2. SYNOPSIS

Study center(s)

This was a multicenter study that randomized patients at a total of 39 study centers in 12 countries: Argentina, Brazil, Chile, France, India, Italy, Japan, Mexico, Peru, Russian Federation, South Africa, and Turkey.

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	The overall objective of the study is to evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	Proportion of patients alive and free of respiratory failure at Day 14 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

Objective		Outcome variable
Priority	**Description**	**Description**
Secondary	To evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	• Proportion of patients alive and free of respiratory failure (as defined above) at Day 28 • Percent change from baseline in CRP (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • Change from baseline in ferritin (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • Change from baseline in absolute lymphocyte counts (time frame: baseline, Days 3, 5, 7, 10, 14, 28) • All-cause mortality at Day 90 • Proportion of patients alive and discharged from the ICU at Days 14 and 28 • Time from randomization to first occurrence of respiratory failure or death on study (up to 28 days after randomization) due to any cause • Number of days alive and free of respiratory failure from randomization to 28 days after randomization • Number of days with respiratory failure from randomization to 28 days after randomization • Number of days hospitalized from randomization to 28 days after randomization • Number of days in ICU (length of stay) from randomization to 90 days after randomization • Number of days alive outside of hospital from randomization to 28 days after randomization • Number of days alive outside of hospital from randomization to 90 days after randomization • Relative change from baseline in oxygenation index (SpO_2/FiO_2) to Days 3, 5, 7, and 10 • Time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale through Day 28 • Time to $SpO_2 > 94\%$ on room air
Secondary	To evaluate the safety of acalabrutinib in patients with COVID-19 when administered with BSC	Type, frequency, severity, and relationship to study treatment of any TEAEs or abnormalities of laboratory tests, SAEs, or AEs leading to discontinuation of study treatment.
Secondary	To assess PK of acalabrutinib and its active metabolite in patients with COVID-19 when administered with BSC	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points. PK parameters (eg, AUC and C_{max}) estimated, as appropriate.

Objective		Outcome variable
Priority	**Description**	**Description**
Exploratory [a]	CCI [redacted]	

[a] The exploratory objectives and endpoints are not reported in this CSR; they will be described in a separate report, which will be included as an appendix.

ACP-5862 = Active metabolite of acalabrutinib; AE = Adverse event; AUC = Area under the concentration-time curve; BSC = Best supportive care; CCI [redacted] C_{max} = Maximum observed concentration; COVID-19 = Coronavirus disease 2019; CRP = C-reactive protein; CSR = Clinical study report; FiO_2 = Fraction of inspired oxygen; ICU = Intensive care unit; CCI [redacted]; PK = Pharmacokinetic(s); SAE = Serious adverse event; SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2; SpO_2 = Oxygen saturation; TEAE = Treatment-emergent adverse event; CCI [redacted]

Study design

This was a multicenter, randomized, open-label, Phase II study to evaluate the efficacy and safety of acalabrutinib plus best supportive care (BSC) versus BSC in patients with coronavirus disease 2019 (COVID-19; severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) who were hospitalized.

Patients were randomly assigned (1:1) to receive one of the following 2 treatments:

- Arm 1: Acalabrutinib 100 mg bis in die (BID [twice daily]) × 10 days + BSC (n = 70, planned)
- Arm 2: BSC alone (n = 70, planned)

For the purpose of this study, BSC was per discretion of the investigator and institutional guidelines. However, refer to Section 5.2 and Section 6.5.3 of the Study protocol for prohibited or restricted concomitant therapy. Patients were randomized based on the following stratification factors, which were considered prognostic factors for poor outcome:

- Age (≥ 65 vs < 65 years)

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

Target subject population and sample size

The target population for this study was adult patients (age ≥ 18 years) with confirmed infection with SARS-CoV-2 per World Health Organization criteria within 7 days of randomization and COVID-19 pneumonia requiring hospitalization. Patients unable to swallow pills were to be excluded from the study (ie, patients with respiratory failure at the time of screening due to COVID-19 pneumonia, which would impede their ability to swallow pills; or patients who, in the opinion of the treating physician, were likely to require mechanical ventilation within the immediate 24 hours and would, therefore, be unable to swallow pills).

The planned total number of patients in the study was approximately 140. Patients who met the eligibility criteria were to be randomized in a 1:1 ratio to either Arm 1 (acalabrutinib plus BSC; n = 70) or Arm 2 (BSC; n = 70). In total, 177 patients were randomized.

