pneumonia (such as worsening of respiratory status or complications associated with pneumonia) will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying disease. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying disease, or if they do not fit the expected pattern of progression for the disease under study.

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

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

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow up AEs, see Section 8.6.3.

8.6.1 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.6.2 Time Period and Frequency for Collecting AE and SAE Information

After the signing of the ICF, all SAEs must be reported. After randomization, all AEs/SAEs, irrespective of attribution of causality, must be reported.

AE reporting, irrespective of seriousness, ends 28 (± 3) days after the last dose of study treatments(s) for those on acalabrutinib + BSC (Arm 1) and 38 (± 3) days from randomization for those on BSC only (Arm 2).

SAEs considered related to study treatments(s) or study procedures occurring after the end of the AE reporting period (as defined above) must be reported. Information on concomitant medications at the time of the treatment-related SAE will also be collected.

All SAEs will be recorded and reported to the Sponsor or designee within 1 day (ie, immediately but **no later than 24 hours** from when he or she becomes aware of it), as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for reporting SAEs are provided in Section 8.7.1.

8.6.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs/non-SAEs/AEs of special interest (AESIs; as defined in Section 8.6.12), will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up.

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. The Sponsor retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.6.4 Adverse Event Data Collection

The following variables will be collected for each AE:

- AE diagnosis/description
- The date when the AE started and stopped
- Maximum Common Terminology Criteria for Adverse Events (CTCAE) grade
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Action taken regarding investigational product
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Seriousness criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medications
- Description of SAE

The grading scales found in the revised NCI CTCAE Version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE Version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

8.6.5 Causality Collection

The Investigator will assess causal relationship between investigational product and each AE, and answer ‘yes’ or ‘no’ to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B of this protocol.

8.6.6 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/you were last asked?'*, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.6.7 Adverse Events Based on Examinations and Tests

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated procedures (eg, safety laboratory tests and vital signs) should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE/SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see Section 8.6.9 and Section 8.6.10.

8.6.8 Hy's Law

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

8.6.9 Disease Under Study

Systemic symptoms of the disease under study are those which might be expected to occur as a direct result of the clinical presentation associated with COVID-19 pneumonia and respiratory illness. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the investigational product.

8.6.10 Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to COVID-19 pneumonia for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events, which are unequivocally due to COVID-19 pneumonia, should not be reported as an AE or SAE during the study. Events attributable to disease progression of COVID-19 include pulmonary failure, ARDS, sepsis, shock, multiorgan failure and death.

8.6.11 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be documented in the eCRF in the Death page. It should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported as an SAE within 24 hours. It should also be documented in the Death page in the eCRF. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Death page in the eCRF, but every effort should be made to determine a cause of death. A post-mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to Sponsor Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined follow-up period after the administration of the last dose of study treatment should be documented in the Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study treatment, then it should also be reported as an SAE.

8.6.12 Adverse Events of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of the acalabrutinib safety profile and require close monitoring and rapid communication by the

Investigators to the Sponsor. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and reported as per Section 8.7.1.

The following events are AESIs for subjects receiving acalabrutinib and must be reported to the Sponsor expeditiously (see Section 8.7.1 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

- **Ventricular arrhythmias** (eg, ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation)

8.7 Safety Reporting and Medical Management

8.7.1 Reporting of Serious Adverse Events

All SAEs have to be reported to the Sponsor, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the eCRF. Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and Investigators.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate Sponsor representatives within 1 day (ie, immediately but **no later than 24 hours** from when he or she becomes aware of it).

The designated Sponsor representative works with the Investigator to ensure that all the necessary information is provided to the Sponsor Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform Sponsor representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours** from when he or she becomes aware of it).

For all studies except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and file the report/information with the Investigator's Brochure and will notify the IRB/IEC according to local requirements, if appropriate.

For further guidance on the definition of a SAE, see Appendix B.

8.7.2 Pregnancy

All pregnancies, partner pregnancies, and outcomes of pregnancy/partner pregnancy should be reported to the Sponsor, with the exception of any pregnancy that is discovered before the subject has received any study treatment.

If a pregnancy is reported, the Investigator should inform the Sponsor within 1 day (ie, immediately but no later than 24 hours of when he/she becomes aware of the pregnancy).

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.7.2.1 Maternal Exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate Sponsor representatives within 1 day (ie, immediately but no later than 24 hours of when he/she becomes aware of the pregnancy).

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor subject safety data entry site within either 1 day or 5 calendar days for SAEs (see Section 8.7.1), and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.7.2.2 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 2 days after the last dose of acalabrutinib.

Pregnancy of a subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality), occurring from the date of the first dose until 2 days after the last dose of acalabrutinib, should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the partner must be obtained before the Pregnancy Report Form is completed.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. The local study team should adopt the Master Pregnant Partner Form in line with local procedures/requirements and submit it to the relevant regulatory authority/IRB/ethics committee prior to use.

8.7.3 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects. Any study treatment overdose or incorrect administration of study treatment should be noted on the Overdose eCRF.

All AEs associated with an overdose or incorrect administration of study treatment should be recorded on the Adverse Event eCRF. If the associated AE fulfils serious criteria, the event should be reported to the Sponsor immediately (ie, no later than 24 hours after learning of the event).

For overdoses associated with a SAE, the standard reporting timelines apply; see Section 8.6.2. For other overdoses, reporting must occur within 30 days.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site.

