| **Clinical Study Protocol** | |
|---|---|
| Study Intervention | Acalabrutinib |
| Study Code | D822FC00005 |
| Version | 3.0 |
| Date | 04 September 2020 |

# An Open-label, Multiple-dose Study to Evaluate the Pharmacokinetics, and Safety and Tolerability of Acalabrutinib Suspension Delivered via Nasogastric Tube, Coadministered With a Proton-pump Inhibitor, in Participants Hospitalized With COVID-19

| | |
|---|---|
| **Sponsor Name:** | **Acerta Pharma B.V. a member of AstraZeneca group of companies** |
| Legal Registered Address: | Kloosterstraat 9, 5349 AB Oss, The Netherlands |
| **Regulatory Agency Identifier Number(s):** | **IND number 149513** |

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

**Protocol Number: D822FC00005**

Amendment Number: 2

Study Intervention: Acalabrutinib

Study Phase: Ib

**Short Title: Study of Acalabrutinib Suspension Delivered via Nasogastric Tube With a Proton-pump Inhibitor in Participants Hospitalized with COVID-19**

**Study Physician Name and Contact Information will be provided separately**

# PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

| DOCUMENT HISTORY | |
|---|---|
| **Document** | **Date** |
| Amendment 2 (Version 3.0) | 04 September 2020 |
| Amendment 1 (Version 2.0) | 25 June 2020 |
| Original Protocol (Version 1.0) | 20 May 2020 |

## Amendment 2 (04 September 2020)

The overall rationale for the amendment was to provide clarification regarding laboratory tests for HBV and HCV during screening.

COVID-19 pneumonia requiring hospitalization is an acute disease that requires a rapid screening evaluation to ensure prompt initiation of study treatment. The Sponsor is aware that at some institutions, the turnaround times for local hepatitis virus tests are prolonged (days rather than hours), leading to substantial delays in treatment initiation. Thus, the Sponsor has reviewed the risks and benefits of initiating treatment before these test results are available. In the acute setting of severe COVID-19 disease, the potential benefits of initiating treatment in a timely manner outweigh potential risks, especially considering that 1) HBV/HCV events are expected to be infrequent based on Sponsor data from oncology studies, 2) the short duration of therapy is anticipated to further reduce risk, and 3) HBV/HCV events can be monitored and, if necessary, managed with antiviral therapies.

No reports of HCV reactivation have been received in the acalabrutinib clinical program to date, and there are no published reports of HCV reactivation following treatment with BTK inhibitors that are available to the Sponsor. Hepatitis B virus reactivations in the setting of acalabrutinib treatment are infrequently reported. Among 4053 participants across all clinical studies investigating acalabrutinib to date, 9 participants had reactivations (1 fatal, 8 non-serious) after a median duration of therapy of 248 days (range 43 to 582 days). Hepatitis B virus reactivations have rarely been reported with other BTK inhibitors, such as ibrutinib, where a larger number of patients have been treated to date in clinical studies and real-world settings; ibrutinib has been approved for use since 2014 (Hammond et al 2018). Furthermore, when HBV reactivations occur, they are typically observed following months to years of treatment and are easily managed with antiviral therapy with good outcomes; in many cases, the BTK inhibitor is continued.

| Section Number and Name | Description of Change | Brief Rationale | Substantial/ Non-substantial |
|---|---|---|---|
| 1.3 Schedule of Activities (Table 1) | Removed Day 1 column from Table 1. Made changes to "Daily until hospital discharge" column to adjust for this change. | Clarification | Non-substantial |
| 1.3 Schedule of Activities (Table 1),<br>5.1 Inclusion Criteria | Revised SARS-CoV-2 PCR virus testing Inclusion Criterion 3 in Section 5.1 and aligned the SoA (Table 1) accordingly. | To allow flexibility | Non-substantial |
| 1.3 Schedule of Activities (Table 1),<br>8.2.5.1 Local Laboratory Tests,<br>8.2.5.1.1 Hepatitis Serology Guidelines | Added text to footnote d of Table 1 to indicate that treatment with acalabrutinib can start after blood samples for all HBV and HCV serology tests and for both HBV and HCV PCR tests have been collected, even if the results are not available at the time of the first dose. In addition, added hepatitis serology guidelines that should be followed (Section 8.2.5.1.1). | See rationale provided above this table | Substantial |
| 1.3 Schedule of Activities (Table 1),<br>8.2.5.2 Central Laboratory Tests | In Table 1, specified that a nasopharyngeal swab will be collected for SARS-CoV-2 viral load/viral shedding. In Section 8.2.5.2, changed [redacted] | To correct typographical error | Non-substantial |
| 2.3.1.3 Hepatitis B and C Reactivation | Added information about HCV and HBV reactivation with acalabrutinib | To support hepatitis serology guidelines | Substantial |
| 5.1 Inclusion Criteria | Revised Inclusion Criterion 5 to indicate that feeding tube must remain in place for a minimum of 3 days <u>after study enrollment</u> | Clarification | Non-substantial |
| 5.2 Exclusion Criteria | Revised Exclusion Criterion 9 to align with the hepatitis serology guidelines | Clarification and consistency | Substantial |
| | Added an exception to Exclusion Criterion 12 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 | Substantial |

| Section Number and Name | Description of Change | Brief Rationale | Substantial/ Non-substantial |
|---|---|---|---|
| | | associated with COVID-19 (Cai et al 2020, Guan et al 2020a) | |
| | Revised Exclusion Criterion 19 to clarify that aspirin and therapeutic/ high doses of low-molecular-weight heparin are not allowed, but that aspirin and prophylactic/low doses of low-molecular-weight heparin are allowed | Clarification | Non-substantial |
| 7.1 Discontinuation of Study Intervention, 7.2 Participant Withdrawal from the Study | Added that participants with positive HBsAg, HBV-DNA, or HCV-RNA test result after first dose administration will be discontinued from study intervention (Section 7.1) and withdrawn from the study (Section 7.2) | To align with hepatitis serology guidelines | Substantial |
| Clinical Study Protocol Signature Page | Removed | Utilizing different signoff process | Non-substantial |

ALT = alanine aminotransferase; AST = aspartate aminotransferase; COVID-19 = coronavirus disease 2019; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; PCR = polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SoA = Schedule of Activities; ULN = upper limit of normal.

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# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

### Protocol Title

An Open-label, Multiple-dose Study to Evaluate the Pharmacokinetics, and Safety and Tolerability of Acalabrutinib Suspension Delivered via Nasogastric Tube, Coadministered With a Proton-pump Inhibitor, in Participants Hospitalized With COVID-19

### Short Title

Study of Acalabrutinib Suspension Delivered via Nasogastric Tube With a Proton-pump Inhibitor in Hospitalized COVID-19 Participants

### Rationale

This study is being conducted to support the ongoing clinical development of acalabrutinib (CALQUENCE®)[1] in hospitalized COVID-19 patients. Because many COVID-19 patients may be unable to swallow capsules due to respiratory failure (eg, they may require endotracheal intubation for ventilator support and NG tube placement), it is important to have a clinically acceptable method to administer acalabrutinib (capsules) via NG tube. Furthermore, due to the acute illness of COVID-19 patients, many hospitalized patients are placed on high doses of PPIs or continuous H2-receptor antagonists to prevent stress ulcers. This study is designed to determine the PK, and safety and tolerability of acalabrutinib suspension, when coadministered with a PPI, in participants with confirmed SARS-CoV-2 infection requiring hospitalization due to respiratory failure (as defined in the table below) attributable to COVID-19 pneumonia and who have an NG tube in place.

### Objectives and Endpoints

| Objective | Endpoint/Variable |
|---|---|
| **Primary Objectives** | **Primary Endpoints/Variables** |
| • To characterize the PK of acalabrutinib and its active metabolite (ACP-5862) following administration of acalabrutinib suspension, when coadministered with a PPI, in participants with COVID-19 | • Primary PK parameters for acalabrutinib and ACP-5862 include $AUC_{12h}$, $AUC_{last}$, and $C_{max}$. Additional PK parameters are described in the protocol. |
| • To assess the safety and tolerability of acalabrutinib suspension in participants with COVID-19 when administered in the presence of PPIs and BSC | • Type, frequency, severity, and relationship to study intervention of any treatment-emergent AEs or abnormalities of laboratory tests, SAEs, or AEs leading to discontinuation of study intervention |

[1] CALQUENCE® is a trademark of the AstraZeneca group of companies.

| Objective | Endpoint/Variable |
|---|---|
| **Secondary Objective** | **Secondary Endpoints/Variables** |
| • To evaluate the preliminary efficacy of adding acalabrutinib suspension to BSC for treatment of participants with COVID-19 | • Proportion of participants alive and free of respiratory failure at Days 14 and 28<br>For the purpose of this study, **respiratory failure** is defined based on resource utilization of any of the following modalities:<br>◦ Endotracheal intubation and mechanical ventilation<br>◦ 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)<br>◦ Noninvasive positive pressure ventilation or continuous positive airway pressure<br>◦ Extracorporeal membrane oxygenation<br>• Percent change from baseline in CRP (time frame: baseline, Days 3, 5, 7, 14, 28)<br>• Time to improvement defined as time to clinical improvement of ≥ 2 points (from first dose date) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 1 or 2 on the ordinal scale), whichever comes first, by Day 28 |
| **Exploratory Objectives** | **Exploratory Endpoints/Variables** |
| [redacted] | [redacted] |

## Overall Design

This is an open-label, multi-dose study to evaluate the PK, and safety and tolerability of acalabrutinib suspension, when coadministered with a PPI, in participants with confirmed SARS-CoV-2 infection requiring hospitalization due to respiratory failure (as defined in the table above) attributable to COVID-19 pneumonia and who have an NG tube in place. Approximately 20 participants will be included to ensure at least 16 participants are evaluable. Participants are considered evaluable if they have an evaluable PK profile, ie: (1) complete PK Visit 2 assessments; (2) receive active treatment; and (3) do not have unavailable or

incomplete data that may influence the PK analysis.

In addition to receiving BSC, participants will receive acalabrutinib suspension (ie, acalabrutinib 100 mg suspension in COCA-COLA® delivered via NG tube) bid for 14 days (a maximum of 28 doses). Best supportive care is per discretion of the Investigator and institutional guidelines. Standard NG tubes supplied by the hospital will be used. Nasogastric tube placement in the stomach will be confirmed by chest x-ray.

To assess the effect of PPIs, all participants must be receiving treatment with a PPI at the start of the study. Treatment with a PPI can begin at any time prior to enrollment, provided participants have received PPI treatment for at least 24 hours prior to the first dose of acalabrutinib suspension. Any PPI is permitted, provided it meets the minimum equivalent daily dose of 20 mg rabeprazole. Participants must be on this dosage of PPI at the start of the study. They may be weaned off PPIs during the study if medically appropriate.

Blood samples for plasma PK assessment of acalabrutinib and its metabolite (ACP-5862) will be collected at pre-dose and 0.5, 1, 2, 4, 6, and 12 hours following treatment with acalabrutinib suspension as described in the table below. Note that the sample at 12 hours must be collected prior to the subsequent acalabrutinib dose (for trough PK sample).

| PK Visit | Description | Rationale |
|---|---|---|
| PK Visit 1 | First PK sampling will occur on Day 1 (ie, first dosing day for acalabrutinib suspension) | Allows an early assessment of acalabrutinib and ACP-5862 PK in participants receiving acalabrutinib suspension via NG tube |
| PK Visit 2 | Second PK sampling will occur a minimum of 4 days after the start of PPI treatment, irrespective of the timing of NG tube placement and any time after 2 doses of acalabrutinib suspension have been given (ie, PK sampling can begin prior to the third dose, or anytime thereafter)<br>PK Visit 2 can occur as early as Day 2 (if participant has been on a PPI for ≥ 4 consecutive days prior to receiving the third acalabrutinib dose), and up to Day 4 (if participant initiated PPI treatment 24 hours prior to receiving the first dose of acalabrutinib on Day 1) | PPI exposure must occur for 4 consecutive days to reach the maximum PPI on-target effect<br>PK sample can commence at any point after the second dose of acalabrutinib suspension to ensure steady-state levels of the active metabolite and maximal [redacted] has been reached |
| PK Visit 3 | Third PK sampling will occur 3 days after PK Visit 2, OR on the last day the participant receives acalabrutinib treatment, whichever comes first | Allows an additional opportunity to assess the steady-state PK of acalabrutinib and ACP-5862 PK following delivery of acalabrutinib suspension via NG tube |

Safety assessments, including AE reporting, will be performed through 28 (± 3) days after the last dose of the acalabrutinib suspension.

**Disclosure Statement**

This is a single-arm, treatment study that is not blinded.

**Number of Participants**

Approximately 20 participants will be enrolled to have at least 16 evaluable participants.

