2. SYNOPSIS

Study center(s)

This was a multicenter study that enrolled patients at a total of 4 study centers in Brazil.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Objectives and Outcome Variables

Objective		Outcome variable
Priority	**Description**	**Description**
Primary	To characterize the PK of acalabrutinib and its active metabolite (ACP-5862) following administration of acalabrutinib suspension, when coadministered with a PPI, in patients 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.
Primary	To assess the safety and tolerability of acalabrutinib suspension in patients 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	To evaluate the preliminary efficacy of adding acalabrutinib suspension to BSC for treatment of patients with COVID-19	• Proportion of patients alive and free of respiratory failure at Days 14 and 28 • For the purpose of this study, respiratory failure is defined based on resource utilization of any of the following modalities: ° Endotracheal intubation and mechanical ventilation ° Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5) ° Noninvasive positive pressure ventilation or continuous positive airway pressure ° Extracorporeal membrane oxygenation • Percent change from baseline in CRP (time frame: baseline, Days 3, 5, 7, 14, 28) • 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

Objective		Outcome variable
Priority	**Description**	**Description**
[redacted]		

[a] The exploratory objectives and endpoints are not reported in this clinical study report; they may be described in a separate report and/or included as part of a publication.

AE = Adverse event; AUC_{12h} = Area under the concentration-time curve from 0 to 12 hours; 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]

Study design

This was an open-label, multi-dose, Phase Ib study to evaluate the pharmacokinetics (PK), safety, and tolerability of acalabrutinib suspension, when coadministered with a proton-pump inhibitor (PPI), in patients with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection requiring hospitalization due to respiratory failure attributable to coronavirus disease 2019 (COVID-19) pneumonia and who had a nasogastric (NG) tube in place.

In addition to receiving best supportive care (BSC), patients received acalabrutinib suspension (ie, acalabrutinib 100 mg suspension in degassed COCA-COLA® delivered via NG tube) twice daily (bid) for 14 days (a maximum of 28 doses).

For the purpose of this study, BSC was per discretion of the investigator and institutional guidelines. Standard NG tubes supplied by the hospital were used. Nasogastric tube placement in the stomach was confirmed by chest x-ray.

To assess the effect of PPIs, all patients must have been receiving treatment with a PPI at the start of the study. Treatment with a PPI could begin at any time prior to enrollment, provided patients had received PPI treatment for at least 24 hours prior to the first dose of acalabrutinib suspension.

Blood samples for plasma PK assessment of acalabrutinib and its metabolite (ACP-5862) were collected pre-dose and at 0.5, 1, 2, 4, 6, and 12 hours following treatment with acalabrutinib suspension. Safety assessments, including adverse event (AE) reporting, were performed through 28 (± 3) days after the last dose of the acalabrutinib suspension.

Target subject population and sample size

The target population for this study was adult patients (age ≥ 18 years) with SARS-CoV-2 confirmed by polymerase chain reaction test or other commercial or public health assay in any specimen, and evidence of respiratory failure attributable to COVID-19 pneumonia. Patients were to have confirmed placement of an NG tube or other type of oral or percutaneous gastric feeding tube and to have received treatment with PPIs. Approximately 20 patients were to be included in the study to ensure at least 16 patients were evaluable. Patients were considered evaluable if they had an evaluable PK profile, ie: (1) had completed PK Visit 2 assessments; (2) had received active treatment; and (3) did not have unavailable or incomplete data that may have influenced the PK analysis.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Treatment with acalabrutinib suspension (ie, acalabrutinib 100 mg suspension in degassed COCA-COLA delivered via NG tube) commenced on Day 1. All patients must have received PPI treatment for ≥ 24 hours prior to the first dose of acalabrutinib suspension. All patients received acalabrutinib suspension bid, approximately 12 hours apart, for 14 days (a maximum of 28 doses).

The following batch numbers of acalabrutinib were used: [redacted] and [redacted]

Duration of treatment

Acalabrutinib treatment was to be taken bid for 14 days (a maximum of 28 doses).

Statistical methods

Pharmacokinetics

A listing of PK blood sample collection times as well as derived sampling time deviations was provided. Plasma acalabrutinib and ACP-5862 concentrations and the following PK parameters were summarized for the PK Analysis Set (all patients who received ≥ one dose of acalabrutinib and had ≥ one post-dose evaluable PK data point for acalabrutinib) using appropriate descriptive statistics:

- Primary PK parameters: area under the concentration-time curve from 0 to 12 hours (AUC_{12h}), area under the concentration-time curve from time 0 to last measurable time point (AUC_{last}), and maximum observed concentration (C_{max}).

- Secondary PK parameters: half-life, time to C_{max}, and terminal rate constant (acalabrutinib and ACP-5862); apparent oral clearance and apparent volume of distribution (acalabrutinib); and C_{max}, AUC_{last}, and AUC_{12h} (metabolite to parent ratio).