It was assumed that the proportion of patients who were alive and free of respiratory failure at Day 14 would be 70% under BSC. A targeted difference of 20% between the 2 treatment arms (ie, 90% for acalabrutinib plus BSC) was of clinical interest. With a total sample size of 140, the study had approximately 85% power, with a 2-sided type I error of 0.05, to detect a difference of 20% between the 2 arms.

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

Acalabrutinib treatment was to be administered within 6 hours of randomization on Day 1 and acalabrutinib 100 mg capsules were to be taken orally, BID, with water. The capsules were to be swallowed intact. Acalabrutinib could be taken with or without food. Retreatment with acalabrutinib was not allowed.

Patients on concomitant proton-pump inhibitors were to take acalabrutinib with at least 100 mL of COCA-COLA® at room temperature. Blood glucose levels of diabetic patients were to be monitored as clinically indicated and blood glucose-lowering medications adjusted accordingly.

BSC was administered in both arms per investigator's discretion and institutional guidelines, taking into account protocol defined prohibited or restricted concomitant therapy.

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

Duration of treatment

Acalabrutinib treatment was to be taken BID for 10 days (a maximum of 20 doses).

Statistical methods

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

For patients randomized to Arms 1 or 2, efficacy data were summarized for the full analysis set (FAS) population, which was defined as all patients who were randomized, to be analyzed according to the arm to which they were randomly assigned, following the 'intent-to-treat' principle. An estimate of the primary endpoint, the proportion of patients who were alive and free of respiratory failure at Day 14 and its 95% confidence interval (CI) (using Wald method with continuity correction) was calculated for each treatment arm. The Cochran-Mantel-Haenszel $\chi 2$ test stratified by age (≥ 65 vs < 65 years) and comorbidities (present vs absent) was used to compare the proportion of patients who were alive and free of respiratory failure at Day 14 between the 2 treatment arms. An unstratified analysis was also performed. Finally, the difference in the proportion of patients who were alive and free of respiratory failure at Day 14 was also provided with 95% CIs.

Safety data were summarized for the treated population (safety analysis set) and were based on the treatment they actually received. If a patient received at least 1 dose of acalabrutinib, the patient was considered as acalabrutinib-treated, regardless to which arm the patient was randomized. Safety assessments consisted of monitoring and recording adverse events (AEs), serious adverse events (SAEs), and AEs leading to discontinuation of study treatment; measurements of protocol specified hematology, clinical chemistry, and other laboratory variables; measurement of protocol specified vital signs; and other protocol specified tests that were deemed critical to the safety evaluation of the study treatment.

Subject population

A total of 236 patients were enrolled into the study and, of these, 59 patients were not randomized (54 patients were screen failures, 3 patients withdrew from the study, 1 patient died, and 1 patient was withdrawn by the decision of a physician). Of the 236 patients enrolled into the study, 89 patients (37.7%) were randomized to acalabrutinib plus BSC (Arm 1) and 88 patients (37.3%) to BSC alone (Arm 2); only patients in Arm 1 received study treatment

(acalabrutinib). All but 3 of the randomized patients in Arm 1 (86 patients [96.6%]) received study treatment. No patients remained on treatment at the time of analysis.

A total of 19 patients (22.1%) who received study treatment in Arm 1 discontinued treatment with acalabrutinib. The most common reasons for discontinuation of study treatment were inability to swallow pills (6 of the 19 patients [31.6%]) and AEs (5 of the 19 patients [26.3%]; respiratory failure [reported for 2 patients], and atrial fibrillation, hypertensive crisis and transaminases increased [each reported for 1 patient]).

In total, 151 of the 177 randomized patients (85.3%) completed the study, 74 patients (83.1%) in Arm 1 and 77 patients (87.5%) in Arm 2. Of the patients who terminated the study, the majority (17 of the 26 patients [65.4%]) were due to death.

Summary of efficacy results

Based on the FAS, the percentage of patients alive and free of respiratory failure at Day 14 was similar in the 2 treatment arms (74 patients [83.1%] in Arm 1 and 80 patients [90.9%] in Arm 2); the difference between the 2 arms (Arm 1 – Arm 2) was not statistically significant (-7.8%; 95% CI: -18.7, 3.2). The lack of a statistically significant difference between the 2 treatment arms was supported by the sensitivity analysis in patients without respiratory failure at baseline (difference between the 2 arms of -4.8%; 95% CI: -14.8, 5.1).

There was no statistically significant difference between the 2 treatment arms in the percentage of patients alive and free of respiratory failure at Day 28 (difference between the 2 arms of -4.4%; 95% CI: -15.6, 6.8). Again, these results were supported by the sensitivity analysis, for patients without respiratory failure at baseline (difference between the 2 arms of -1.3%; 95% CI: -11.6, 9.0).