**Note**: "Enrolled" means a participant's, or his/her legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

**Intervention Groups and Duration**

Treatment with acalabrutinib suspension (ie, acalabrutinib 100 mg suspension in COCA-COLA delivered via NG tube) will be initiated on Day 1. All participants must have received PPI treatment for at least 24 hours prior to the first dose of acalabrutinib suspension. All participants will receive acalabrutinib suspension bid, approximately 12 hours apart, for 14 days (a maximum of 28 doses). The acalabrutinib suspension must be prepared according to the Handling Instructions.

**Safety Review Committee**

An SRC will be established to conduct scheduled reviews of safety and other relevant data, enable early identification of safety signals in the study, and minimize the risk to participants during the study, in accordance with the SRC charter (see Section 9.6 for details).

**Statistical Methods**

Pharmacokinetics

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Plasma acalabrutinib and ACP-5862 concentrations and PK parameters listed below will be summarized using appropriate descriptive statistics.

- Primary PK parameters: $AUC_{12h}$, $AUC_{last}$, and $C_{max}$.
- Secondary PK parameters: $t_{1/2}$, $t_{max}$, and $\lambda_z$ (acalabrutinib and ACP-5862); CL/F and Vz/F (acalabrutinib); and $C_{max}$, $AUC_{last}$, and $AUC_{12h}$ (metabolite to parent ratio).

Safety

Safety assessments will consist of monitoring and recording of AEs, SAEs, and AEs leading to discontinuation of study intervention; measurement of protocol-specified vital signs, ECG, laboratory variables and other protocol-specified safety tests or measurements. All safety

analyses will be performed on the Safety Analysis Set. Verbatim descriptions of AEs will be mapped according to the latest version of MedDRA and graded according to NCI CTCAE v5.0 or higher. Treatment-emergent AEs will be summarized, unless otherwise specified. Treatment-emergent AEs are defined as AEs starting or ongoing AEs worsening after the first dose of study intervention and AEs with start date up to the last dose of study intervention plus 28 (± 3) days.

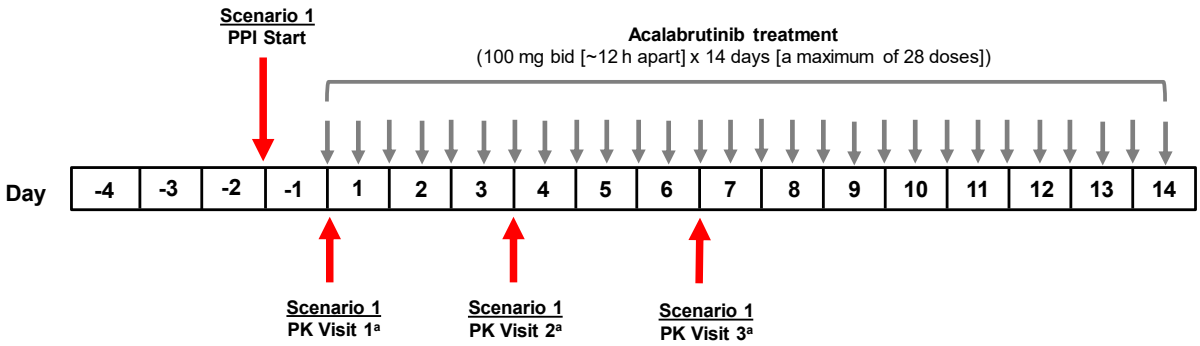
Efficacy

All efficacy analyses will be performed on the Efficacy Evaluable Set. For the proportion of participants alive and free of respiratory failure at Days 14 and 28, point estimates and their 90% confidence intervals will be calculated. Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented for the percent change from baseline in CRP at the specified time points. Time to improvement defined as time to clinical improvement of at least 2 points (from first dose date) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 1 or 2 on the ordinal scale), whichever comes first, by Day 28 (this will also define the “responder” for the response rate analyses), will be analyzed using the Kaplan-Meier method.

## 1.2 Schema

The study design is illustrated in Figure 1.

**Figure 1 Study Design**




| Scenarios of PK visits relative to PPI start | PPI Dosing Starts (≥24 h prior to first acalabrutinib dose) | PK Visit 1[a] (coincides with Day 1 of study) | PK Visit 2[a] (≥4 d after start of PPI **and** any time after 2 doses of acalabrutinib) | PK Visit 3[a] (3 days after PK Visit 2 **or** on last day of acalabrutinib treatment) |
|---|---|---|---|---|
| **Scenario 1** (shown in figure) | Day -1 | Prior to first acalabrutinib dose | Day 3 (prior to fifth dose) | Day 6 (prior to 11th dose) |
| **Scenario 2** | Day -2 | Prior to first acalabrutinib dose | Day 2 (prior to third dose) | Day 5 (prior to ninth dose) |
| **Scenario 3** | Day -3 | Prior to first acalabrutinib dose | Day 2 (prior to third dose) | Day 5 (prior to ninth dose) |
| **Scenario 4** | Day -4 or earlier | Prior to first acalabrutinib dose | Day 2 (prior to third dose) | Day 5 (prior to ninth dose) |

[a] Blood samples for plasma PK assessment of acalabrutinib and its metabolite (ACP-5862) will be collected at pre-dose and 0.5, 1, 2, 4, 6, and 12 hours following treatment with acalabrutinib suspension. Note that the sample at 12 hours must be collected prior to the subsequent acalabrutinib dose (for trough PK sample).

Note: PK Visit 2 can occur as early as Day 2 (if participant has been on a PPI for ≥ 4 consecutive days prior to receiving the third acalabrutinib dose), and up to Day 4 (if participant initiated PPI treatment 24 hours prior to receiving the first dose of acalabrutinib on Day 1). See Table 4 for more information.

bid = twice daily; PK = pharmacokinetic(s); PPI = proton-pump inhibitor.

## 1.3 Schedule of Activities

The SoA for the study is presented in Table 1.

## Table 1 Schedule of Activities

| Assessments | Screening (Day -3 to Day -1 [n]) | Daily until hospital discharge | Day 14 or discharge [f] | Day 20 (±3 days) after first dose | Day 28 (±3 days) after first dose | Safety follow-up 28 (±3) days after last dose of acalabrutinib [g,h] | Details in CSP section |
|---|---|---|---|---|---|---|---|
| Informed consent | X | | | | | | A 3 |
| Demography | X | | | | | | 5.4 |
| Determine eligibility | X | | | | | | 5.1, 5.2 |
| Medical history and COVID-19 epidemiology | X | | | | | | 8.2.1 |
| Physical examination (symptom driven, including lung auscultation), height, weight | X | | | | | | 8.2.2 |
| Chest imaging | X [r] | As clinically indicated | | | | | 8.2.2 |
| Electrocardiogram | X [n] | As clinically indicated | X | | | | 8.2.4 |
| Echocardiogram | As clinically indicated | As clinically indicated | | | | | 8.2.4 |
| Pulmonary assessments (oxygen usage, ventilator parameters) | X | X | X | | X | | 8.1.1 |
| Clinical assessments (mSOFA) | X | Day 3, 5, 7, and 10 | X | | | | 8.1.2.1 |
| 9-point category ordinal scale | X | X | X | | X | | 8.1.1.2 |
| Vital signs (blood pressure, respiratory rate, pulse oximetry, heart rate, and body temperature) | X [s] | X | | X | X | | 8.2.3 |
| Arterial blood gases [p] | X | X | X | | X | | 8.1.1.1, 8.2.3 |
| Local laboratory assessments: | | | | | | | |
| Urine or serum pregnancy test (for WOCBP only) | X | | | X | | X | 8.2.5.1 |
| Hematology [b] | X | X | X | X | X | X | 8.2.5.1 |
| Serum or plasma chemistry [c] | X | X | X | X | X | X | 8.2.5.1 |
| Hepatitis B and C testing [d] | X | As clinically indicated | | | | As clinically indicated | 8.2.5.1, 8.2.5.1.1 |

## Table 1 Schedule of Activities

| Assessments | Screening (Day -3 to Day -1 [n]) | Daily until hospital discharge | Day 14 or discharge [f] | Day 20 (±3 days) after first dose | Day 28 (±3 days) after first dose | Safety follow-up 28 (±3) days after last dose of acalabrutinib [g,h] | Details in CSP section |
|---|---|---|---|---|---|---|---|
| Fibrinogen [o] | X | qod | | | | | 8.2.5.1 |
| PT, aPTT, and INR [o] | X | qod | | | | | 8.2.5.1 |
| D-dimer [o] | X | qod | X | | X | | 8.2.5.1 |
| CRP | X | X | X | | X | | 8.2.5.1 |
| Cardiac troponin I [o] | X | qod | | | | | 8.2.5.1 |
| SARS-CoV-2 RT-PCR virus testing for eligibility [e] | X | | | | | | 8.2.5.1 |
| Central laboratory assessments: [q] | | | | | | | |
| [redacted] | | | | | | | |
| Acalabrutinib PK [i,k] | | Pre-dose and 0.5, 1, 2, 4, 6, and 12 hours[j] post-dose (on **PK Visit 1, PK Visit 2, and PK Visit 3[i]**) | | | | | 4.1, 8.5.1 |
| [redacted] | | | | | | | |
| Acalabrutinib administration | | bid (q12h) × 14 days (maximum) | | | | | 6.1.2 |
| Adverse events | X | X | X | X | X | X[h] | 8.3 |
| Concomitant medications | X | X | X | X | X | X[h] | NA |
| Survival status | | | X | X | X | X[h] | NA |

## Table 1 Schedule of Activities

| Assessments | Screening (Day -3 to Day -1 [n]) | Daily until hospital discharge | Day 14 or discharge [f] | Day 20 (±3 days) after first dose | Day 28 (±3 days) after first dose | Safety follow-up 28 (±3) days after last dose of acalabrutinib [g,h] | Details in CSP section |
|---|---|---|---|---|---|---|---|

[a] Pre-dose.

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

[c] Serum or plasma chemistry: albumin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, 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. Participants can be started on acalabrutinib **after** blood samples for all HBV and HCV serology tests and for both HBV and HCV PCR tests have been collected, even if the results are not yet available at the time of first dose administration. Follow the hepatitis serology guidelines described in Section 8.2.5.1.1.

[e] Hospitalized with coronavirus (SARS-CoV-2) infection, confirmed by PCR test or other commercial or public health assay in any specimen, as documented by either of the following: 1) PCR positive in sample collected < 72 hours prior to first dose; OR 2) PCR positive in sample collected ≥ 72 hours prior to first dose (but no more than 14 days prior to first dose), documented inability to obtain a repeat sample (eg, due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc), AND progressive disease suggestive of ongoing SARS-CoV-2 infection.

[f] If a participant is discharged prior to Day 14, he/she needs to visit the site for an assessment 2 to 4 days after discharge. Assessments should match those for Day 14.

[g] All participants should have follow-up assessments for safety 28 (± 3) days after the last dose of acalabrutinib.

[h] Telemedicine is recommended for capturing adverse events, concomitant medications, and survival status. 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.

[i] **PK Visit 1**: PK sampling will occur on Day 1 (ie, first dosing day for acalabrutinib suspension).

**PK Visit 2**: PK sampling can occur as early as Day 2 (if participant has been on a PPI for ≥ 4 consecutive days prior to receiving the third acalabrutinib dose), and up to Day 4 (if participant initiated PPI treatment 24 hours prior to receiving the first dose of acalabrutinib on Day 1). See Section 4.1 for additional details.

**PK Visit 3:** PK sampling will occur 3 days after PK Visit 2, OR on the last day the participant receives acalabrutinib treatment, whichever comes first.

[j] PK sampling will occur at pre-dose and 0.5 (± 5 min), 1 (± 5 min), 2 (± 15 min), 4 (± 15 min), 6 (± 15 min), and 12 (± 60 min) hours post-dose, [redacted] sampling will occur at pre-dose and 4 (± 15 min) and 12 (± 60 min) hours post-dose. The 12-hour post-dose PK [redacted] samples will be collected immediately prior to administration of the subsequent acalabrutinib dose.

[k] The timing of PK [redacted] sample collections should be aligned as closely as possible and will be prioritized over other blood samples being collected simultaneously, except in the case of an adverse event for which relevant assessment/blood sample collection will be prioritized.

[l] [redacted]

[m] [redacted]

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

[o] Fibrinogen, PT, aPTT, INR, D-dimer, and cardiac troponin I should be performed more frequently if clinically indicated.

## Table 1 Schedule of Activities

| Assessments | Screening (Day -3 to Day -1 [n]) | Daily until hospital discharge | Day 14 or discharge [f] | Day 20 (±3 days) after first dose | Day 28 (±3 days) after first dose | Safety follow-up 28 (±3) days after last dose of acalabrutinib [g,h] | Details in CSP section |
|---|---|---|---|---|---|---|---|

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

[q] For all central laboratory assessments, sample collection windows of ± 1 day will be allowed for each of Days 4, 7, and 10.

[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 enrollment).

