AstraZeneca

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

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomic and Therapeutic Class
AZ	AstraZeneca
BID	Twice a day
BMI	Body Mass Index
BP	Blood Pressure
BSC	Best supportive care
CI	Confidence Interval
CNS	Central Nervous System
CRP	C-reactive Protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for AEs
CTMS	Clinical Trial Management System
DMC	Data Monitoring Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECI	Events of Clinical Interest
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form

FAS	Full Analysis Set
FiO_2	Fraction of Inspired Oxygen
ICU	Intensive Care Unit
IPD	Important Protocol Deviation
IRT	Immune Response Technology
ITT	Intention-to-treat
KM	Kaplan-Meier
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mSOFA	Modified Sequential Organ Failure Assessment
PID	Percentage of intended dose
PD	Pharmacodynamic
PK	Pharmacokinetic
PKAS	Pharmacokinetic Analysis Set
PPAS	Per-Protocol Analysis Set
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
SpO_2	Oxygen Saturation
TEAE	Treatment Emergent Adverse Event
WHO-DD	World Health Organization-Drug Dictionary

AMENDMENT HISTORY

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
Primary and secondary endpoints	27 July 2020	Added secondary endpoints for time to clinical improvement and time to $SpO_2 > 94\%$ on room air.	Y (v5.0)	Emerging as important endpoints in the assessment of COVID-19.
	27 July 2020	Updated formula used for oxygenation index.	Y (v5.0)	Clarification based on study assessments.
	27 July 2020	Reduced PK analyses.	Y (v5.0)	Align with reduced data collection in SoA.
Statistical analysis method for primary or secondary endpoints	27 July 2020	Updated confidence interval method from Blyth-Still-Casella to Wald with continuity correction.	Y (v5.0)	Align with comparator studies.
	27 July 2020	Updated confidence interval from 90% to 95%.	Y (v5.0)	Typo in previous version.
	27 July 2020	Added detail on primary analysis and multiplicity adjustment of the overall Type I error for the primary analysis to account for the added interim efficacy analysis.	Y (v5.0)	For clarity and to preserve statistical rigor.
	05 August 2020	Removed language "Formal statistical analysis (with generation of a p-value) will not be undertaken for these endpoints."	NA	P-values will be generated for the primary and key secondary efficacy endpoints to support possible regulatory interactions.
	28 August 2020	Added respiratory failure status at baseline as a subgroup analysis for the primary endpoint	NA	Changes to eligibility criteria throughout CSP amendments mean that some patients may have respiratory failure at baseline.
Derivation of primary or secondary endpoint	27 July 2020	Updated imputation rules for missing or partial AE and CM dates.	NA	Accommodate all possible scenarios for programming purposes.
	27 July 2020	Updated derivation of exposure variables.	NA	Accommodate limitations in data collection.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
	27 July 2020	Updated safety follow-up timepoint for BSC alone arm to 38 (+3) days after randomization.	Y (v5.0)	Align more closely with timing of safety follow-up for Acalabrutinib + BSC arm.
	27 July 2020	Updated visit windows.	Y (v5.0)	Accommodate changes to the SoA and for clarity.
	27 July 2020	Added derivation of BSC from the eCRF.	NA	Clarification.
	27 July 2020	Updated the details of the AESI and ECI definitions.	NA	To align with study-specific requirements.
	27 July 2020	Added that the primary efficacy endpoint at Day 14 and equivalent secondary endpoint at Day 28 will be restricted to subjects who have had the opportunity for follow-up.	NA	To reduce bias and for clarification.
	27 July 2020	Added that proportions, difference and CIs for the primary efficacy endpoint at Day 14 and equivalent secondary endpoint at Day 28 will also be reported in the FAS excluding subjects who have withdrawn or been lost to follow-up prior to Day 14 and Day 28, respectively.	NA	Clarification.
	30 July 2020	Added details on the derivation of hospital or ICU stay for each endpoint requiring this information.	NA	Clarification.
	27 August 2020	Removed derivation of FiO_2 for a Venturi mask and added the derivation of FiO_2 for a simple mask. Also clarified FiO_2 units are %.	NA	Changes in data collection method
	27 August 2020	Removed language on not including all AE entries in the table summaries.	NA	Changes in data collection method.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
	28 August 2020	Updated definition of baseline and visit windows for all variables.	NA	Previous definitions could not be accurately derived due to limited data collection.
	07 September 2020	Added further detail on imputing start day and month for partial AE or CM dates.	NA	Clarification.
	09 September 2020	Corrected rules for handling withdrawn of LTFU subjects when deriving the endpoint "Days in ICU over the course of 90 days".	NA	Typo.
	30 September 2020	Added details on oxygenation index formula and FiO2 imputation for subjects not on any oxygen or mechanical ventilation.	NA	Clarification.
Data presentations	27 July 2020	Removed weight categories from demographic summary tables.	NA	Not required for interpretation (continuous summary statistics are sufficient).
	27 July 2020	Updated list of pre-specified AE summaries.	NA	Clarification.
	27 July 2020	Removed percent change summary and added line graph of mean change from baseline for secondary lab and oxygenation index endpoints.	NA	Typo in previous version.
	27 August 2020	Added details on additional oxygen and mechanical ventilation summaries.	NA	To allow for clearer interpretation of the data.
	27 August 2020	Added details on additional ordinal scale summaries.	NA	To allow for clearer interpretation of the data.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
	27 August 2020	Added a summary of the proportion of subjects who experienced respiratory failure or died over the course of 28 days.	NA	To allow for clearer interpretation of the data and to align with DMC charter.
	30 September 2020	Added a summary of the proportion of subjects who required invasive ventilation or ECMO over the course of 28 days.	NA	Emerging as important summary in the assessment of COVID-19.
	30 September 2020	Updated table categories for days with respiratory failure, days hospitalized and days in ICU.	NA	Distinguish between subjects with no occurrences and those with at least one.
	30 September 2020	Replaced 'histogram' with 'bar chart' for summaries of days with respiratory failure, days in ICU and days hospitalized.	NA	Clarification.
Other	27 July 2020	Reduced the list of important protocol deviations.	NA	To accommodate ongoing changes in BSC and guidelines.
	27 July 2020	Updated timings and scope of iDMC reviews.	Y (v5.0)	Due to projected rapid enrolment and for transparency and to preserve the trial integrity.
	27 August 2020	Change 'iDMC' to 'DMC' throughout	N (v5.0)	External members added to the DMC (after CSP v5.0 was released) so it is no longer fully internal. This change is aligned with the DMC charter v4.0.
	07 September 2020	Updated list of outputs to be reviewed by the DMC.	NA	To align with the DMC charter v4.0.