At Day 28, most patients in both arms had an ordinal scale score of ≤ 4 (67 of the 76 patients [88.2%] in Arm 1 and 73 of the 82 patients [89.0%] in Arm 2), which equates to an improvement in oxygenation status (no ventilation or high flow oxygen required); there was no clinically significant difference between the percentage of patients with low scores (0 or 1, equating to no limitation of activities or uninfected) in Arm 1 (72.4%) compared with Arm 2 (72.0%).

Summary of safety results

For the 86 patients in Arm 1 who received study treatment, the mean actual duration of exposure was 9.0 days (standard deviation [SD]: 3.0 days), the mean average daily dose was 184.00 mg, and the mean percentage of intended dose received was 85.47% (SD: 30.47%). The actual daily dose received ranged from 100 mg to 300 mg, while the average daily dose ranged from 100.0 mg to 200.0 mg. Five patients (5.8%) each had 1 interruption to their study treatment (2 due to patients forgetting to take the dose, 1 due to an AE, 1 due to ‘other’ [the

nurse not giving the drug to the patient], and 1 due to the patient not able to swallow the tablet).

A higher percentage of patients in Arm 1 reported at least 1 AE (43 patients [50.0%]) compared with Arm 2 (37 patients [40.7%]). Most AEs were non-serious and either mild or moderate in severity (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 or 2). In Arm 1, 5 patients (5.8%) had an AE leading to discontinuation of study treatment; for 2 of these 5 patients, the AE leading to discontinuation was serious.

The most commonly reported AEs (reported by 4 or more patients) in Arm 1 were headache (10 patients [11.6%]; 2 patients [2.2%] in Arm 2) and asthenia (4 patients [4.7%]; no patients in Arm 2). The most commonly reported AEs in Arm 2 were diarrhea (5 patients [5.5%]; 2 patients [2.3%] in Arm 1) and hypertension (4 patients [4.4%]; 1 patient [1.2%] in Arm 1). In Arm 1, the only AE considered by the investigator to be possibly related to investigational product (IP; acalabrutinib) in more than 1 patient was headache (2 patients [2.3%]).

In total, 17 patients died during the study: for 4 patients (4.5%) in Arm 1 and 7 patients (8.0%) in Arm 2, the death was related to the disease under investigation only; 3 patients in Arm 1 and 2 patients in Arm 2 died due to the disease under investigation and a fatal AE (cardiac arrest, respiratory failure, and sepsis in Arm 1; and chronic obstructive pulmonary disease and septic shock in Arm 2). For the remaining patient (1 patient [1.1%] in Arm 1) the death was related to a fatal AE (respiratory failure). No fatal AE reported as the primary cause of death was considered to be causally related to IP; the investigator considered that there was a reasonably possibility that the secondary cause of death for Patient PPD (pneumonia) was causally related to IP. The only SAEs reported for more than 1 patient in either treatment arm were pneumonia (2 patients [2.3%] in Arm 1; no patients in Arm 2) and respiratory failure (2 patients [2.3%] in Arm 1; no patients in Arm 2). Two patients (2.3%) had an SAE that was considered to be causally related to IP (mucosal infection and pneumonia). No preferred term (PT) was reported at CTCAE Grade 3 or higher for more than 2 patients in either treatment arm; only 1 PT (respiratory failure) was reported as leading to discontinuation for more than 1 patient.

In total, 23 patients (26.7%) in Arm 1 and 17 patients (18.7%) in Arm 2 had at least 1 event of clinical interest (ECI) during this study; there were no trends observed and none of the ECIs reported were considered to be a cause for concern. In total, 8 patients (9.3%) in Arm 1 had at least 1 ECI considered to be causally related to IP. No AEs of special interest were reported in either treatment arm during this study.

There were no clinically significant events seen in clinical laboratory, vital signs and other observations across either treatment arm.

Conclusion(s)

- Addition of acalabrutinib to BSC did not improve the proportion of patients alive and free of respiratory failure at Day 14 or at Day 28.
- Sensitivity analysis of Day 14 and Day 28 data in patients without respiratory failure at baseline did not change study outcome.
- Median time to clinical improvement was similar in the 2 treatment arms.
- Patient oxygenation status qualitatively improves over time in both arms, but interpretation is difficult given imbalances in baseline characteristics across the 2 arms; specifically the percentage of patients with at least 2 comorbidities at baseline.
- No new safety signals were observed during this study; the AEs reported were consistent with the acalabrutinib safety profile and/or with COVID infections.