[s] 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 intervention should be used.

anti-HBc = antibody to hepatitis B core antigen; aPTT = activated partial thromboplastin time, bid = twice daily; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CSP = Clinical Study Protocol; CT = computed tomography; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; ICU = intensive care unit; INR = international normalized ratio; mSOFA = modified Sequential Organ Failure Assessment; NA = not applicable; [redacted] PCR = polymerase chain reaction; [redacted] PK = pharmacokinetics; PPI = proton-pump inhibitor; PT = prothrombin time; qod = every other day; q12h = every 12 hours; 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.

# 2 INTRODUCTION

Acalabrutinib is a BTK inhibitor that is being developed for the treatment of hospitalized COVID-19 patients.

## 2.1 Study Rationale

This study is being conducted to support the ongoing clinical development of acalabrutinib in hospitalized COVID-19 patients. Because many COVID-19 patients may be unable to swallow capsules due to respiratory failure (eg, they may require endotracheal intubation for ventilator support and NG tube placement), it is important to have a clinically acceptable method to administer acalabrutinib (capsules) via NG tube. Furthermore, due to the acute illness of COVID-19 patients, many hospitalized patients are placed on high doses of PPIs or continuous H2-receptor antagonists to prevent stress ulcers. This study is designed to determine the PK, and safety and tolerability of acalabrutinib suspension, when coadministered with a PPI, in participants with confirmed SARS-CoV-2 infection requiring hospitalization due to respiratory failure (as defined in Section 8.1.1.1) attributable to COVID-19 pneumonia and who have an NG tube in place.

## 2.2 Background

### 2.2.1 Coronavirus Disease 2019

Coronavirus disease 2019 is a new pandemic disease caused by SARS-CoV-2, a novel coronavirus that originated from Wuhan, China. Most COVID-19 cases (~80%) are mild respiratory illnesses. However, moderate and severe COVID-19 cases require hospitalization and can progress quickly to severe acute lung injury and acute respiratory distress syndrome (Huang et al 2020, Zhou et al 2020), which can lead to death due to respiratory and cardiac failure. The death rate from COVID-19 across different populations range from 2.4% in China (updated data) to 7.2% in Italy (Livingston and Bucher 2020, Wu and McGoogan 2020), with the highest rate reported among older patients and those who are immunocompromised or have other comorbidities or lymphocytopenia (Guan et al 2020b, Livingston and Bucher 2020, Onder et al 2020, Wang et al 2020). The mortality rate in critically ill patients with COVID-19 (ie, those requiring mechanical ventilation) is nearly 50% (Wu and McGoogan 2020).

In patients with severe COVID-19, SARS-CoV-2-induced cytokine storm or “hyperimmune response” is hypothesized to cause immunopathologic damage to the lungs by modulating 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 IL-1β, IL-6, IL-8, IL-10, TNFα, and MCP-1 (Chen et al 2020, Herold et al 2015, Yoshikawa et al 2009). Other risk factors for severe COVID-19 illness include the presence of neutrophilia, organ dysfunction (elevated lactate dehydrogenase), coagulation abnormalities, thrombocytopenia, and lymphocytopenia, suggesting findings

observed in both hemophagocytic syndrome and immune deficiency (Guan et al 2020b, Lippi et al 2020, Wu et al 2020).

### 2.2.2 Bruton Tyrosine Kinase

Bruton tyrosine kinase 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 engagement of the B-cell receptor has been well established (Buggy and Elias 2012). Bruton tyrosine kinase is also involved in Fc gamma receptor signaling in myeloid cells, mast cell degranulation, osteoclast differentiation, and TLR signaling in neutrophils. Bruton tyrosine kinase inhibition is associated with decreased proinflammatory cytokines in patients with hematologic malignancies and reduced severity of anti-CD20 antibody-induced infusion reactions (Byrd et al 2016, Lujan et al 2020).

Substantial clinical data exist implicating BTK activation in acute pulmonary injury mediated by macrophages and neutrophils and subsequent acute respiratory distress syndrome. Bruton tyrosine kinase activation has shown to be an essential component of lung injury induced by infectious pathogens, sepsis, and hemorrhagic lung injury that is mediated by excessive inflammatory macrophages and neutrophils (Krupa et al 2013, Krupa et al 2014, Zhou et al 2014). Genetic knock down of BTK impaired this lung injury (Krupa et al 2014, Zhou et al 2014). This has been confirmed in subsequent pharmacologic studies with the BTK inhibitor, ibrutinib. In the setting of murine pneumococcal pneumonia, ibrutinib has also been shown to negatively affect both monocyte and neutrophil influx into the lung and also alveolar macrophage activation, neutrophil influx, cytokine release and plasma leakage. Antibiotic-mediated killing of bacteria was not impaired (de Porto et al 2019). A similar study, with seasonal influenza A virus demonstrated that intranasal administration of ibrutinib starting 72 hours after lethal infection with influenza A diminished weight loss and led to improved overall survival (Hoerauf et al 1994). Moreover, ibrutinib treatment had a dramatic effect on morphological changes to the lungs, including decreased alveolar hemorrhage, interstitial thickening, and the presence of alveolar exudate concomitant with diminished inflammatory mediators (TNFα, IL-1β, IL-6, KC, and MCP-1). This murine study suggests BTK inhibition may represent a new immunomodulating treatment for virus-induced lung damage driven by excess inflammation (Florence et al 2018). Ibrutinib and other BTK inhibitors, such as acalabrutinib, may also have an added advantage at diminishing inflammation induced by macrophages and monocytes as shown by both genetic and pharmacologic studies in which this kinase regulates TLR4-activated expression of IL-6 or other pathways involving STAT (Gottar-Guillier et al 2011, Guryanova et al 2011, Palmer et al 2008).

Together, these data support BTK inhibitors, such as acalabrutinib, to diminish the lung pathology mediated by SARS-CoV-2 and justify application of this approach for clinical investigation in patients with COVID-19.

### 2.2.3 Acalabrutinib

Acalabrutinib is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center, and acalabrutinib is the S-enantiomer. Acalabrutinib is a potent, highly selective covalent inhibitor of BTK (Covey 2015). Acalabrutinib is formulated as a capsule. For clinical testing, acalabrutinib has been manufactured and formulated according to current Good Manufacturing Practices.

Acalabrutinib is currently approved in the United States for the treatment of adult patients with mantle cell lymphoma who have received at least 1 prior therapy, and CLL or small lymphocytic lymphoma (CALQUENCE 2019).

#### 2.2.3.1 Nonclinical Experience

In vitro and in vivo safety pharmacology and in vivo toxicology studies with acalabrutinib have demonstrated a favorable nonclinical safety profile. For detailed information on nonclinical safety of acalabrutinib, refer to the IB and the prescribing information (CALQUENCE 2019).

#### 2.2.3.2 Clinical Experience

As of 30 October 2019, acalabrutinib has been administered to more than 3300 participants in clinical studies, including participants with hematologic malignancies, solid tumors, or rheumatoid arthritis, and participants who are healthy or those with mild to moderate hepatic impairment. No SAEs have been reported in the hepatic impairment trial or in the healthy subject trials. Some participants with CLL have been receiving acalabrutinib therapy for more than 5 years. Acalabrutinib has been administered as monotherapy and in combination with other kinase inhibitors, anti-CD20 antibodies, chemoimmunotherapy (eg, bendamustine/rituximab), and an anti-programmed cell death-1 antibody. No dose-limiting toxicities have been reported with acalabrutinib monotherapy or when administered in combination with the aforementioned agents. Current clinical safety data support combining acalabrutinib with other agents.

Based on the safety profile of acalabrutinib to date, no overt toxicities have been identified that would preclude acute treatment of patients with moderate to severe COVID-19 symptoms. Patients with hematologic malignancies treated with acalabrutinib have shown a significant reduction in several cytokines/chemokines, including pro-inflammatory markers such as: TNFα ($p < 0.001$), IL-10 ($p < 0.001$), MCP-1 ($p < 0.01$), MIP-1 beta ($p < 0.001$), MIP-1 alpha ($p < 0.001$), IL-16 ($p < 0.001$), TARC ($p < 0.001$), CXCL13 ($p < 0.001$), Granzyme A ($p < 0.001$) (Byrd et al 2016, Covey 2015), 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).

For detailed information on the clinical safety and efficacy of acalabrutinib, refer to the IB and the prescribing information (CALQUENCE 2019). Risks associated with acalabrutinib are described in Section 2.3.1 and are based on events observed in participants with cancer who have been treated long-term with acalabrutinib 100 mg bid.

#### 2.2.3.3 Metabolism and Transport

Based on available nonclinical and clinical data, acalabrutinib is extensively and almost completely metabolized by multiple CYP and non-CYP metabolic pathways. CYP3A-mediated oxidation is the major route of metabolism in humans.

Based on metabolite profiles from plasma and excreta of rat, dog, and human following an oral dose of [$^{14}$C]-acalabrutinib, 3 primary metabolic pathways were identified: amide hydrolysis, resulting in loss of the 2-aminopyridine group; glutathione conjugation of the butynamide moiety; and hydroxylation, predominantly in the pyrrolidine ring. The most abundant circulating metabolite in human was ACP-5862, which was formed by CYP3A-mediated oxidation.

ACP-5862 was the only human metabolite in plasma that accounted for more than 10% of total acalabrutinib-related material. Cytochrome P450-mediated metabolism of acalabrutinib and ACP-5862 are catalyzed primarily by CYP3A4/5.

For details on the metabolism of acalabrutinib, refer to the IB and prescribing information (CALQUENCE 2019).

#### 2.2.3.4 Effect of Raised Gastric pH on Acalabrutinib Bioavailability

Due to the basic properties of acalabrutinib, the drug solubility is pH-dependent and clinical evaluation of acid-reducing agents has demonstrated that increased stomach pH would lead to reduced exposure. When acalabrutinib 100 mg is administered following once daily dosing of 40 mg omeprazole (a PPI), there is a 42% reduction in AUC and a 73% reduction in $C_{max}$ as compared to when the drug is dosed in normal acidic pH conditions (Study ACE-HV-112). Currently, the use of PPIs (such as, omeprazole, esomeprazole or rabeprazole) while taking acalabrutinib is not recommended due to a potential decrease in acalabrutinib exposure. Recommendations regarding coadministration with H2-receptor antagonists and antacids are provided in the prescribing information (CALQUENCE 2019). Due to the acuity of COVID-19, many patients are placed on high-dose PPIs or continuous H2-receptor

antagonists to prevent stress ulcers. Moreover, many COVID-19 patients may already be taking an acid-reducing agent for gastroesophageal reflux disease. Proton-pump inhibitors inhibit acid-producing pumps in the stomach and have a prolonged [redacted] effect that extends beyond 24 hours after administration. H2-receptor antagonists also reduce acid production by the stomach, but their acid-reducing effect is not as prolonged as that of PPIs unless they are administered continuously. The findings of the current study will support the coadministration of acalabrutinib (delivered via NG tube) with a PPI.

#### 2.2.3.5 Rationale for Developing an Acalabrutinib Suspension in COCA-COLA

Given its pH-dependent solubility, acalabrutinib requires an acidic medium to dissolve rapidly. A readily and globally available diluent was researched that could allow dissolution of acalabrutinib. The microenvironmental pH of acalabrutinib was measured in COCA-COLA at 4.36 (from a starting COCA-COLA pH of 2.49). At this pH, acalabrutinib solubility is of 1.468 mg/mL. Therefore, nearly complete dissolution of acalabrutinib is expected in 100 mL COCA-COLA after a limited amount of time, compatible with extemporaneous preparation and nasogastric administration. Furthermore, in vitro dissolution data, simulating acalabrutinib in a gastric environment following treatment with acid-reducing agents such as PPIs and 100 to 240 mL of (Pepin et al 2019a, Pepin et al 2019b), the anticipated exposure to acalabrutinib when 100 mg acalabrutinib capsules are dosed orally with 100 mL of COCA-COLA in participants taking acid-reducing agents, is not significantly different from the values observed when 100 mg acalabrutinib capsules are dosed with water in participants with an acidic stomach environment.

Overall, these results suggest that developing a formulation of acalabrutinib in COCA-COLA could potentially allow for the co-administration of acalabrutinib with PPIs, by overcoming the effect of raised gastric pH on acalabrutinib bioavailability.

This approach has been used to manage the PPI restriction for weak basic drugs such as erlotinib (van Leeuwen et al 2016) where administration with COCA-COLA significantly improved erlotinib bioavailability during concomitant use of esomeprazole.

## 2.3 Benefit-Risk Assessment

More detailed information about the known and expected benefits and potential risks of acalabrutinib may be found in the IB and prescribing information (CALQUENCE 2019).

### 2.3.1 Risk Assessment

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 2 summarizes the risks associated with acalabrutinib (any grade, ≥ Grade 3, and median time to first onset) based on 1040 participants with hematologic malignancies who received acalabrutinib monotherapy (data on file).

Refer to Section 6.6 for acalabrutinib dose modification and toxicity management guidance.

**Table 2 Risks Associated with Acalabrutinib Monotherapy in Participants With Hematologic Malignancies (N = 1040)**

| Events | Number (%) of participants | | 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 malignancies | 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.