8.7.4 Medication Error

If a medication error occurs in the course of the study, then the Investigator (or other site personnel) informs the appropriate Sponsor representatives within 1 day (ie, immediately but no later than 24 hours of when the Investigator (or other site personnel) becomes aware of the error.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is completed within 1 calendar day (in the event of initial fatal/life-threatening errors or follow-up fatal/life-threatening errors) or 5 calendar days (in the event of other

serious initial and follow-up errors) if there is an SAE associated with the medication error (see Section 8.7.1), and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix B.

8.8 Efficacy Assessments

8.8.1 Improvements on the 9-Point Ordinal Scale

For the purposes of this study, the condition of each potential subject in the study will be assessed using a 9-point category ordinal scale below. Assessments will be performed as described in the SoA.

0.* Uninfected, no clinical or virological evidence of infection

1. Ambulatory, no limitation of activities

2. Ambulatory, limitation of activities

3. Hospitalized – mild disease, no oxygen therapy

4. Hospitalized – mild disease, oxygen by mask or nasal prongs

5. Hospitalized – severe disease, non-invasive ventilation or high flow oxygen

6. Hospitalised – severe disease, intubation and mechanical ventilation

7. Hospitalized – severe disease, ventilation and additional organ support, such as pressors, renal replacement therapy, extracorporeal membrane oxygenation

8. Death

*Score of zero on 9-point category ordinal scale will not be evaluated in this study.

To be considered a “responder” to treatment with a target candidate, a subject needs to show an improvement of at least 2 points (from randomization) on this scale. The time to clinical improvement of 2 points will be assessed as a secondary endpoint.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Overall study design is described in Section 4.1 of the protocol. Subjects who are hospitalized for COVID-19 symptoms and meet the eligibility criteria will be randomized 1:1 to receive acalabrutinib plus BSC (Arm 1: n=30) vs BSC (Arm 2: n=30).

Stratification by age (≥65 vs <65 years) and comorbidities (present vs absent) will be applied to randomization.

The primary objective of the study is to evaluate the safety and preliminary efficacy of acalabrutinib plus BSC (Arm 1) vs BSC (Arm 2). There is no formal hypothesis testing for the safety and efficacy endpoints. The primary focus for the efficacy is to estimate the treatment effect as measured by the difference between treatment arms in the proportion of subjects who are alive and free of respiratory failure.

9.2 Sample Size Determination

The planned total number of subjects in this study is 60.

Based on the reported rate of deaths and need for ICU admission (a surrogate for respiratory failure) in subjects who are hospitalized for COVID-19 (Arentz et al 2020, Bhatraju et al 2020, CDC 2020, Grasselli et al 2020), it assumed that the proportion of subjects who are alive and free of respiratory failure at Day 28 is 70% under BSC. A targeted difference of 20% between two treatment arms (ie, 90% for acalabrutinib + BSC) is of clinical interest. With a total sample size of 60, the half-width of the 2-sided 90% confidence interval for the observed treatment difference is 16.4% using unpooled estimate for variance. It has approximately 64% power, with a 2-sided type I error of 0.1, to detect a difference of 20% between the 2 arms.

9.3 Populations for Analyses

The analysis populations are defined as shown in Table 6.

Table 6 Analysis Populations

Population/ Analysis set	Description
Full analysis set (ITT population)	The full analysis set will include all subjects who are randomized and will be used for all efficacy analyses. Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Subjects who were randomized but did not subsequently go on to receive study treatment will be included in the analysis in the treatment arm to which they were randomized, following the “intent-to-treat” principle.
Per-protocol analysis set	The per-protocol analysis set will be a subset of the ITT population including only subjects without important detected protocol deviations affecting the efficacy endpoints. Subjects will be summarized according to the actual treatment first received. The primary endpoint of the study will also be summarized for this population.

Table 6 Analysis Populations

Population/ Analysis set	Description
Safety analysis set	The safety analysis set (Safety population) is based on the treatment subjects actually received. In this study, the treatment is either acalabrutinib + BSC or BSC only. If a subject receives at least 1 dose of acalabrutinib, the subject is considered as acalabrutinib-treated, regardless which arm the subject was randomized to. Subjects who are randomized to acalabrutinib + BSC but do not receive any acalabrutinib will be summarized in the BSC group.
PK analysis set	The PK analysis set will include all subjects who receive ≥1 dose of acalabrutinib and had ≥1 post-dose evaluable PK data point for acalabrutinib. The population will be defined by AstraZeneca, the pharmacokineticist and the statistician prior to any analyses being performed.

BSC = best supportive care; ITT = Intent-to-treat; PK = pharmacokinetic.

9.4 Interim Analysis

There are no formal interim futility and interim efficacy analyses in this Phase 2 study.

9.5 Missing Data Handling

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed per prespecified, conservative imputation rules.

The specification for handling death in the analysis of endpoints that do not contain mortality as a component will be provided in the Statistical Analysis Plan (SAP).

9.6 Statistical Analyses

A comprehensive SAP will be developed and finalized before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. Any deviations from the SAP will be reported in the Clinical Study Report.

The primary analysis of the study will take place when all randomized subjects have been followed for 38 (± 3) days from randomization.

An updated analysis for those endpoints requiring 90-day assessments will take place after the last randomized subject has had 90 days follow up from randomization.

9.6.1 Safety Analyses

Safety assessments will consist of monitoring and recording AEs, SAEs and AEs leading to discontinuation of study treatment; measurements of protocol-specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study treatment. All safety analyses will be performed on the safety analysis set as defined in Section 9.3.