Safety

Safety assessments consisted of monitoring and recording of AEs, serious adverse events (SAEs), and AEs leading to discontinuation of study intervention; measurement of protocol-specified vital signs, electrocardiogram, laboratory variables and other protocol-specified safety tests or measurements. All safety analyses were performed on the Safety Analysis Set (ie, all patients who received ≥ one dose of acalabrutinib). Treatment-emergent AEs were summarized, unless otherwise specified. Treatment-emergent AEs were defined as AEs starting, or ongoing AEs worsening, after the first dose of study intervention, and AEs with a start date up to the last dose of study intervention plus 28 (+ 3) days.

Efficacy

All efficacy analyses were performed on the Efficacy Evaluable Set (ie, all patients who received ≥ one dose of acalabrutinib). Formal statistical analyses (with generation of a p-value) were not performed for efficacy endpoints. For the proportion of patients alive and free of respiratory failure at Days 14 and 28, point estimates and their 90% confidence intervals were calculated. Summary statistics (n, mean, median, standard deviation (SD), minimum, and maximum) were presented for the percent change from baseline in C-reactive protein 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 was also analyzed using the Kaplan-Meier method.

Subject population

A total of 9 patients were enrolled into the study, all of whom received treatment. A total of 5 patients (55.6%) discontinued treatment; the most common reason for discontinuation of study treatment was AEs (3 of the 5 patients [60.0%]). In total, 7 patients (77.8%) completed the study; for both patients withdrawn from the study, the reason was death.

Summary of efficacy results

Due to the fact that the study terminated early and only 9 patients were enrolled, insufficient data were available to draw any meaningful conclusions relating to the efficacy endpoints.

Summary of pharmacokinetic results

The average exposures (AUC_{12h}, AUC_{last}, and C_{max}) of acalabrutinib were consistent between Day 1 (PK Visit 1) and Day 2 (PK Visit 2) but lower on Day 5 (PK Visit 3), although there was a large overlap in individual exposures across visits. Lower plasma concentrations

observed in 2 of the 7 patients (Patients PPD and PPD) contributed substantially to the reduced exposures on Day 5. A similar trend was noted for ACP-5862 with average exposures lower on Day 5 relative to Day 2.

Overall, the exposures of acalabrutinib and ACP-5862 observed in the current study appeared consistent with PK data in patients with hematological malignancies who received acalabrutinib 100 mg bid (Study ACE-CL-001). These results are also consistent with those observed in healthy subjects (Study D822FC00004).

Summary of safety results

For the 9 patients in this study, the mean actual duration of exposure was 10.0 days (SD: 5.2 days), the mean average daily dose was 185.32 mg, and the mean percentage of intended dose received was 65.48% (SD: 33.12%). The actual daily dose received ranged from 100 to 300 mg, while the average daily dose ranged from 164.7 to 200.0 mg. Five patients (55.6%) had interruptions to their study treatment (3 patients (33.3%) with one interruption, one patient (11.1%) with 3 interruptions, and one patient (11.1%) with 7 interruptions); the reasons for the interruptions were given as either AE or other.

All 9 patients had experienced at least one AE during the study. Most patients (8 patients [88.9%]) had at least one AE of Common Terminology Criteria for Adverse Events (CTCAE) Grade $\geq$ 3 and 5 patients (55.6%) had at least one SAE. One patient (Patient PPD had an SAE (pulmonary embolism), a CTCAE Grade 3 AE that led to discontinuation of treatment (abdominal distension), and an AE with an outcome of death (PPD . The majority of patients (66.7%) had an AE that either resulted in a dose interruption or in discontinuation of study treatment.

The most commonly reported AEs (reported by more than 3 patients) were anemia (reported by 5 patients [55.6%]) and pneumonia bacterial (reported by 3 patients [33.3%]).

In total, 2 patients (22.2%) died during the study: for one patient (Patient PPD death was related to the disease under investigation only; for the other patient (Patient PPD PPD death was related to disease under investigation and an AE with outcome of death (PPD , which was not considered to be causally related to investigational product (IP). The only SAE that occurred in more than one patient was pneumonia bacterial (2 patients [22.2%]). One patient (Patient PPD had an SAE that was considered to be causally related to IP (transaminases increased). Only one preferred term (PT; anemia) was reported at CTCAE Grade 3 or higher for more than 2 patients. No PTs were reported as leading to discontinuation in more than one patient. One patient (Patient PPD had a fatal event of clinical interest of pneumonia bacterial (CTCAE Grade 5); none of the other event of clinical interests reported were considered to be a cause for concern and no trends were observed; no AEs of special interest were reported during the study.

There were no clinically significant events seen in clinical laboratory, vital signs and other observations during this study.

Conclusion(s)

The COVID-19 pandemic was not judged to have meaningfully impacted the overall conclusions of this study.

- The systemic exposures (AUC_{12h}, AUC_{last}, and C_{max}) of acalabrutinib and ACP-5862 observed in the current study were generally consistent with PK data in patients with hematological malignancies following an acalabrutinib 100 mg bid regimen. Overall, these results support the evaluation of 100 mg acalabrutinib delivered as a suspension via nasogastric tube, co-administered with a PPI, in COVID-19 patients.
- No new safety signals were observed during this study; the AEs reported were consistent with the acalabrutinib safety profile and/or with COVID infections.