#### 2.3.1.1 Hemorrhage

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

#### 2.3.1.2 Infections

Serious infections, including fatal events, have been reported in participants treated with acalabrutinib (eg, aspergillosis). Participants should be monitored for signs and symptoms of infection and treated as medically appropriate.

#### 2.3.1.3 Hepatitis B and C Reactivation

No reports of HCV reactivation have been received in the acalabrutinib clinical program to date, and there are no published reports of HCV reactivation following BTK inhibitors that are available to the Sponsor.

Hepatitis B virus reactivations are frequently reported in the setting of acalabrutinib treatment. Among 4053 participants across all clinical studies investigating acalabrutinib to date, 9 participants had HBV reactivation (1 fatal, 8 non-serious) after a median duration of therapy of 248 days (range, 43 to 582 days). One participant experienced a serious Grade 4 event that subsequently resulted in liver failure and death. Participants 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 participant with a rising viral load (above lower limit of detection) should discontinue study intervention 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 participants who develop HBV reactivation.

#### 2.3.1.4 Progressive Multifocal Leukoencephalopathy

Across the acalabrutinib clinical development program, 2 participants with underlying malignancies 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.

#### 2.3.1.5 Cytopenias

Grade 3 or 4 events of cytopenias, including anemia, neutropenia, and thrombocytopenia have occurred in participants with underlying malignancies treated with acalabrutinib. Monitor blood counts as specified in the SoA (Table 1) and as medically appropriate.

#### 2.3.1.6 Secondary Primary Malignancies

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

#### 2.3.1.7 Atrial Fibrillation

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

More detailed information about the known and expected benefits and potential risks of acalabrutinib may be found in the IB and prescribing information (CALQUENCE 2019).

### 2.3.2 Benefit Assessment

The lack of established treatments and vaccines against the novel SARS-CoV-2 virus has driven major medical centers to an unprecedented overload, which has undoubtedly contributed to the mortality observed with COVID-19. The highest mortality rate (~50%) has been reported in critically ill patients (Wu and McGoogan 2020). 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 ICU use are also needed without delay.

Significant evidence exists that in patients with severe respiratory problems, the immune system and inflammation contribute to disease severity. Macrophages and neutrophils are key to producing cytokines driving this inflammatory process. Recently, BTK inhibition has been 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 lung homogenates (Florence et al 2018). Consistent with these findings, patients with hematologic malignancies treated with acalabrutinib have shown statistically significant decreases in TNFα ($p < 0.001$), IL-10 ($p < 0.001$), MCP-1 ($p < 0.01$) (Byrd et al 2016), and IL-6 ($p < 0.05$) (data on file), suggesting that BTK inhibition may represent a new immunomodulatory treatment for virally-induced lung damage driven by a hyperimmune response in patients with COVID-19. 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).

Overall, strong nonclinical evidence and encouraging reports suggest targeting BTK may effectively reduce the morbidity and mortality associated with COVID-19 illness.

### 2.3.3 Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants and limit the number of participants participating in this study, the risks associated with acalabrutinib are justified by the anticipated benefits that may be afforded to participants with confirmed SARS-CoV-2 infection requiring hospitalization due to respiratory failure (as defined in Section 8.1.1.1) attributable to COVID-19 pneumonia and who have an NG tube in place.

# 3 OBJECTIVES AND ENDPOINTS

The objectives and endpoints are listed in Table 3.

**Table 3 Objectives and Endpoints**

| Objective | Endpoint/Variable |
|---|---|
| **Primary Objectives** | **Primary Endpoints/Variables** |
| • To characterize the PK of acalabrutinib and its active metabolite (ACP-5862) following administration of acalabrutinib suspension, when co-administered with a PPI, in participants with COVID-19 | • Primary PK parameters for acalabrutinib and ACP-5862 include $AUC_{12h}$, $AUC_{last}$, and $C_{max}$. Additional PK parameters are described in the protocol. |
| • To assess the safety and tolerability of acalabrutinib suspension in participants with COVID-19 when administered in the presence of PPIs and BSC | • Type, frequency, severity, and relationship to study intervention of any treatment-emergent AEs or abnormalities of laboratory tests, SAEs, or AEs leading to discontinuation of study intervention |
| **Secondary Objective** | **Secondary Endpoints/Variables** |
| • To evaluate the preliminary efficacy of adding acalabrutinib suspension to BSC for treatment of participants with COVID-19 | • Proportion of participants alive and free of respiratory failure at Days 14 and 28<br>For the purpose of this study, **respiratory failure** is defined based on resource utilization of any of the following modalities:<br>◦ Endotracheal intubation and mechanical ventilation<br>◦ 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)<br>◦ Noninvasive positive pressure ventilation or continuous positive airway pressure<br>◦ Extracorporeal membrane oxygenation<br>• Percent change from baseline in CRP (time frame: baseline, Days 3, 5, 7, 14, 28)<br>• Time to improvement defined as time to clinical improvement of ≥ 2 points (from first dose date) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 1 or 2 on the ordinal scale), whichever comes first, by Day 28 |

**Table 3 Objectives and Endpoints**

| Objective | Endpoint/Variable |
|---|---|
| **Exploratory Objectives** | **Exploratory Endpoint/Variable** |
| [redacted] | |

AE = adverse event; $AUC_{last}$ = area under the concentration-time curve from time 0 to last measurable time point; BSC = best supportive care; [redacted] $C_{max}$ = maximum observed concentration; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; [redacted] PK = pharmacokinetic(s); PPI = proton-pump inhibitor; SAE = serious adverse event; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted]

# 4 STUDY DESIGN

## 4.1 Overall Design

This is an open-label, multi-dose study to evaluate the PK, and safety and tolerability of acalabrutinib suspension, when coadministered with a PPI, in participants with confirmed SARS-CoV-2 infection requiring hospitalization due to respiratory failure (as defined in Section 8.1.1.1) attributable to COVID-19 pneumonia and who have an NG tube in place. Approximately 20 participants will be included to ensure at least 16 participants are evaluable. Participants are considered evaluable if they have an evaluable PK profile, ie: (1) complete PK Visit 2 assessments; (2) receive active treatment; and (3) do not have unavailable or incomplete data that may influence the PK analysis.

In addition to BSC, participants will receive acalabrutinib suspension (ie, acalabrutinib 100 mg suspension in COCA-COLA delivered via NG tube) bid for 14 days (a maximum of 28 doses). Best supportive care is per discretion of the Investigator and institutional guidelines. Standard NG tubes supplied by the hospital will be used. Nasogastric tube placement in the stomach will be confirmed by chest x-ray.

To assess the effect of PPIs, all participants must be receiving treatment with a PPI at the start of the study. Treatment with a PPI can begin at any time prior to enrollment, provided participants have received PPI treatment for at least 24 hours prior to the first dose of acalabrutinib suspension (Figure 1). Any PPI is permitted, provided it meets the minimum equivalent daily dose of 20 mg rabeprazole (Appendix H). Participants must be on this dosage

of PPI at the start of the study. They may be weaned off PPIs during the study if medically appropriate.

Blood samples for plasma PK assessment of acalabrutinib and its metabolite (ACP-5862) will be collected at pre-dose and 0.5, 1, 2, 4, 6, and 12 hours following treatment with acalabrutinib suspension as described in Table 4 below and illustrated in Figure 1. Note that the sample at 12 hours must be collected prior to the subsequent acalabrutinib dose (for trough PK sample).

**Table 4 Pharmacokinetic Sampling Relative to Start of Proton-pump Inhibitor Treatment**

| PK Visit | Description | Rationale |
|---|---|---|
| PK Visit 1 | First PK sampling will occur on Day 1 (ie, first dosing day for acalabrutinib suspension) | Allows an early assessment of acalabrutinib and ACP-5862 PK in participants receiving acalabrutinib suspension via NG tube |
| PK Visit 2 | Second PK sampling will occur a minimum of 4 days after the start of PPI treatment, irrespective of the timing of NG tube placement and any time after 2 doses of acalabrutinib suspension have been given (ie, PK sampling can begin prior to the third dose, or anytime thereafter)<br>PK Visit 2 can occur as early as Day 2 (if participant has been on a PPI for ≥ 4 consecutive days prior to receiving the third acalabrutinib dose), and up to Day 4 (if participant initiated PPI treatment 24 hours prior to receiving the first dose of acalabrutinib on Day 1) | PPI exposure must occur for 4 consecutive days to reach the maximum PPI on-target effect<br>PK sample can commence at any point after the second dose of acalabrutinib suspension to ensure steady-state levels of the active metabolite and maximal [redacted] has been reached |
| PK Visit 3 | Third PK sampling will occur 3 days after PK Visit 2, OR on the last day the participant receives acalabrutinib treatment, whichever comes first | Allows an additional opportunity to assess the steady state PK of acalabrutinib and ACP-5862 PK following delivery of acalabrutinib suspension via NG tube |

[redacted] NG = nasogastric; PK = pharmacokinetic(s); PPI = proton-pump inhibitor.

Safety assessments, including AE reporting, will be performed through 28 (± 3) days after the last dose of the acalabrutinib suspension.

## 4.2 Scientific Rationale for Study Design

This open-label, multiple-dose study is intended to evaluate the PK, and safety and tolerability of acalabrutinib suspension delivered via NG tube, when coadministered with a PPI, to inform supportive care in COVID-19 patients.

Since PK and safety assessments are the primary objectives of the study, an open-label design was selected. The study will be conducted in participants with confirmed SARS-CoV-2 infection requiring hospitalization due to respiratory failure (as defined in Section 8.1.1.1)

attributable to COVID-19 pneumonia and who have an NG tube in place.

## 4.3 Justification for Dose

The dose and regimen of acalabrutinib in this study is 100 mg bid (approximately every 12 hours apart), which is consistent with the recommended dosing regimen of acalabrutinib for clinical use (CALQUENCE 2019). The dose of 100 mg acalabrutinib to be administered in this study in hospitalized COVID-19+ patients requiring ventilator support is not anticipated to exceed the acalabrutinib exposure or $C_{max}$ reported in patients with hematologic malignancies. Thus, based on the results from previous clinical studies in hematologic malignancies, the 100-mg dose should provide sufficient plasma exposure for the PK analysis of acalabrutinib and its active metabolite, ACP-5862.

The 14-day treatment duration in this study was selected based on balancing the course of the illness and minimizing exposure to an immunosuppressive agent.

## 4.4 End of Study Definition

The end of the study is defined as the last expected visit/contact of the last participant in the study.

A participant is considered to have completed the study if he/she has completed his/her last scheduled procedure shown in the SoA (Table 1).

All participants who discontinue study intervention 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, as outlined in Section 1.3.

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

Refer to Appendix A 5 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.

## 5.1 Inclusion Criteria

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

1. Participant or legally authorized representative must be able to understand the purpose and risks of the study and provide written informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

2. Male or female participants at least 18 years of age at the time of signing the informed consent.
3. Participants who are hospitalized with coronavirus (SARS-CoV-2) infection, confirmed by PCR test or other commercial or public health assay in any specimen, as documented by either of the following:
   a) PCR positive in sample collected < 72 hours prior to first dose, OR
   b) PCR positive in sample collected ≥ 72 hours prior to first dose (but no more than 14 days prior to first dose), documented inability to obtain a repeat sample (eg, due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc), AND progressive disease suggestive of ongoing SARS-CoV-2 infection.
4. Evidence of respiratory failure attributable to COVID-19 pneumonia (documented radiographically) before enrollment where 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.
5. Nasogastric tube or other types of oral or percutaneous gastric feeding tube; placement must be radiographically confirmed and expected to remain in place, as judged by the Investigator, for a minimum of 3 days after study enrollment.
6. Has received treatment with PPIs (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) for a minimum of 24 hours immediately prior to enrollment; any PPI will be permitted, provided it meets the minimum equivalent daily dose of 20 mg rabeprazole.
7. Willing to follow contraception guidelines when discharged from the hospital (Appendix F).

## 5.2 Exclusion Criteria

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

**Medical Conditions**

1. Any serious and uncorrectable medical condition or abnormality of clinical laboratory tests that, in the Investigator's judgment, precludes the participant's safe participation in and completion of the study.
2. Suspected uncontrolled active bacterial, fungal, viral, or other infection (besides infection with SARS-CoV-2).

3. In the opinion of the Investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments.
4. Current refractory nausea and vomiting, malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach, extensive small bowel resection that is likely to affect absorption, symptomatic inflammatory bowel disease, partial or complete bowel obstruction, or gastric restrictions and bariatric surgery, such as gastric bypass.
5. Pregnant or breastfeeding.
6. Uncontrolled or untreated symptomatic arrhythmias, myocardial infarction within the last 6 weeks, or congestive heart failure (New York Heart Association Grade 3 or 4).