Verbatim descriptions of AEs will be mapped per the most recent version of Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms and graded per National Cancer Institute (NCI) CTCAE, v5.0 or higher. Extent of exposure to study treatment, all AEs, SAEs, any AEs leading to study treatment discontinuation, and study treatment related AEs will be summarized. The frequency of AEs will be summarized by system organ class and preferred terms per MedDRA by the worst reported NCI CTCAE grade. TEAEs will be summarized, unless otherwise specified. In this study, for Arm 1 (acalabrutinib + BSC), TEAEs are defined as AEs starting or ongoing AEs worsening after the first dose of study treatment and AEs with start date up to the last dose of study treatment plus 28 (± 3) days; for Arm 2 (BSC only), TEAEs are defined as AEs starting or ongoing AEs worsening after the date of randomization and AEs with start date up to 38 (± 3) days from randomization.

Laboratory abnormalities will be defined based on laboratory normal ranges (universal normal ranges, if central laboratory). Selected laboratory parameters may be analysed with shift tables and summaries of changes from baseline to worst post-treatment value.

Vital sign and all other safety assessments will be tabulated and summarized.

Full details of AE, laboratory assessments, vital sign assessments and all other safety assessments will be provided in the SAP.

9.6.2 Efficacy Analyses

Primary Endpoint

The primary endpoint is the proportion of subjects who are alive and free of respiratory failure at Day 28 (see Section 3 for a definition of respiratory failure). The point estimate and its 90% confidence interval (CI; using Wald method with continuity correction) will be calculated for each treatment arm. The Cochran-Mantel-Haenszel $\chi 2$ test stratified by age ($\geq$ 65 vs < 65 years) and comorbidities (present vs absent) will be used to compare the proportion of subjects who are alive and free of respiratory failure at Day 28 between the two treatment arms. An unstratified analysis will also be performed. Finally, the difference in the proportion of subjects who are alive and free of respiratory failure at Day 28 will also be

provided with 90% CIs. The treatment difference will be also estimated using a logistic regression (Ge 2011) with indicators for treatment and the randomization stratification factors (2 × 2) as well as baseline respiratory failure (with vs without).

The primary endpoint of the study will be summarized by subgroups that include age group, sex, race, ethnicity, comorbidities, baseline respiratory failure, and history of substance abuse.

The primary endpoint will be summarized and analysed as per the methods above for the full analysis set (ITT population) as well as the per-protocol analysis set.

Additional sensitivity analyses and subgroup analyses of the primary endpoint may be performed as appropriate.

Secondary Endpoints

The proportion of subjects alive and free of respiratory failure at Day 14 will be summarized using the full analysis set.

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented by treatment arm for continuous secondary efficacy endpoints (refer to Section 3). Summary statistics for the number of days hospitalized from randomization to 28 days after randomization and the number of days in ICU from randomization to 90 days after randomization will be summarized.

Time from randomization to first occurrence of respiratory failure or death on study (up to 28 days after randomization) due to any cause will be analysed using Kaplan-Meier method; hazard ratio and corresponding 90% CIs will be estimated using Cox proportional hazards models, stratified by randomization stratification factors. If a subject did not have an event and did not drop out prior to Day 28, the data will be censored at Day 28; if a subject did not have an event but dropped out prior to Day 28, the data will be censored at the last date known to be alive and free of respiratory failure.

Similarly, time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale through Day 28 will be analysed using Kaplan-Meier method.

The statistical analysis plan will provide the further details.

9.6.3 Pharmacokinetic and Pharmacodynamic Analyses

PK assessments will be conducted in up to 15 evaluable subjects and PD assessments in up to 15 evaluable subjects randomized to Arm 1 (acalabrutinib + BSC). Subjects are considered evaluable if they have an evaluable PK/PD profile, ie, (1) receive acalabrutinib treatment and (2) do not have data that are unavailable or incomplete (ie, provide data from all PK/PD visits indicated in the SoA).

The statistical analysis and reporting of PK and PD parameters will be provided in the SAP.

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Appendix A Regulatory, Ethical and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) GCP Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator, and reviewed and approved by the IRB/IEC, before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the Sponsor policy on Bioethics and Human Biological Samples.

A 2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date and time the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorized representative.

Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the sample storage period. If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analysed at the time of the request, the Sponsor will not be obliged to destroy the results of this research.

A 4 Data Protection

Each subject will be assigned a unique identifier by the Sponsor. Any subject records or data sets transferred to the Sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 5 Committee Structures

An iDMC will be formed. Detailed information regarding the composition of the iDMC and detailed iDMC procedures will be provided in a separate charter. The iDMC will be responsible for reviewing the safety data periodically and provide recommendations according to the charter.

The safety of all Sponsor clinical studies is closely monitored on an ongoing basis by Sponsor representatives in consultation with Patient Safety. Issues identified will be addressed; for example, this could involve amendments to the CSP and letters to Investigators.

A 6 Dissemination of Clinical Study Data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical trial and/or summary of main study results may also be available on other websites according to the regulations of the countries in which the main study is conducted.

A 7 Data Quality Assurance

All subject data relating to the study will be recorded on printed CRF or eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF/eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF/eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review to confirm that data entered into the CRF/eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the

retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

A 8 Source Documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF/eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definitions of what constitutes source data can be found in the Clinical Study Agreement.