Category: Change refers to	Date	Description of change	In line with the CSP?	Rationale
	07 September 2020	Added detail on total number of subjects randomized as this was known at the time of the SAP amendment.	NA	Transparency.
	30 September 2020	Updated list of outputs to be reviewed by the DMC.	NA	Transparency.

1. STUDY DETAILS

This statistical analysis plan (SAP) contains a more detailed description of the analyses in the clinical study protocol (CSP). This SAP is based on version 5 of the CSP.

This SAP will apply to the study to determine the efficacy and safety of acalabrutinib with best supportive care (BSC) versus BSC in subjects hospitalized with COVID-19. The target population for this study is adult subjects (age ≥18 years) with confirmed infection with SARS-CoV-2 per World Health Organization (WHO) criteria and COVID-19 pneumonia requiring hospitalization.

1.1 Study objectives

1.1.1 Primary objectives

The primary objectives for this study and the corresponding endpoints/variables are shown in Table 1.

Table 1   Primary objectives and endpoints

Primary Objectives	Primary Endpoints/Variables
To evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	Proportion of subjects alive and free of respiratory failure 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 ≥50%) • Non-invasive positive pressure ventilation or continuous positive airway pressure • Extracorporeal membrane oxygenation

1.1.2 Secondary objectives

The secondary objectives for this study and the corresponding endpoints/variables are shown in Table 2.