   Exception: Participants with controlled, asymptomatic atrial fibrillation during screening are allowed to enroll on study.
7. History of stroke or intracranial hemorrhage within 2 months of study intervention.
8. History of primary immunodeficiency, tuberculosis, PML, aspergillus or other invasive mold/fungal infection, or received organ or bone marrow transplantation within 6 months of enrollment.
9. Known active hepatitis B or C infection as determined by active treatment, medical history or any routine clinical or laboratory evidence that, in the judgement of the Investigator, suggests chronic or active viral hepatitis.

   NOTE: Any participant who does not meet this criterion and for whom hepatitis serology data are not available prior to the first dose, can start treatment, provided they 1) do not have a medical history of HBV or HCV infection, 2) there is no clinical or laboratory evidence to suggest chronic or active viral hepatitis, and 3) blood samples for all HBV and HCV serology and viral load tests (HBV DNA PCR and HCV RNA PCR) are collected prior to the first dose. Refer to guidance in Section 8.2.5.1.1 on how to manage viral hepatitis testing.
10. Known human immunodeficiency virus with viral load and CD4 counts < 500 cells/$mm^3$.
11. Participants who are unable to undergo multiple venipunctures because of poor tolerability or lack of easy venous access.

**Laboratory Assessments**

12. Alanine aminotransferase, AST and/or TBL ≥ 3 × 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 × ULN if considered due to underlying COVID-19 disease, but cannot be associated with concurrent elevated bilirubin (up to 2 × ULN).
13. Absolute neutrophil count < 500/μL at screening (per local laboratory).

14. Platelet count < 50,000/μL at screening (per local laboratory).
15. Estimated creatinine clearance of < 10 mL/min calculated using the Cockcroft-Gault formula [(140age) × mass (kg)/(72 × creatinine mg/dL) multiply by 0.85 if female].

**Prior/Concomitant Therapy**

16. Treatment with a strong CYP3A inhibitor (within 7 days before first dose of study intervention) or inducer (within 14 days before first dose of study intervention).
17. Received BTK inhibitor within 7 days before enrollment.
18. Requires or is receiving specific anticoagulation with warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) within 7 days prior to enrollment. Other anticoagulants are permitted.
19. Participants on dual antiplatelet **and** therapeutic/high-dose anticoagulant therapy (eg, aspirin and therapeutic/high doses of low-molecular-weight heparin are not allowed; however, aspirin and prophylactic/low doses of low-molecular-weight heparin are allowed).
20. History of hypersensitivity (ie, allergic response) to active or inactive excipients of acalabrutinib or other BTK inhibitors.
21. Known cytoreductive chemotherapy treatment within 14 days of enrollment.

## 5.3 Lifestyle Considerations

Participants discharged from the hospital must follow the contraception requirements outlined in Appendix F.

Restrictions relating to concomitant medications are described in Section 6.5.

## 5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials 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 participants should be assigned the same participant number as for the initial screening.

# 6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

## 6.1 Study Intervention(s) Administered

### 6.1.1 Investigational Medicinal Products

Details of the investigational medicinal products are provided in Table 5.

**Table 5 Investigational Medicinal Products**

| **Intervention Name** | **Acalabrutinib** | **Acalabrutinib** |
|---|---|---|
| **Type** | Drug | Drug |
| **Formulation** | Suspension extemporaneously constituted from acalabrutinib capsules and 100 mL flat COCA-COLA (see Handling Instructions) | Capsule[a] |
| **Strength/concentration** | 100 mg/100 mL | 100 mg |
| **Dosage level** | 100 mg | 100 mg |
| **Route of administration** | Nasogastric | Oral |
| **Regimen** | bid (multiple dose) | bid (multiple dose) |
| **Use** | Experimental | Experimental |
| **Sourcing** | Sponsor (AstraZeneca)[b] | Sponsor (AstraZeneca) |
| **Former name/alias** | ACP-196 | ACP-196 |

[a] Acalabrutinib capsules will only be taken orally if a participant is no longer intubated and can swallow pills during the treatment period.
[b] Note: COCA-COLA will be supplied locally.
bid = twice daily.

The COCA-COLA needed to constitute the acalabrutinib suspension will be supplied locally and must meet the criteria below:

- COCA-COLA original (minimum 250 mL countenance, bottles with caps). If cans are used instead, 200 to 500 mL bottles with caps are needed to degas the soda to avoid foaming. A volume of 100 mL of flat COCA-COLA is needed for the preparation of the 100 mg acalabrutinib suspension.
- Hard plastic or glass bottles of 200 to 500 mL capacity with screw caps to constitute the suspensions; preferably amber glass.

## 6.1.2 Dosing Instructions and Duration

### 6.1.2.1 Dosing and Duration of Treatment

Treatment with acalabrutinib suspension (ie, acalabrutinib 100 mg suspension in COCA-COLA delivered via NG tube) will be initiated on Day 1. All participants must have received PPI treatment for ≥ 24 hours prior to the first dose of acalabrutinib suspension. All participants will receive acalabrutinib suspension bid, approximately 12 hours apart, for 14 days (a maximum of 28 doses). The acalabrutinib suspension must be prepared according to the Handling Instructions. **NOTE:** COCA-COLA contains glucose (5 g per 100 mL). Blood glucose levels of diabetic participants must be monitored as clinically indicated and blood glucose-lowering medications adjusted accordingly.

Administration of acalabrutinib suspension should not occur within a 2-hour window before or after feeding or delivery of other drugs. Nasogastric tubing should be flushed with water prior to and after acalabrutinib suspension delivery according to the Handling Instructions.

### 6.1.2.2 Dosing of Participants Who are no Longer Intubated

If a participant is no longer intubated and can swallow pills during the treatment period, the participant should continue taking acalabrutinib 100 mg capsules orally bid. Capsules should be swallowed intact. Acalabrutinib can be taken with or without food.

- If a participant remains on a PPI and switches to taking capsules orally, 100 mg acalabrutinib capsules should be dosed orally with at least 100 mL of-COCA-COLA.
- If a participant is no longer taking a PPI and switches to taking capsules orally, acalabrutinib capsules should be taken with water.

### 6.1.2.3 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 14 days (a maximum of 28 doses).

If the 3-hour dosing window is missed, the dose must be skipped on that day. Acalabrutinib 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 AE or for any other reason, missed doses should be completed so the participant receives a maximum of 28 doses of acalabrutinib, even if this is beyond the 14-day dosing period.

### 6.1.2.4 Vomiting After Acalabrutinib Treatment

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

#### 6.1.2.5 Discharged From Hospital Before Treatment Completion

Participants who are discharged from the hospital before they have completed 14 days (a maximum of 28 doses) of acalabrutinib therapy must complete the remaining doses at home. They should adhere to their established dosing schedule. These participants must complete a drug dosing diary to be sent electronically to the study site.

## 6.2 Preparation/Handling/Storage/Accountability of Interventions

### 6.2.1 Preparation and Handling

Refer to the Handling Instructions for the preparation and handling of acalabrutinib suspension in COCA-COLA delivered via NG tube to participants.

### 6.2.2 Storage and 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 IB for additional information regarding the drug product to be used in this study.

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

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled 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 intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

## 6.3 Measures to Minimize Bias: Randomization and Blinding

This is an open-label study and blinding is not applicable.

## 6.4 Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date, and time if applicable, of dose administered in the clinic will be recorded in the source documents and recorded in the eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

For participants who are discharged from the hospital before they have completed 14 days (a maximum of 28 doses) of acalabrutinib and must complete the remaining doses (capsules) at home, compliance with study intervention will be assessed via a drug dosing diary that must be sent electronically to the study site at each visit and documented in the source documents and eCRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of acalabrutinib suspensions or capsules dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

## 6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study including the 28-day follow-up period following the last dose of study intervention.

Best supportive care should be entered as a concomitant medication in the eCRF.

### 6.5.1 Premedications

All participants must be receiving treatment with a PPI at the start of the study. Treatment with a PPI can begin at any time prior to enrollment, provided participants have received PPI

treatment for at least 24 hours prior to the first dose of acalabrutinib suspension. Any PPI is permitted, provided it meets the minimum equivalent daily dose of 20 mg rabeprazole.

Participants in the ICU may receive higher doses of PPI, and medications more appropriate for NG tube delivery, such as esomeprazole or lansoprazole. Higher doses of PPIs are allowed, if medically necessary. Please refer to Appendix H for equivalency charts.

If a participant no longer requires PPIs during the course of treatment, PPIs may be stopped. Please refer to treatment guidelines (Section 6.1.2) in such cases.

Any other premedication prior to treatment with acalabrutinib suspension is not necessary, but steroids as premedication for hypersensitivity reactions (eg, CT scan premedication) are allowed.

### 6.5.2 Permitted Concomitant Therapy

Best supportive care for COVID-19 (per Investigator discretion and institutional guidelines) is required for all participants 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 in the study.

**Medications Prohibited Through Day 28**

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

**Medications Prohibited Through Day 14**

**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). Concomitant administration with a strong inhibitor of CYP3A has the potential to increase

acalabrutinib exposure. Conversely, concomitant administration with a strong inducer of CYP3A has the potential to decrease exposure of acalabrutinib and could reduce efficacy. Therefore, the concomitant use of strong inhibitors or inducers of CYP3A (see Appendix E) should be avoided in the study. If a participant requires a strong CYP3A inhibitor or inducer while on treatment with acalabrutinib, acalabrutinib treatment must be discontinued. Refer to Section 6.5.4 for additional information on drugs with potential drug-drug interactions.

**Other BTK inhibitors:** BTK inhibitors other than acalabrutinib are prohibited.

**Certain anticoagulants:** Warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited in the study. Participants 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 [redacted] occupancy steady-state in target B-cell and monocytic populations. Therefore, the Sponsor recommends that all eligible participants with COVID-19 begin dosing with acalabrutinib 100 mg bid. The duration of acalabrutinib therapy will be limited to 14 days (a maximum of 28 doses). Table 6 provides guidance for participants taking moderate CYP3A inhibitors and acid-reducing agents while on study. Refer to Appendix E for a list of common CYP3A inhibitors/inducers and gastric acid-reducing medicines.

**Table 6 Acalabrutinib Use with Moderate CYP3A Inhibitors and Gastric Acid-reducing Agents**

| | **Coadministered Medicines** | **Recommended Acalabrutinib Use** |
|---|---|---|
| **CYP3A Inhibitor** | Moderate CYP3A inhibitor | Monitor participants closely for adverse reactions if taking moderate CYP3A inhibitors. For participants 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** | H2-receptor antagonists | Take acalabrutinib 2 hours before taking a H2-receptor antagonist. |
| | Antacids | Separate dosing by ≥ 2 hours. |

**Gastric Acid-reducing Medications**

Acalabrutinib solubility decreases with increasing pH. Coadministration of acalabrutinib with an antacid (1 g calcium carbonate) decreased acalabrutinib AUC by 53% in healthy participants.

If the participant has discontinued treatment with a PPI, but 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.

Dose modification of acalabrutinib is not necessary when coadministered with antacids or an H2-receptor antagonist.

Recommendations regarding coadministration with H2-receptor antagonists and antacids are provided in the prescribing information (CALQUENCE 2019).

## 6.6 Dose Modification

In general, no acalabrutinib dose modification is required if a participant experiences a Grade 1 or Grade 2 AE. Acalabrutinib therapy should be modified or discontinued, however, for the AEs described in Table 7.

**Table 7 Guidelines for Acalabrutinib Dose Modification or Discontinuation**

| 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<br>• If neutropenia has improved to Grade 1 or baseline within 3 days of event onset, restart acalabrutinib<br>• 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<br>• Consider introducing growth factors (eg, G-CSF), evaluate participant for infection, and begin antibiotic treatment per institutional guidelines |
| Presence of significant bleeding events with or without thrombocytopenia, such as:<br>• Grade 3 or 4 hemorrhage<br>• Any grade serious hemorrhage event<br>• Any grade intracranial hemorrhage or hematoma | Discontinue acalabrutinib |

**Table 7 Guidelines for Acalabrutinib Dose Modification or Discontinuation**

| Event | Acalabrutinib Dose Modification/Discontinuation |
|---|---|
| Grade 4 platelet count decrease (< 25,000/mm3) | • Hold acalabrutinib and consider platelet transfusions, as clinically indicated<br>• If thrombocytopenia has improved to ≤ Grade 2 within 3 days of event onset, restart acalabrutinib<br>• 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 |
| 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<br>• If infection does not respond to appropriate antimicrobial therapy within 48 to 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 participant during any AE.

Acalabrutinib 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 AE or for any other reason, missed

doses should be completed so the participant receives a maximum of 28 doses of acalabrutinib, even if this is beyond the 14-day dosing period.

### 6.6.1 Acalabrutinib Dose Modifications in Special Populations

#### 6.6.1.1 Renal Impairment

After administration of a single 100 mg radiolabeled acalabrutinib dose in healthy participants, 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 participants with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73 $m^2$, as estimated by MDRD equation). Acalabrutinib PK and clinical safety has not been evaluated in participants 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, metabolized, and distributed. The plasma-protein binding is 97.5% and is noncovalent (potentially dialyzable). However, acalabrutinib covalently binds to the target, BTK, and will not be dialyzable. As such, it is unlikely that a clinically meaningful lowering of total BTK occupancy in target cell populations will be impacted. If participants 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.