A 9 Study and Site Closure

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. The study may be stopped if, in the judgment of the Sponsor, trial subjects are placed at undue risk because of clinically significant findings that:

- Meet individual stopping criteria or are otherwise considered significant
- Are assessed as causally related to study treatment,
- Are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF/eCRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study treatment development

A 10 Publication Policy

The results of this study may be published or presented at scientific meetings once the primary analysis is completed and the study is unblinded. No other publications prior to that timepoint is allowed.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Subsequent to the primary publication, if an Investigator plans to publish any subset of data, or case report, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Appendix B Adverse Event Definitions and Additional Safety Information

B 1 Definition of Adverse Events

An AE is the development of any untoward medical occurrence (other than progression of the disease under evaluation) in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (eg, nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

B 2 Definition of Serious Adverse Events

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life-threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred, or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that, had an AE occurred in a more severe form, it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important Medical Event or Medical Treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalization, disability or incapacity but may jeopardize the subject or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 Intensity Rating Scale

The grading scales found in the revised NCI CTCAE v5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate and severe events into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf).

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. The Sponsor would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a Sponsor study treatment that either causes harm to the subject or has the potential to cause harm to the subject.

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

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the subject received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error, eg, medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated, eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed, eg, kept in the fridge when it should be at room temperature
- Wrong subject received the medication (excluding IRT errors)
- Wrong drug administered to subject (excluding IRT errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT - including those which lead to one of the above listed events that would otherwise have been a medication error
- Subject accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product

Medication errors are not regarded as AEs, but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody of Biological Samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

The Sponsor will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the Sponsor-assigned biobanks and will be registered by the Sponsor Biobank Team during the entire lifecycle.

If required, the Sponsor will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is the sooner.

C 2 Withdrawal of Informed Consent for Donated Biological Samples

If a subject withdraws consent specifically to the subsequent use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research. A general withdrawal of consent to study treatment does not imply a withdrawal of consent to subsequent analyses of biological samples. In case a subject withdraws the general informed consent and additionally wants to withdraw consent for further analyses of his/her biological samples, the subject is required to sign an opt-out.

As collection of the biological sample(s) is an integral part of the study, then the subject is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to Sponsor
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site

- Ensures that the subject and Sponsor are informed about the sample disposal.

The Sponsor ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association Regulations on Labeling and Shipment of Biological Samples

Air transportation of biological samples (including biohazardous materials and potentially biohazardous materials) is regulated under International Airline Transportation Association (IATA) Dangerous Goods Regulations (DGR; 61st edition [2020]) Division 6.2—Infectious Substances. The IATA DGR definition of infectious substances includes any substance that is known or reasonably expected to contain pathogens, ie, microorganisms (including bacteria, viruses, rickettsiae, parasites, fungi) or other agent, such as a proteinaceous infectious particle (prion), that can cause disease in humans or animals.

As Division 6.2 infectious substances, biological samples transported by air must be classified as Category A, Category B, or Exempt; secured in IATA-compliant packaging; and identified using the appropriate United Nations shipping number and label requirements corresponding to the species, sample type, and infectious nature of material being shipped. See Table 7 for details.

Under IATA regulations, subject specimens from clinical trials will fall into Category B or Exempt. Clinical trial samples can often be packed and transported at ambient temperature. However, in cases where biological samples must be refrigerated or frozen for transport (eg, using dry ice or liquid nitrogen), additional dangerous goods specifications will apply; refer to DGR Section 3.6.2.2.3.8 (e). IATA-compliant couriers and materials should be used for transportation and packaging, and where applicable, packing should be done by IATA-certified personnel.

Transportation of biological samples by road or rail is routinely subject to local regulations requiring shipment in safe, appropriate packaging materials to contain any risk of infection or contamination at all times, in addition to the use of approved couriers. Wherever possible, compliance with IATA Instruction 650 standards for biological sample containment are encouraged for road or rail transport of subject specimens.

Table 7 IATA Dangerous Goods Regulations Classification of Infectious Substances

Category [a]	Description	Shipping instructions	UN number and labeling
Category A infectious substances	Any infectious substance transported in a form that, when exposure occurs, [b] is capable of causing permanent disability, life threatening disease, or fatal disease in otherwise healthy humans or animals. *(Examples include Ebola and Lassa fever virus.)*	Category A pathogens must be: • Packed and shipped in accordance with IATA Instruction 620 • Identified using the appropriate UN shipping number and label information	UN 2814 "Infectious substances affecting humans or both humans and animals" UN 2900 "Infectious substances affecting animals only"
Category B infectious substances	Any infectious substance that does not meet the criteria for inclusion in Category A. Category B infectious substances are not in a form capable of causing permanent disability, life threatening disease, or fatal disease in otherwise healthy humans or animals when exposure occurs. [b] *(Examples include hepatitis A, B, C, D, and E viruses, and HIV types 1 and 2.)*	Category B pathogens must be: • Packed and shipped in accordance with IATA Instruction 650 • Identified using the appropriate UN shipping number and label information	UN 3373 "Biological substance, Category B"
Exempt substances	Subject specimens for which there is minimal likelihood that pathogens are present. *(Examples may include blood-based samples, tissue cultures, or other biological samples.)*	Exempt substances must be: • Packed and shipped in accordance with requirements specified in Division 6.2, Section 3.6.2.2.3.8 of the IATA DGR [a] • Identified using the appropriate label information	"Exempt human specimen" "Exempt animal specimen"

DGR = Dangerous Goods Regulation; IATA = International Airline Transportation Association; UN = United Nations.
Note: IATA Dangerous Goods Regulations, 61st Edition. 01 January 2020. International Air Transport Association. Available at: https://www.iata.org/en/programs/cargo/dgr/download/.

[a] For transport purposes, the classification of infectious substances according to risk groups was removed in the DGR 46th edition (2005). There is no direct relationship between risk groups and Categories A and B.

[b] Exposure occurs when an infectious substance is released outside of the protective packaging, resulting in physical contact with humans or animals.