#### 6.6.1.2 Hepatic Impairment

Acalabrutinib clinical safety has not been evaluated in patients with severe hepatic impairment. If acalabrutinib is administered to participants with hepatic impairment, monitor participants carefully for AEs and follow the recommended dose modifications in Table 7.

The PK acalabrutinib in participants with hepatic impairment has been studied. Briefly, the AUC of acalabrutinib increased 1.9-fold in participants with mild hepatic impairment (Child-Pugh class A), 1.5-fold in participants with moderate hepatic impairment (Child-Pugh class B), and 5.3-fold in participants with severe hepatic impairment (Child-Pugh class C) compared with participants with normal liver function. No clinically relevant PK difference in ACP5862 was observed in participants with severe hepatic impairment (Child-Pugh class C) compared with participants with normal liver function. No clinically relevant PK differences in acalabrutinib and ACP5862 were observed in participants with mild or moderate hepatic impairment (TBL ≤ ULN and AST > ULN, or TBL > ULN and any AST) relative to participants with normal hepatic function (TBL and AST within ULN).

## 6.7 Intervention After the End of the Study

There is no intervention following the end of the study.

# 7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

## 7.1 Discontinuation of Study Intervention

Participants may discontinue study intervention for the following reasons:

- Positive HBsAg, HBV-DNA, or HCV-RNA test result after the first dose
- Completed treatment
- Pregnancy
- Adverse event
- Investigator's decision
- Participant withdrawal of consent from study
- Decision by the Sponsor to terminate the study
- Lost to follow-up
- Death
- Other

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

A participant that decides to discontinue study intervention will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study intervention should be documented in the eCRF.

Participants should have follow-up assessments for safety 28 (± 3) days after the last dose of acalabrutinib (whether due to discontinuation or completion of dosing) (see Table 1).

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 Participant Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

Participants with a positive HBsAg, HBV-DNA, or HCV-RNA test result after the first dose will be withdrawn from the study.

A participant 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).

At the time of withdrawal from the study, if possible, an Early Study Intervention Discontinuation visit should be conducted. If this visit occurs prior to Day 14, the Day 14 schedule of assessments should be followed, and if it occurs between Days 14 and 28, the Day 28 schedule of assessments should be followed. See SoA (Table 1) for data to be collected on these days and for follow-up and any further evaluations that need to be completed. The participant will discontinue the study intervention and be withdrawn from the study at that time.

If the participant 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 participant withdraws from the study, it should be confirmed if he/she is still agreeing for existing samples to be used consistent with the original consent. If he/she requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried in line with what was stated in the informed consent and local regulation. The Investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

## 7.3 Lost to Follow-up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant’s last known mailing address or local equivalent methods). These contact attempts should be documented in the participant’s medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomised, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

# 8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Table 1), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Table 1).

## 8.1 Efficacy and Clinical Assessments

### 8.1.1 Efficacy Assessments

#### 8.1.1.1 Pulmonary Assessments to Evaluate Respiratory Failure

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.

Arterial blood gases, and oxygen and ventilator use data will be captured to assess respiratory failure as described above.

If a participant requires oxygen supplementation, data will be recorded, including method of oxygen supplementation, maximum daily flow rate and $FiO_2$.

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

For participants on mechanical ventilation, the following ventilator settings will be recorded: tidal volume, $FiO_2$, 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 participants on mechanical ventilation, an arterial blood gas (pH, $PaO_2$, partial pressure of carbon dioxide, 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 blood gasses should be collected from participants if the sample is easily accessible and the procedure will not be painful to participants (ie, participant is in the ICU or has arterial port). All available data from the arterial blood gases should be entered into the database. If the collection of arterial blood 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.

Respiratory data will be used to evaluate the efficacy endpoints of proportion of participants alive and free of respiratory failure at Days 14 and 28.

#### 8.1.1.2 Improvements on 9-point Category Ordinal Scale

For the purposes of this study, the condition of each potential participant in the study will be assessed using a 9-point category ordinal scale in Table 8. Assessments will be performed as described in the SoA (Table 1).

**Table 8 9-point Category Ordinal Scale**

| Scale | Description |
|---|---|
| 0 [a] | 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 |

**Table 8 9-point Category Ordinal Scale**

| Scale | Description |
|---|---|
| 4 | Hospitalized – mild disease, oxygen by mask or nasal prongs |
| 5 | Hospitalized – severe disease, non-invasive ventilation or high flow oxygen |
| 6 | Hospitalized – 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 |

[a] 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 participant needs to show an improvement of at least 2 points (from first dose) on this scale. Time to clinical improvement of 2 points will be assessed as a secondary endpoint.

### 8.1.2 Clinical Assessments

#### 8.1.2.1 Modified Sequential Organ Failure Assessment Scores

A modified Sequential Organ Failure Assessment 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/$FiO_2$ (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. Assessments will be performed as described in the SoA (Table 1).

## 8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

### 8.2.1 Medical History

Collect and record the participant'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.

### 8.2.2 Physical Examinations and Chest Imaging

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 enrollment). Post-treatment assessment will continue as clinically indicated.

Physical examination and chest imaging will be performed at time points specified in the SoA

(Table 1).

### 8.2.3 Vital Signs

The vital signs to be collected are blood pressure, respiratory rate, pulse oximetry, heart rate, and body temperature. 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 intervention should be used. The oxygen-hemoglobin saturation of the blood will be assessed using standard pulse oximetry or by arterial blood gas for those participants who have an arterial blood gas obtained.

Vital signs will be performed at time points specified in the SoA (Table 1).

### 8.2.4 Electrocardiograms and Echocardiograms

A single 12-lead ECG will be done during the screening period and at Day 14 or upon discharge from the hospital. The ECG should be collected during the treatment period, as clinically indicated per SoA (Table 1). For all ECGs, details of rhythm, ECG intervals, and an overall evaluation will be recorded.

An echocardiogram should be collected at screening or during the treatment period, as clinically indicated per SoA (Table 1). 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.

### 8.2.5 Clinical Safety Laboratory Assessments

#### 8.2.5.1 Local Laboratory Tests

The following laboratory tests will be done as specified in the SoA (Table 1) using the site's local laboratories:

- Hematology studies must include complete blood count with differential including, but not limited to white blood cell count, hemoglobin, platelet count, absolute neutrophil count or percentage, red blood cell count, absolute monocyte count or percentage, and absolute lymphocyte count or percentage.
- Serum or plasma chemistry will include albumin, ALP, ALT, AST, bicarbonate, blood urea nitrogen, calcium, chloride, creatinine, glucose, lactate dehydrogenase, magnesium,

phosphate, potassium, sodium, TBL (direct and indirect bilirubin, if available), total protein, and uric acid.

- Urine or serum pregnancy testing (women of childbearing potential only; Appendix F)
- C-reactive protein
- Fibrinogen, D-dimer*
- Prothrombin time, aPTT, 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 recorded in the database) (see hepatitis serology guidelines in Section 8.2.5.1.1)
- SARS-CoV-2 reverse transcriptase-polymerase chain reaction viral test. Sites should report this as positive/negative.

*These laboratory tests should be performed more frequently than described in the SoA (Table 1), if clinically indicated.

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

**NB.** In case a participant shows an AST **or** ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, refer to Appendix D for actions required in cases of increases in liver biochemistry and evaluation of Hy's Law'.

#### 8.2.5.1.1 Hepatitis Serology Guidelines

If feasible, hepatitis serology data should be obtained prior to administration of the first dose. However, if not feasible, sites should proceed as described below.

Participants must not meet Exclusion Criterion 9 (see Section 5.2):

- Known active hepatitis B or C infection as determined by active treatment
- Medical history or any routine clinical or laboratory evidence, that in the judgement of the Investigator, suggests chronic or active viral hepatitis.

Blood samples for all HBV and HCV serology tests, and for both HBV and HCV PCR tests must then be collected **before** administration of the first dose.

- If results become available before administration of the first dose, participants with positive HBsAg, HBV-DNA, or HCV-RNA test results will be excluded and should be treated per institutional guidelines.

  - Participants who are anti-HBc positive and who are HBsAg negative will need to have a negative or undetectable hepatitis B viral load (HBV-DNA) by quantitative PCR result.
  - Participants who are HCV antibody positive will need to have a negative PCR.
- If results are not available at the time of first dose administration, participants can be started on acalabrutinib. If any of the HBsAg, HBV-DNA, or HCV-RNA test results are positive after the first dose, the following must occur:
  - Discontinue further treatment with acalabrutinib.
  - Withdraw the participant from the study.
  - Modify BSC as clinically indicated per Investigator judgement.
  - Initiate a monitoring and therapeutic plan for HBV/HCV infection according to institutional guidelines and Investigator judgement.

#### 8.2.5.2 Central Laboratory Tests

Samples will be collected as specified in the SoA (Table 1) and sent to a central laboratory for the following laboratory tests:

- Plasma samples for acalabrutinib/ACP-5862 PK

[redacted]

**NOTE:** PK, [redacted] 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 is provided in Appendix C.

## 8.3 Adverse Events and Serious 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.

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

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

### 8.3.1 Time Period and Frequency for Collecting AE and SAE Information

Adverse events will be collected from the time of signature of the ICF through 28 (± 3) days after the last dose of study intervention.

Serious adverse events will be recorded from the time of signing the ICF.

If the Investigator becomes aware of an SAE with a suspected causal relationship to the study intervention that occurs after the end of the clinical study in a participant treated by him or her, the Investigator shall, without undue delay, report the SAE to the Sponsor.

### 8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's last AE an assessment 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 participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

**Adverse event variables**

The following variables will be collected for each AE:

- Adverse event (verbatim)
- The date and time when the AE started and stopped
- The CTCAE grade and grade changes, with the date they changed
- Whether the AE is serious or not
- Investigator causality rating against the study intervention (yes or no)
- Action taken with regard to study intervention
- Outcome

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

- Date AE met criteria for SAE
- Date Investigator became aware of SAE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death

- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

### 8.3.3 Causality Collection

The Investigator should assess causal relationship between study intervention 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 study intervention?'

For SAEs, causal relationship should 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.

### 8.3.4 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the participant or reported in response to the open question from the study site staff: 'Have you/the child 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.

### 8.3.5 Adverse Events Based on Examinations and Tests

The results from the CSP mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the study intervention or are considered to be clinically relevant as judged by the Investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

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.

### 8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 × ULN together with TBL ≥ 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.

### 8.3.7 Disease Progression

Disease progression can be considered as a worsening of a participant's condition attributable to COVID-19 pneumonia for which the study intervention 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, acute respiratory distress syndrome, sepsis, shock, multiorgan failure and death.

### 8.3.8 Disease Under study

Systemic symptoms of the disease under study are those that 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 study intervention.

### 8.3.9 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the study intervention, or to the study procedure(s). All SAEs will be recorded in the eCRF.

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

For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSARs 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 IB and will notify the IRB/IEC according to local requirements, if appropriate.

Refer to Appendix B for further guidance on the definition of a SAE.

### 8.3.10 Pregnancy

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

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.

#### 8.3.10.1 Maternal Exposure

If a participant becomes pregnant during the course of the study, study intervention should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study intervention 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 participant 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 or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.3.9) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

#### 8.3.10.2 Paternal Exposure

Male participants 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 participant'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 participant'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.

### 8.3.11 Medication Error

If a medication error occurs during the course of the study, the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) or 5 (other serious initial and follow up) calendar days if there is an SAE associated with the medication error (see Section 8.3.11) and within 30 days for all other medication errors.

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

### 8.3.12 Adverse Events of Special Interest

Adverse events of special interest 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 8.3.9.

The following events are AESIs for participants receiving acalabrutinib and must be reported to the Sponsor expeditiously (see Section 8.3.9 for reporting instructions), irrespective of regulatory seriousness criteria or causality:

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

## 8.4 Overdose

For this study, any dose of study intervention greater than the dose that was intended to be given will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.
- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study intervention occurs in the course of the study, the Investigator or other site personnel inform appropriate Sponsor representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Sponsor representative works with the Investigator to ensure that all relevant information is provided to the Sponsor Patient Safety data entry site within 1 or 5 calendar days for overdoses associated with an SAE (see Section 8.3.9) and within 30 days for all other overdoses.

## 8.5 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. Refer to Appendix C for further details on handling of human biological samples.

Samples will be stored for a maximum of 15 years from the date of the issue of the CSR in line with consent and local requirements, after which they will be destroyed/repatriated.

- Pharmacokinetic samples will be disposed of after the Bioanalytical Report finalization or six months after issuance of the draft Bioanalytical Report (whichever is earlier), unless consented for future analyses.

- Pharmacokinetic samples may be disposed of or anonymised by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

The timing of PK [redacted] sample collections should be aligned as closely as possible and will be prioritized over other blood samples being collected simultaneously, except in the case of an AE for which relevant assessment/blood sample collection will be prioritized.

### 8.5.1 Pharmacokinetics

Blood samples will be collected for the measurement of plasma concentrations of acalabrutinib and its metabolite, ACP-5862, as specified in the SoA (Table 1). Briefly, blood samples will be collected at 3 separate study visits at pre-dose and 0.5, 1, 2, 4, 6, and 12 hours post-dose. The 12-hour post-dose sample will be collected immediately prior to administration of the subsequent dose. The PK samples will be collected as described in Table 4.

Samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and the Sponsor, eg, for safety reasons. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak or trough matrix concentrations) to ensure appropriate monitoring.

Samples collected for analyses of plasma concentration of acalabrutinib and ACP-5862 may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

#### 8.5.1.1 Determination of Drug Concentration

Samples for determination of drug concentration in plasma will be assayed by bioanalytical test sites operated by or on behalf of AstraZeneca, using an appropriately validated bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation, if performed, will be reported in a separate Bioanalytical Report.

### 8.5.2 [redacted]

[redacted]

### 8.5.3 Immunogenicity

No antidrug antibody samples will be collected in this study.

## 8.6 [redacted]

[redacted]

## 8.7 Optional Genomics Initiative Sample

Optional Genomics Initiative research is not applicable to this study.

## 8.8 Health Economics

Health economics is not applicable to this study.

# 9 STATISTICAL CONSIDERATIONS

## 9.1 Statistical Hypotheses

The primary objective of the study is to characterize the PK of acalabrutinib and its active metabolite (ACP-5862) and assess the safety and tolerability of acalabrutinib suspension when coadministered with a PPI in participants with COVID-19. There is no formal hypothesis testing for safety and efficacy endpoints.

## 9.2 Sample Size Determination

A sample size of 16 evaluable participants with COVID-19 was chosen based on the desire to gain adequate information while exposing as few participants as possible to the study procedures and study intervention. Given the inherent variability in the COVID-19 patient population, broad inclusion and exclusion criteria, and possible variability in treatment duration and PPI usage, approximately 20 participants will be enrolled in the study in order to have at least 16 evaluable participants able to complete PK Visit 2 (allowing for ~25% dropout rate due to disease progression).

**Note**: "Enrolled" means a participant's, or his/her legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study but are not randomly assigned/assigned in the study, are considered "screen failures", unless otherwise specified by the protocol.

## 9.3 Populations for Analyses

The analysis populations are defined in Table 9.

**Table 9 Populations for Analysis**

| Population/Analysis set | Description |
|---|---|
| PK Analysis Set | The PK Analysis Set will include all participants who received ≥ 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. |
| Safety Analysis Set | The Safety Analysis Set will include all participants who received ≥ 1 dose of study intervention |
| Efficacy Evaluable Set | The Efficacy Evaluable Set will include all participants who received ≥ 1 dose of study intervention |
| [redacted] | |

ITT = intent to treat; PK = pharmacokinetic; [redacted] PPI = proton-pump inhibitor.

## 9.4 Statistical Analyses

The SAP will be finalized prior to database lock and will include a more technical and detailed description of the statistical analyses described in this section. This section summarizes the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints. Additional statistical analyses other than those described in this section may be performed if deemed appropriate.

### 9.4.1 General Considerations

For efficacy continuous endpoints, the baseline is defined as the last observation prior to the first dose of acalabrutinib suspension.

No missing data imputation will be applied for efficacy analysis.

For safety analysis, where individual data points are missing because of dropouts or other reasons, the data will be summarized based on reduced denominators.

Sensitivity analysis may be done by excluding participants with significant protocol deviations as appropriate.

### 9.4.2 Pharmacokinetic Analysis

A listing of PK blood sample collection times as well as derived sampling time deviations will be provided. Plasma acalabrutinib and ACP-5862 concentrations and PK parameters listed below will be summarized using appropriate descriptive statistics, which will be fully outlined in the SAP.

- Primary PK parameters: $AUC_{12h}$, $AUC_{last}$, and $C_{max.}$
- Secondary PK parameters:
  - Acalabrutinib and ACP-5862: $t_{1/2}$, $t_{max}$, and $\lambda_z$.
  - Acalabrutinib: CL/F and Vz/F.
  - Metabolite to parent ratio for $C_{max}$, $AUC_{last}$, and $AUC_{12h.}$

No formal statistical test will be conducted for the PK parameters.

### 9.4.3 Safety Analysis

Safety assessments will consist of monitoring and recording of all AEs, SAEs, and AEs leading to discontinuation of study intervention, measurement of protocol-specified vital signs, ECG, laboratory variables, and other protocol-specified safety tests or measurements. 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 MedDRA terms

and graded per NCI CTCAE, v5.0 or higher. Extent of exposure to study intervention, all AEs, SAEs, any AEs leading to study intervention discontinuation, and study intervention related AEs will be summarized. The frequency of AEs will be summarized by system organ class and preferred term per MedDRA and by the worst reported NCI CTCAE grade. Treatment-emergent AEs will be summarized, unless otherwise specified. Treatment-emergent AEs are defined as AEs starting or ongoing AEs worsening after the first dose of study intervention and AEs with start date up to the last dose of study intervention plus 28 (± 3) days.

Laboratory abnormalities will be defined based on laboratory normal ranges (universal normal ranges, if central laboratory). Selected laboratory parameters may be analyzed 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.

### 9.4.4 Efficacy Analyses

All efficacy analyses will be performed on the Efficacy Evaluable Set.

#### 9.4.4.1 Alive and Free of Respiratory Failure

The proportion of participants alive and free of respiratory failure will be assessed at Days 14 and 28. Point estimates and their 90% confidence intervals (using Wald method with continuity correction) will be calculated.

Only the participant's survival status and respiratory failure (as defined in Section 8.1.1.1) status on Days 14 and 28 will be considered for this endpoint. If they experience respiratory failure after enrollment but recover by Days 14 or 28, per the definition of respiratory failure, they will be considered alive and free of respiratory failure at these time points.

#### 9.4.4.2 Percent Change in C-reactive Protein

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented for the percent change from baseline in CRP at Days 3, 5, 7, 14, and 28. Baseline is defined as the last observation prior to the first dose of acalabrutinib suspension.

#### 9.4.4.3 Time to Clinical Improvement on 9-point Ordinal Scale

Time to improvement defined as time to clinical improvement of at least 2 points (from first dose date) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 1 or 2 on the ordinal scale), whichever comes first, by Day 28 (this will also define the "responder" for the response rate analyses), will be analyzed using Kaplan-Meier method with Kaplan-Meier estimates and their 90% confidence intervals. If a

participant did not have an improvement and did not drop out prior to Day 28, the data will be censored at Day 28. If a participant did not have an improvement but dropped out prior to Day 28, the data will be censored at the last date known that without improvement.

### 9.4.5 [redacted] and Exploratory Analysis

[redacted]

## 9.5 Interim Analyses

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

## 9.6 Safety Review Committee

This study will have an SRC. The SRC will conduct scheduled reviews of safety and other relevant data. In addition, The SRC will meet to review any of the following events should they occur during the study:

- Any death due to acalabrutinib (per Investigator)
- Any Grade 4 hemorrhage due to acalabrutinib (per Investigator)

The SRC will consist of the AstraZeneca Study Physician or delegate, Principal Investigator or equivalent delegate from active investigational sites, and Global Safety Physician or delegate. Other attendees may also be invited as appropriate.

Details on the process of ongoing evaluation of safety data by the SRC and the committee composition is described further in the SRC charter.

# 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# 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 International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, 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 and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO but the accountability remains with the Sponsor.

**Regulatory Reporting Requirements for SAEs**

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators.
- For all studies except those utilizing medical devices, Investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

## 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 participant or his/her legally authorized representative and answer all questions regarding the study.

Participants or their legally authorized representative must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, 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 participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants 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 participant or the participant's legally authorized representative.

Participants 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 participant 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 analyzed at the time of the request, the Sponsor will not be obliged to destroy the results of this research.

## A 4 Data Protection

Each participant will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant 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 and use of their data must also be explained to the participant in the informed consent

The participant 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 Dissemination of Clinical Study Data

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

## A 6 Data Quality Assurance

All participant data relating to the study will be recorded on 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 or electronically signing the eCRF.

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

The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants 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 7 Source Documents

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

Data entered in the 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.

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

## A 8 Study and Site Start and 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. 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 participants by the Investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

## A 9 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 time point 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 Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

## B 1 Definition of Adverse Events

An adverse event is the development of any untoward medical occurrence in a participant or clinical study participant 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 (for example 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 intervention has been administered.

## B 2 Definitions of Serious Adverse Event

A serious adverse event 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-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above.

**Life Threatening**

'Life-threatening' means that the participant 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 participant'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).

**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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

**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, hospitalisation, disability or incapacity but may jeopardise the participant 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 iv 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 anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

**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 v5.0 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).

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 3 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 participant 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. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca 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 recognised 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 no available facts or arguments to suggest a causal relationship, 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 4 Medication Error

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

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 participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognised 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 participant
- 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

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

- Participant accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant 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

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 participants 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 record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives 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 AstraZeneca-assigned biobanks or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team during for the remainder of the sample life cycle.

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 participant withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analyzed, the Sponsor is not obliged to destroy the results of this research.

Following withdrawal of consent for biological samples, further study participation should be considered in relation to the withdrawal processes outlined in the informed consent.

The Investigator:

- Ensures participant’s withdrawal of informed consent to the use of donated samples is highlighted immediately to the Sponsor or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented
- Ensures that the participant and Sponsor are informed about the sample disposal.

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action documented and study site notified.

## C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

**LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES**

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

**Category A Infectious Substances** are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

**Category A pathogens** are eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

**Category B Infectious Substances** are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name.

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

**Exempt** - Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations.
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

# 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 PHL cases and 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 participant 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 Sponsor clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the study intervention.

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**

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

**Hy's Law**

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the study intervention, 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 (ie, 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 participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

**Central Laboratories Being Used**

When a participants 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 Sponsor 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 Sponsor 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 participant 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 Sponsor representative
- Determine whether the participant meets PHL criteria (see Section D 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits

- Promptly enter the laboratory data into the laboratory eCRF

# D 4 Follow-up

## D 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet PHL criteria, the Investigator will:

- Inform the Sponsor representative that the participant has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the CSP.

## D 4.2 Potential Hy's Law Criteria Met

If the participant does meet PHL criteria, the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study intervention (See Section D 2).
- Notify the Sponsor 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 participants that met PHL criteria prior to starting study intervention, the Investigator is not required to submit a PHL SAE unless there is a significant change# in the participant's condition.
- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact the Investigator will:
  - Monitor the participant 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 3 Liver eCRF Modules as information becomes available.

**#A 'significant' change** in the participant's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) 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 study intervention, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The Sponsor 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 eCRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the Sponsor standard processes.

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

- Send updated SAE (report term 'Hy's Law') according to Sponsor 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 study intervention and seriousness criteria is medically important, according to 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

**Table D10 Hy's Law Laboratory Kit for Central Laboratories**

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

[a] HCV RNA; HCV DNA are only tested when IgG anti-HCV is positive or inconclusive
[b] CD-transferrin and Transferrin are not available in China. Study teams should amend this list accordingly

# D 7 REFERENCES

**Aithal et al, 2011**
Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

**FDA Guidance for Industry, July 2009**
FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation

# Appendix E Examples of Coadministered Drugs That Need Additional Consideration

The lists of drugs in Table E11, Table E12, and Table E13 are not exhaustive. Any questions about drugs not on this list should be addressed to the Study Physician of this study.

## Table E11 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 E12 CYP3A Inducers

| Strong inducers of CYP3A | Moderate inducers of CYP3A |
|---|---|
| Carbamazepine | Bosentan |

## Table E12 CYP3A Inducers

| Strong inducers of CYP3A | Moderate inducers of CYP3A |
|---|---|
| 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/DrugInteactionsLabeling/ucm093664.htm#inVivo. Accessed 23 July 2019.

## Table E13 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 described below.

## F 1 Female Participants 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 postmenopausal 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 postmenopausal 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 postmenopausal range for the institution.
- Women ≥50 years of age would be considered postmenopausal 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 participants of childbearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study intervention), and who intend to be sexually active with a nonsterilized male partner, must use ≥ 1 highly effective method of contraception (see Table F14) consistent with local regulations regarding the use of contraception for participants 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 participant 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 participant. Female participants should refrain from breastfeeding throughout this period.

## F 2 Male Participants with a Female Partner of Childbearing Potential

Non-sterilized male participants (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 participants 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 participants 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 participants must also use a highly effective method of contraception throughout this period (see Table F14).

## 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 F14. 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 F14 Highly Effective Methods of Contraception (<1% Failure Rate)

| Barrier/intrauterine methods | Hormonal methods |
|---|---|
| • Copper T intrauterine device<br>• Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a] | • Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®)<br>• Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®)<br>• Injection: Medroxyprogesterone injection (eg, Depo-Provera®)<br>• Combined pill: Normal and low dose combined oral contraceptive pill<br>• Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®)<br>• 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, will be recorded in the eCRF as specified in the SoA (Table 1).