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

D 1 Introduction

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

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The Investigator will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

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

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law

AST or ALT ≥ 3x ULN **together with** Total Bilirubin (TBL) ≥ 2x ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law

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

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

D 3 Identification of Potential Hy's Law Cases

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

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

Central laboratories being used:

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

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

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory without delay
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

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

- Determine whether the subject meets PHL criteria (see Section D 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

Local laboratories being used:

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

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Section D 2 within this Appendix for definition) by reviewing laboratory reports from all previous visits

- Promptly enter the laboratory data into the laboratory CRF

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria not met

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

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

D 4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment
- Notify the AstraZeneca representative who will then inform the central Study Team
- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data
- Subsequent to this contact the Investigator will:
  - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used
  - Complete the three Liver CRF Modules as information becomes available

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

D 5 Review and Assessment of Potential Hy's Law Cases

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

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

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

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

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

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

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

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

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to Clinical Study Protocol (CSP) process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory tests

Hy's Law Laboratory Kit for Central Laboratories

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

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive
** Carbohydrate deficient transferrin (CD-transferrin) is not available in China. Study teams should amend this list accordingly

Reference

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

Appendix E Examples of Coadministered Drugs That Need Additional Consideration

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

Table 8 CYP3A Inhibitors

Strong inhibitors of CYP3A	Moderate inhibitors of CYP3A
Boceprevir	aprepitant
clarithromycin [a]	cimetidine
cobicistat [a]	ciprofloxacin
conivaptan [a]	clotrimazole
danoprevir and ritonavir [b]	crizotinib
diltiazem [a]	cyclosporine
elvitegravir and ritonavir [b]	dronedarone [a]
grapefruit juice	erythromycin
Idelalisib	fluconazole
indinavir and ritonavir [b]	fluvoxamine
itraconazole [a]	imatinib
Ketoconazole	tofisopam
lopinavir and ritonavir [a,b]	verapamil [a]
Nefazodone	
nelfinavir [a]	
paritaprevir and ritonavir and (ombitasvir and/or dasabuvir) [b]	
Posaconazole	
ritonavir [a,b]	
saquinavir and ritonavir [a,b]	
telaprevir [a]	
tipranavir and ritonavir [a,b]	
Troleandomycin	
Voriconazole	

[a] Inhibitor of P-glycoprotein.

[b] Ritonavir is usually given in combination with other anti-HIV or anti-HCV drugs in clinical practice. Caution should be used when extrapolating the observed effect of ritonavir alone to the effect of combination regimens on CYP3A activities.

Table 9 CYP3A Inducers

Strong inducers of CYP3A	Moderate inducers of CYP3A
Carbamazepine	bosentan
Enzalutamide	efavirenz
Mitotane	etravirine
Phenytoin	modafinil
Rifampin	
St. John's wort [a]	

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

Source: US FDA. Drug development and drug interactions: table of substrates, inhibitors and inducers. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo. Accessed 23 July 2019.

Table 10 Other Drugs Needing Additional Considerations

Proton pump inhibitors	H2-receptor antagonists
Dexlansoprazole	cimetidine
Esomeprazole	famotidine
Lansoprazole	nizatidine
Omeprazole	
Rabeprazole	
Pantoprazole	

Source: US FDA. Established pharmacologic class text phrase. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/lawsactsandrules/ucm428333.pdf. Accessed 23 July 2019.

Appendix F Contraception Requirements

Contraception requirements for this study are as follows.

F 1 Female Subjects of Childbearing Potential

Please note, females of childbearing potential are defined as those who are post-menarche, not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all hormonal replacement therapy and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all hormonal replacement therapy, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago.

Female subjects of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study treatments), and who intend to be sexually active with a nonsterilized male partner, must use at least one highly effective method of contraception (see Table 11) consistent with local regulations regarding the use of contraception for subjects participating in clinical trials, from the time of signing the ICF throughout the total duration of the drug treatment and the drug washout period (2 days after the last dose of acalabrutinib).

Non-sterilized male partners of a female subject of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. The reliability of total sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. Female subjects should refrain from breastfeeding throughout this period.

F 2 Male Subjects with a Female Partner of Childbearing Potential

Non-sterilized male subjects (including males sterilized by a method other than bilateral orchidectomy, eg, vasectomy) who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening throughout

the total duration of the drug treatment and the drug washout period (2 days after the last dose of acalabrutinib). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period.

Vasectomized (ie, sterile) males are considered fertile and should still use a male condom plus spermicide as indicated above during the clinical trial.

Even if the female partner is pregnant, male subjects should still use a condom, as indicated above during the clinical trial, if there is a concern about damaging the developing fetus from drug in ejaculate.

Female partners (of childbearing potential) of male subjects must also use a highly effective method of contraception throughout this period (see Table 11).

F 3 Highly Effective Methods of Contraception

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly, are described in Table 11. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

Table 11 Highly Effective Methods of Contraception (<1% Failure Rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] This is also considered a hormonal method.

Appendix G Child-Pugh Score

Cirrhosis severity, as determined by the Child-Pugh score (Pugh 1973), will be recorded in the eCRF as specified in the SoAs.

The modified Child-Pugh classification of liver disease severity according to the degree of ascites by clinical exam, serum concentrations of bilirubin and albumin, prothrombin time, and degree of encephalopathy is shown in Table 12. The severity of cirrhosis is classified as follows:

- Child-Pugh class A (well-compensated disease): score of 5 to 6
- Child-Pugh class B (significant functional compromise): score of 7 to 9
- Child-Pugh class C (decompensated disease): score of 10 to 15

Table 12 Child-Pugh Classification of Cirrhosis Severity

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 µmol/L)	2 to 3 mg/dL (34.2 to 51.3 µmol/L)	>3 mg/dL (>51.3 µmol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (28 g/L)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

INR = international normalized ratio.