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 G15. 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 G15 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.

## REFERENCE

**Pugh et al, 1973**
Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60(8):646-9.

# Appendix H Proton-pump Inhibitor Equivalence Table

Table H16 shows the PPI doses relating to evidence synthesis and recommendations in the original NICE clinical guidelines.

**Table H16 Proton-pump Inhibitor Doses Relating to Evidence Synthesis and Recommendations in the Original Guideline (CG17; 2004)**

| Proton-pump inhibitor | Full/standard dose | Low dose (on-demand) | Double dose |
|---|---|---|---|
| Esomeprazole | 20 mg[a] once daily | Not available | 40 mg[c] once daily |
| Lansoprazole | 30 mg once daily | 15 mg once daily | 30 mg[b] twice daily |
| Omeprazole | 20 mg once daily | 10 mg[b] once daily | 40 mg once daily |
| Pantoprazole | 40 mg once daily | 20 mg once daily | 40 mg[b] twice daily |
| Rabeprazole | 20 mg once daily | 10 mg once daily | 20 mg[b] twice daily |

[a] Lower than the licensed starting dose for esomeprazole in GERD, which is 40 mg, but considered to be dose-equivalent to other PPIs. When undertaking meta-analysis of dose-related effects, NICE classed esomeprazole 20 mg as a full-dose equivalent to omeprazole 20 mg.
[b] Off-label dose for GERD.
[c] 40 mg is recommended as a double dose of esomeprazole because the 20-mg dose is considered equivalent to omeprazole 20 mg.
GERD = gastroesophageal reflux disease; NICE = National Institute for Health and Care Excellence; PPI = proton-pump inhibitor.

Proton-pump inhibitors listed in Table H17 may be used more frequently in the ICU setting and are allowed on study.

**Table H17 Proton-pump Inhibitors Allowed in Intensive Care Unit**

| Medication | Route | Dose in the ICU |
|---|---|---|
| Esomeprazole | PO<br>NG or IV | 40 mg daily |
| Lansoprazole | PO<br>NG or IV | 15 or 30 mg daily |
| Omeprazole | PO<br>NG or IV | 20 to 40 mg daily |
| Pantoprazole | PO<br>NG or IV | 40 mg daily |

ICU = intensive care unit; IV = intravenously; NG = nasogastric; PO = orally.

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# Appendix I Abbreviations

| Abbreviation or special term | Explanation |
|---|---|
| $\lambda_z$ | terminal rate constant |
| AE | adverse event |
| AESI | adverse event of special interest |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| anti-HBc | antibody to hepatitis B core antigen |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{12h}$ | area under the concentration-time curve from 0 to 12 hours |
| $AUC_{0\text{-last}}$ | area under the concentration-time curve from 0 to last measurable time point |
| BCS | Biopharmaceutical Classification System |
| bid | twice daily |
| BSC | best supportive care |
| BTK | Bruton tyrosine kinase |
| CD | cluster of differentiation |
| CL/F | apparent oral clearance |
| CLL | chronic lymphocytic leukemia |
| $C_{max}$ | maximum observed concentration |
| CRP | C-reactive protein |
| CSP | clinical study protocol |
| CSR | clinical study report |
| CT | computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| COVID-19 | coronavirus disease 2019 |
| CYP | cytochrome P450 |
| DILI | drug-induced liver injury |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| eGFR | estimated glomerular filtration rate |
| FDA | Food and Drug Administration |
| $FiO_2$ | fraction of inspired oxygen |
| GCP | Good Clinical Practice |

| Abbreviation or special term | Explanation |
|---|---|
| HBsAg | hepatitis B surface antigen |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIPAA | Health Insurance Portability and Accountability Act |
| HL | Hy's Law |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICU | intensive care unit |
| IFNγ | interferon gamma |
| IEC | Independent Ethics Committee |
| IL | interleukin |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| MCP-1 | monocyte chemoattractant protein-1 |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCI | National Cancer Institute |
| NG | nasogastric |
| $PaO_2$ | partial pressure of oxygen |
| PCR | polymerase chain reaction |
| [redacted] | [redacted] |
| PHL | Potential Hy's Law |
| 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 |
| SRC | Safety Review Committee |
| SUSAR | suspected unexpected serious adverse reaction |
| $t_{1/2}$ | half-life |
| TBL | total bilirubin |

| Abbreviation or special term | Explanation |
|---|---|
| TLR | Toll-like receptor |
| $t_{max}$ | time to $C_{max}$ |
| TNFα | tumor necrosis factor alpha |
| ULN | upper limit of normal |
| Vz/F | apparent volume of distribution |

# Appendix J Protocol Amendment History

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

## Amendment 1 (25 June 2020)

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 Synopsis;<br>1.2 Schema (Figure 1);<br>4.1 Overall Design;<br>6.1.2 Dosing Instructions and Duration;<br>6.4 Study Intervention Compliance;<br>6.5.4 Acalabrutinib Drug-drug Interaction Guidance in the Presence of Life-threatening COVID-19 Infection | Specified that acalabrutinib will be given for 14 days (a maximum of 28 doses) instead of for 14 consecutive days (28 doses total). | Clarification | Non-substantial |
| 1.1 Synopsis;<br>3 Objectives and Endpoints;<br>8.1.1.2 Improvements on 9-point Category Ordinal Scale;<br>9.4.4.3 Time to Clinical Improvement on 9-point Ordinal Scale | Added a footnote to Table 8 in Section 8.1.1.2 to indicate that a score of zero on 9-point category ordinal scale will not be evaluated in this study. Removed zero from this endpoint in Sections 1.1, 3, and 9.4.4.3 | Clarification | Non-substantial |
| 1.3 Schedule of Activities (Table 1) | Changed the Screening column from “(Day -1 or Day 1) to “Day -3 to Day -1)”. Added footnote n to indicate that screening can be performed within 1-3 days prior to dosing; also clarified that ECG can be collected any time during the screening period. | Allow flexibility around timing of screening | Non-substantial |
| | Added a separate column for Day 1. Moved assessment time points for [redacted] | Clarification | Non-substantial |

| Section number and name | Description of change | Brief rationale | Substantial/ non-substantial |
|---|---|---|---|
| | [redacted] from Screening to Day 1. | | |
| | Revised footnote l to indicate that [redacted] | Clarification | Non-substantial |
| | Added footnote q to Table 1 to indicate that for all central laboratory assessments, sample collection windows of ± 1 day will be allowed for each of Days 4, 7, and 10. | Clarification | Non-substantial |
| 1.3 Schedule of Activities (Table 1);<br>8.1.1.1 Pulmonary Assessments to Evaluate Respiratory Failure | Added footnote p to Table 1 and text to Section 8.1.1.1 to clarify that arterial blood gases should be collected from participants if the sample is easily accessible and the procedure will not be painful to participants. Also stated that if collection of arterial blood gases is not clinically indicated, the test should not be performed. | Patient centricity, since taking arterial blood gases is painful | Non-substantial |
| 1.3 Schedule of Activities (Table 1);<br>8.2.2 Physical Examinations and Chest Imaging | Added footnote r in Table 1 and text in Section 8.2.2 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 enrollment). | Clarification | Non-substantial |
| 1.3 Schedule of Activities (Table 1);<br>8.2.3 Vital Signs | Added footnote s in Table 1 and text in Section 8.2.3 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 intervention should be used. | Clarification | Non-substantial |
| 1.3 Schedule of Activities (Table 1); | Revised footnote d in Table 1 and added text to Section 8.2.5.1 to indicate that hepatitis serology must | Clarification | Non-substantial |

| Section number and name | Description of change | Brief rationale | Substantial/ non-substantial |
|---|---|---|---|
| 8.2.5.1 Local Laboratory Tests | 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. | | |
| | Revised Table 1 to indicate that collection of fibrinogen, PT, aPTT, INR, and D-dimer to occur every other day while in the hospital. Added footnote o to Table 1 and text to Section 8.2.5.1 to specify that these laboratory tests, in addition to cardiac troponin I, should be performed more frequently if clinically indicated. Removed BNP assessment.<br>Also, stated in Section 8.2.5.1 that "Safety and CRP 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 |
| 2.2.3.2 Clinical Experience;<br>2.3.2 Benefit Assessment | Cited recent publications reporting activity of acalabrutinib and other BTK inhibitors in COVID-19. | Clarification | Non-substantial |
| 2.3.1 Risk Assessment | Clarified the risks associated with acalabrutinib and added a table showing frequency and time to onset of risks associated with acalabrutinib. In addition, updated subsections for hepatitis B reactivation, PML, and cytopenias. | Clarification | Non-substantial |
| 5.1 Inclusion Criteria | Inclusion Criterion 5: Removed "Percutaneous endoscopic gastrostomy tube will not be allowed." Added "percutaneous" to this inclusion criterion as follows: "Nasogastric tube or other types of oral or **percutaneous** gastric feeding tube; …" | Correction | Non-substantial |
| | Inclusion Criterion 8: Removed the body mass index and weight restriction. | Obesity is a comorbidity that has been associated with severe COVID-19 | Non-substantial |

| Section number and name | Description of change | Brief rationale | Substantial/ non-substantial |
|---|---|---|---|
| | | cases, which is the target population for this study | |
| 5.2 Exclusion Criteria | Exclusion Criterion 9: Revised hepatitis serology criteria. | Clarification | Non-substantial |
| | Exclusion Criterion 12: 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 17: Changed the BTK inhibitor washout period from 14 to 7 days prior to enrollment. | Based on the expected BTK re-synthesis rate in COVID patients, a washout period of 7 days is considered to be adequate in minimizing the effect on BTK occupancy of BTK inhibitors used prior to the current study | Non-substantial |
| 6.1.2 Dosing Instructions and Duration | Revised Section 6.1.2 and restructured with sub-headings for clarity. | Clarification | Non-substantial |
| 6.1.2.1 Dosing and Duration of Treatment | Added text to indicate that COCA-COLA® contains glucose and blood glucose levels of diabetic participants must be monitored as clinically indicated and blood glucose-lowering medications adjusted accordingly. | Clarification | Non-substantial |
| 6.1.2.2 Dosing of Participants Who are no Longer Intubated | For participants who are on PPIs and can swallow pills, changed volume of COCA-COLA from 240 mL to at least 100 mL. For participants not on PPIs and can swallow pills, removed volume (240 mL) of water and just stated that it should be taken with water. | 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/[redacted] | Non-substantial |

| Section number and name | Description of change | Brief rationale | Substantial/ non-substantial |
|---|---|---|---|
| 6.1.2.3 Missed Dosing Windows and Doses; 6.6 Dose Modification | Clarified text regarding missed windows and doses. | Clarification | Non-substantial |
| 6.5.2 Permitted Concomitant Therapy | Clarified BSC agents that will be permitted in this study. | Align with clinical treatment practices | Substantial |
| 6.5.3 Prohibited or Restricted Concomitant Therapy | Clarified that immunomodulatory drugs, intended as treatment for COVID-19 but not considered standard of care according to local institutional guidelines, are prohibited in the study through Day 28. Participants who are taking immunomodulatory drugs for other medical conditions (eg, tocilizumab for rheumatoid arthritis) may continue with treatment upon discussion with the Study Physician. | Clarification | Non-substantial |
| | Added language to indicate that BTK inhibitors other than acalabrutinib are prohibited through Day 14. | Clarification | Non-substantial |
| | Clarified that certain anticoagulants such as warfarin or equivalent vitamin K antagonists (eg, phenprocoumon) are prohibited in the study. Participants 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). | Clarification | Non-substantial |
| | Removed steroid treatment language. | Align with clinical treatment practices | Substantial |

| Section number and name | Description of change | Brief rationale | Substantial/ non-substantial |
|---|---|---|---|
| 6.5.4 Acalabrutinib Drug-drug Interaction Guidance in the Presence of Life-threatening COVID-19 Infection;<br>Appendix E Examples of Coadministered Drugs That Need Additional Consideration<br>(Table E13) | Removed ranitidine. | Removed from market | Non-substantial |
| 8.2.5.2 Central Laboratory Tests | Added text to indicate that PK, [redacted] are considered Tier 1 and should not be missed. The site must follow the SoA. Additional minor edits were made to this section. | Clarification | Non-substantial |
| 8.3.7 Disease progression | Removed “respiratory illness”. | Clarification | Non-substantial |
| B2 Definitions of Serious Adverse Event | Provided full URL for CTCAE v5.0. | Correction | Non-substantial |

anti-HBc = hepatitis B core antibody; aPTT = activated partial thromboplastin time; BNP = brain natriuretic peptide; BSC = best supportive care; BTK = Bruton tyrosine kinase; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalized ratio; [redacted] PK = pharmacokinetics; PML = progressive multifocal leukoencephalopathy; PT = prothrombin time; SoA = Schedule of Activities.

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