Appendix H Abbreviations

Abbreviation or special term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-HBc	Hepatitis B core antibody
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ARDS	Acute respiratory distress syndrome
AUC	Area under the concentration-time curve
bid	Twice daily
BSC	Best supportive care
Btk	Bruton's tyrosine kinase
BUN	Blood urea nitrogen
CBC	Complete blood count
CI	Confidence interval
C_{max}	Maximum observed concentration
COVID-19	Coronavirus disease 2019
CRF	Case report form (electronic/paper)
CRP	C-reactive protein
CSP	Clinical Study Protocol
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DGR	Dangerous Good Regulation
DILI	Drug-induced liver injury
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HL	Hy's law

Abbreviation or special term	Explanation
IATA	International Airline Transportation Association
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
iDMC	Internal Data Monitoring Committee
IEC	Independent Ethics Committee
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
LDH	Lactate dehydrogenase
MCP-1	Monocyte chemoattractant protein-1
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NG	Nasogastric
NYHA	New York Heart Association
$PaCO_2$	Partial pressure of carbon dioxide
PaO_2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PD-1	Programmed cell death 1
PHL	Potential Hy's law
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
PPI	Proton-pump inhibitor
PT	Prothrombin time
qd	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SoA	Schedule of Activities
SOFA	Sequential Organ Failure Assessment
SpO_2	Oxygen saturation
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation or special term	Explanation
TEAE	Treatment-emergent adverse event
TLR	Toll-like receptor
TNFα	Tumor necrosis factor alpha
ULN	Upper limit of normal

Appendix I Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents.

Amendment 3 (23Jun2020)

The overall rationale for the amendment was to address feedback from study sites that are managing local challenges during the COVID-19 pandemic.

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
1.1 Schedule of Activities (Table 1)	Added footnote l to indicate that screening can be performed within 1-3 days prior to dosing	Allow flexibility around timing of screening	Non-substantial
	Added footnote o to indicate that [redacted]	Clarification	Non-substantial
	Added footnote q to indicate that for all central laboratory assessments, sample collection windows of ± 1 day will be allowed for each of Days 3 and 7.	Clarification	Non-substantial
	Added a separate column for Day 1	Clarification	Non-substantial
	Specified in title that Table 1 only applies to Arm 1 (acalabrutinib + BSC)	Clarification	Non-substantial
1.1 Schedule of Activities (Table 2)	Added Table 2 for Arm 2 (BSC only) assessments	Clarification	Non-substantial
1.1 Schedule of Activities (Table 1); 6.1 Treatments Administered	Revised the statement "Acalabrutinib **must** be administered within 6 hours of randomization" to "Acalabrutinib **should** be administered within 6 hours of randomization"	Patient centricity	Non-substantial

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
1.1 Schedule of Activities (Table 1); 8.1.5 Physical Examinations and Chest Imaging, Electrocardiogram, and Echocardiogram	Added footnote r in Table 1 and text in Section 8.1.5 to indicate that per standard of care, chest imaging can be done by chest x-ray or CT scan with contrast, or any other appropriate means to confirm pneumonia prior to or upon hospitalization (within 7 days of randomization).	Clarification	Non-substantial
1.1 Schedule of Activities (Table 1); 8.1.6 Vital Signs	Added footnote s in Table 1 and text in Section 8.1.6 to indicate that during screening, vital signs should be collected as close as possible to the dosing on Day 1. If more than one value is obtained for vital signs during screening, the value closest to the first dose of study drug should be used.	Clarification	Non-substantial
1.1 Schedule of Activities (Table 1); 8.1.8 Laboratory Tests	Revised footnote d in Table 1 and text in Section 8.1.8 to indicate that hepatitis serology should include, at a minimum, HBsAg, anti-HBc, and HCV antibody. Also, stated that if additional hepatitis serology is collected per institutional guidelines, it should be recorded in the database.	Clarification	Non-substantial
1.1 Schedule of Activities (Table 1); 8.1.8 Laboratory Tests; 8.3 On-study Procedures	Revised Table 1 and Sections 8.1.8 and 8.3 so that collection of ferritin, D-dimer, fibrinogen, PT, aPTT, INR, and procalcitonin to occur every other day while in the hospital, and cardiac troponin I to be collected on Day 5 while in the hospital. Added footnote m to specify that these laboratory tests should be collected more frequently if clinically indicated. Removed BNP assessment. Also, stated in Section 8.3 that "Safety, CRP, PK, pharmacodynamic, and correlative laboratory tests are considered Tier 1 and should not be missed. The site must follow the SoA."	Patient centricity; reduce amount of blood collection	Substantial

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
1.1 Schedule of Activities (Table 1); 8.3 On-study Procedures	Revised footnote h in Table 1 and text in Section 8.3 to indicate that if a subject is discharged prior to Day 7 (+ 3 days) (instead of Day 10), he/she needs to visit the site for an assessment 2 to 4 days after discharge	Patient centricity	Non-substantial
	Revised Table 1 to indicate that PK will be collected 0.5 and 2 hours postdose on Day 3, and 1 and 4 hours postdose on Day 7. Added footnote p to clarify that these PK assessments can also be collected during a single visit on Day 3 or after.	Patient centricity and understanding the complexities of multiple blood draws of a subject in isolation due to COVID-19	Non-substantial
1.1 Schedule of Activities (Table 1); 8.4.1 Oxygen Treatments and Ventilator Use	Added footnote n to Table 1 and text to Section 8.4.1 to clarify that arterial gases should be collected from subjects if the sample is easily accessible and the procedure will not be painful to subjects. Also stated that if collection of arterial gases is not clinically indicated, the test should not be performed.	Patient centricity, since taking arterial gases is painful	Non-substantial
1.2 Synopsis; 2.1 Background and Study Rationale	Cited recent publications reporting activity of acalabrutinib and other Btk inhibitors in COVID-19	Clarification	Non-substantial
1.2 Synopsis; 3 Objectives and Endpoints	Reduced the number of PK parameters to be assessed for the PK endpoint	Given the reduced number of plasma samples for PK	Non-substantial
1.2 Synopsis; 6.1 Treatments administered	Revised Section 6.1 and restructured with sub-headers for clarity. Aligned Sections 1.2 and 6.1.	Clarification	Non-substantial
	Added text to Section 6.1.3.1 to indicate that subjects on concomitant PPIs must take acalabrutinib with 8 ounces (approximately 240 mL) of COCA-COLA at room temperature. Other cola beverages are not permitted.	Based on new data generated by Sponsor supporting use of acalabrutinib with concomitant PPIs	Substantial

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
4.5 End of Study Definition; 7.1 Discontinuation of Study Treatment; 8.6.2 Time Period and Frequency for Collecting AE and SAE Information; 9.6.1 Safety Analyses	Specified that safety follow-up will occur 38 (± 3 days) after randomization for those subjects randomized to the BSC arm	Clarification	Non-substantial
5.1 Inclusion Criteria	Inclusion Criterion 3: Revised to indicate that SARS-CoV-2 infection must be confirmed within 7 days (instead of 3 days) prior to randomization	Patient centricity and given lack of RT-PCR resources in local hospitals during the pandemic	Non-substantial
5.2 Exclusion Criteria	Exclusion Criterion 8: Changed "within 24 hours at screening" to "during the screening period"	To align with revised screening period of 1 to 3 days	Non-substantial
	Exclusion Criterion 16: Revised hepatitis serology criteria	Clarification	Non-substantial
	Exclusion Criterion 19: Removed PPI restriction	Based on new data generated by Sponsor supporting removal of exclusion	Substantial
	Exclusion Criterion 19: Revised immunomodulatory/ immunosuppressive treatment exclusion	Clarification	Non-substantial
	Exclusion Criterion 21: Removed steroid restriction	Align with global treatment practices	Substantial
6.1 Treatments Administered; 6.7 Dose Modification and Toxicity Management	Added text to allow participants to make up missed doses	Allow participants to receive the full dosing of acalabrutinib (total of 20 doses)	Substantial
6.3.1.2 Methods for Assigning Treatment Groups	Removed the sentence, "Subjects will be identified to the IRT per country regulations."	Not applicable as only year of birth and gender are collected in the IRT (no full date of birth or initials)	Non-substantial
6.5.2 Permitted Concomitant Therapy	Clarified BSC agents that will be permitted in this study	Align with global treatment practices	Substantial

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
6.5.3 Prohibited or Restricted Concomitant Therapy	Clarified that certain anticoagulants such as warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited for all subjects treated with acalabrutinib	Clarification	Non-substantial
	Removed PPIs as a prohibited concomitant medication	Based on new data generated by Sponsor supporting removal of PPIs as a prohibited concomitant medication	Substantial
	Removed steroid treatment language	Align with global treatment practices	Substantial
	Clarified that immunomodulatory drugs, intended as treatment for COVID-19 but not considered standard of care according to local institutional guidelines, are prohibited for all randomized subjects in the study through Day 28. Subjects who are taking immunomodulatory drugs for other medical conditions (eg, tocilizumab for rheumatoid arthritis) may continue with treatment upon discussion with the Medical Monitor.	Clarification	Non-substantial
6.5.4 Acalabrutinib Drug-drug Interaction Guidance in the Presence of Life-threatening COVID-19 Infection; 6.5.4.2 Active Substances That May Decrease Acalabrutinib Plasma Concentrations	Added PPIs to Table 3 and specified that concomitant use of PPIs should be avoided. However, if PPI concomitant use cannot be avoided, dose modification of acalabrutinib is not necessary, but acalabrutinib must be administered with 240 mL of COCA-COLA to improve acalabrutinib absorption.	Based on new data generated by Sponsor supporting removal of PPIs as a prohibited concomitant medication	Substantial
6.5.4.2 Active Substances That May Decrease Acalabrutinib Plasma Concentrations; Appendix E Examples of Coadministered	Removed ranitidine	Removed from market	Non-substantial

Section number and name	Description of change	Brief rationale	Substantial/ non-substantial
Drugs That Need Additional Consideration (Table 8)			
6.6 Risks Associated with Acalabrutinib	Clarified the risks associated with acalabrutinib and added a table showing frequency and time to onset of risks associated with acalabrutinib	Clarification	Non-substantial
8.1.8 Laboratory Tests; 8.3 On-study Procedures	Removed wording "(at select centers only)" and "(at ALL centers)" for the exploratory samples. Made additional changes to these sections for clarity and to align with the SoA.	Clarification; all centers must collect the samples	Non-substantial
8.6.4 Adverse Event Data Collection; B6 Intensity Rating Scale	Provided full URL for CTCAE V5.0	Correction	Non-substantial
10 References	Updated references using EndNote	Consistency with protocol template	Non-substantial
A7 Data Quality Assurance	Changed "source data verification" to "source data review"	Correction	Non-substantial

AE = adverse event; anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; BSC = best supportive care; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CTCAE = Common Terminology Criteria for Adverse Events; FDA = Food and Drug Administration; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; ICU = intensive care unit; INR = international normalized ratio; IRT = interactive response technology; PBMC = peripheral blood mononuclear cell; PK = pharmacokinetics; PPI = proton-pump inhibitor; PT = prothrombin; RT-PCR = reverse transcriptase-polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SoA = Schedule of Activities; WHO = World Health Organization.

Amendment 2 (13May2020)

Changes were implemented in the protocol amendment to address the FDA comments.

Section # and Name	Description of Change	Brief Rationale
5.2 Exclusion Criteria	Revised Exclusion Criterion 23 to indicate that subjects who require or are receiving anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days prior to randomization are excluded. Also, added that other anticoagulants are permitted.	Revised based on FDA feedback

Section # and Name	Description of Change	Brief Rationale
	Revised Exclusion Criterion 24 to indicate that subjects on combined antiplatelet and therapeutic anticoagulant therapy (eg, aspirin and therapeutic doses of low molecular weight heparin) at study entry will be excluded	
6.5.3 Prohibited or Restricted Concomitant Therapy	Revised this section to reflect prohibition of anticoagulants for all subjects in both treatment arms. Also, clarified that subjects who require prophylaxis or therapeutic anticoagulation for thrombosis (deep vein thrombosis or pulmonary embolism) will be allowed to receive therapeutic anticoagulation with a non-vitamin K inhibitor class of anticoagulants. Should subjects require either a vitamin K antagonist or combined administration of antiplatelet and therapeutic anticoagulation while on study, acalabrutinib treatment must be discontinued.	Revised based on FDA feedback

Amendment 1 (08May2020)

Changes were implemented in the protocol amendment to address the FDA comments.

Section # and Name	Description of Change	Brief Rationale
1.1 Schedule of Activities	Added serum ferritin and CRP assessments at “Day 10 or discharge”	To align with endpoints
1.1 Schedule of Activities; 1.2 Synopsis; 3 Objectives and Endpoints; 8.8.1 Improvements on the 9-Point Ordinal Scale	Added secondary efficacy endpoint of time to clinical improvement of at least 2 points (from randomization) on a 9-point ordinal scale through Day 28	To collect additional data
1.2 Synopsis; 3 Objectives and Endpoints; 9.2 Sample Size Determination; 9.6.2 Efficacy Analyses	Revised the primary efficacy endpoint of respiratory failure from Day 14 to Day 28, and revised the secondary efficacy endpoint of respiratory failure from Day 28 to Day 14	Revised based on FDA feedback
1.2 Synopsis; 9.6.2 Efficacy Analyses; 10 References	Changed method for calculating confidence intervals from Blyth-Still-Casella to Wald method with continuity correction	Revised based on FDA feedback
4.4 Internal DMC	Specified that enrollment also be paused and safety reviewed upon the	Added based on FDA feedback

Section # and Name	Description of Change	Brief Rationale
	occurrence of any Grade 4 hemorrhage due to acalabrutinib (per Investigator)	
5.2 Exclusion Criteria	Exclusion Criterion 17: Added a new criterion to exclude subjects with known active HIV with detectable viral load or CD4 count of <500 cells/mm^3	Added based on FDA feedback
	Exclusion Criterion 18: Revised to exclude subjects on CYP3A inhibitor within 7 days (instead of 14 days) and inducer within 14 days (instead of 7 days) before first dose of study drug	Corrected error
	Exclusion Criterion 24: Added a new criterion to exclude subjects on combined antiplatelet and anticoagulant therapy	Added based on FDA feedback

Section # and Name	Description of Change	Brief Rationale
6.5.3 Prohibited or Restricted Concomitant Therapy	Moved paragraphs for strong CYP3A inhibitors/inducers and proton-pump inhibitors from Section 6.5.3.1 (Medications Prohibited for Subjects Treated with Acalabrutinib) to Section 6.5.3.2 (Medications Prohibited for All Randomized Subject)	Revised based FDA feedback that SoC be consistent across the treatment arms
6.5.3.2 Medications Prohibited for All Randomized Subjects	Clarified in Section 6.5.3.2 that immunomodulatory drugs are prohibited for all subjects in both treatment arms through Day 28 and strong CYP3A inhibitors or inducers, PPIs, and steroids are prohibited for all subjects in both treatment arms through Day 10	Revised based on FDA feedback
	In the steroids paragraph, specified that if corticosteroids exceeding 7.5 mg/day or active inhaled corticosteroids are required for clinical care, acalabrutinib treatment must be discontinued	Revised based on FDA feedback
6.6 Risks Associated with Acalabrutinib	Revised to align with updated Section 6.7	Consistency
6.7 Dose Modification and Toxicity Management	In the table, revised event criteria and dose modification/discontinuation guidelines.	Revised based on FDA feedback and for clarity
8.1.8 Laboratory Tests; 8.3 On-study Procedures	Removed reference to “(at select centers only)” and “(at all centers)” from central laboratory tests	Revised so that all these tests are required at all sites
9.6.2 Efficacy Analyses	Included baseline respiratory failure (with vs without) in the subgroup analysis	Added based on FDA feedback
	Revised to indicate number of days in ICU from randomization to 90 days (instead of 28 days) after randomization	Corrected error
F1 Female Subjects of Childbearing Potential	Removed prednisone, vincristine, doxorubicin, rituximab, and cyclophosphamide from the drug washout period	Not relevant to this study