Table 2   Secondary objectives and endpoints

Secondary Efficacy Objectives	Secondary Efficacy Endpoints/Variables:

To evaluate the efficacy of adding acalabrutinib to BSC for the treatment of COVID-19	• Proportion of subjects alive and free of respiratory failure (defined above) at Day 28
	• Percent change from baseline in C-reactive protein (CRP) (time frame: baseline, Days 3, 5, 7, 10, 14, 28)
	• Change from baseline in ferritin (time frame: baseline, Days 3, 5, 7, 10, 14, 28)
	• Change from baseline in absolute lymphocyte counts (time frame: baseline, Days 3, 5, 7, 10, 14, 28)
	• All-cause mortality at Day 90
	• Proportion of subjects alive and discharged from the intensive care unit (ICU) at Days 14 and 28
	• Time from randomization to first occurrence of respiratory failure or death on study (up to 28 days after randomization) due to any cause
	• Number of days alive and free of respiratory failure from randomization to 28 days after randomization
	• Number of days with respiratory failure from randomization to 28 days after randomization
	• Number of days hospitalized from randomization to 28 days after randomization
	• Number of days in ICU (length of stay) from randomization to 90 days after randomization
	• Number of days alive outside of hospital from randomization to 28 days after randomization
	• Number of days alive outside of hospital from randomization to 90 days after randomization
	• Relative change from baseline in oxygenation index (SpO_2/FiO_2) (time frame: baseline, 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
Safety Objective	**Safety Endpoint/ Variable**
To evaluate the safety of acalabrutinib in subjects with COVID-19 when administered with BSC	Type, frequency, severity, and relationship to study treatment of any treatment-emergent adverse events (TEAEs) or abnormalities of

	laboratory tests, serious adverse events (SAEs), or adverse events (AEs) leading to discontinuation of study treatment
Pharmacokinetic (PK) Objectives	**PK Endpoints/Variables**
To assess PK of acalabrutinib and its active metabolite in subjects with COVID-19 when administered with BSC	Summarized plasma concentrations of acalabrutinib and ACP-5862 at specified time points. Pharmacokinetic parameters (e.g., AUC and C_{max}) estimated, as appropriate.

1.1.3 Exploratory objectives

The exploratory objectives for this study and the corresponding endpoints/variables are shown in Table 3.

Table 3   Exploratory objectives and endpoints

Exploratory Objectives	Exploratory Endpoints/Variables
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1.2 Study design

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

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

- Arm 1: Acalabrutinib 100 mg twice a day (bid) x 10 days + BSC (n=70)
- Arm 2: BSC alone (n=70)

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

- Age (≥ 65 vs < 65 years)

- Comorbidities (present vs absent). "Present" is defined as having at least 1 of the following comorbidities:

  – Cardiovascular disease, as defined by either heart failure New York Heart Association class ≥2 or hypertension requiring treatment
  – Diabetes mellitus requiring treatment
  – Chronic obstructive pulmonary disease or asthma requiring treatment
  – Current active solid tumor or hematologic malignancy

1.3 Number of subjects

The planned total number of subjects in this study is approximately 140. One hundred and forty (140) subjects meeting the eligibility criteria will be randomized in a 1:1 ratio to either Arm 1 (acalabrutinib plus BSC; n=70) or Arm 2 (BSC; n=70).

It is assumed that the proportion of subjects who are alive and free of respiratory failure at Day 14 is 70% under BSC. A targeted difference of 20% between two treatment arms (i.e., 90% for acalabrutinib + BSC) is of clinical interest. With a total sample size of 140, the study has approximately 85% power, with a 2-sided type I error of 0.05, to detect a difference of 20% between the 2 arms.

At the time that the SAP version 3.0 was generated (amendment of version 2.0), the study recruitment was complete with a total of 177 subjects randomized.

2. ANALYSIS POPULATION

2.1 Definition of analysis set

Four analysis sets are defined in this study. A summary of the analysis sets used for each outcome variable in provided in Table 4.

Table 4   Summary of outcome variables and analysis populations

Outcome variable	Analysis populations
Safety data	

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.	Safety analysis set
Exposure and dose intensity: actual treatment duration, percentage of intended dose (PID), average daily dose.	

Efficacy data

Proportion of subjects alive and free of respiratory failure at Day 14	Full analysis set and per-protocol analysis set
Proportion of subjects alive and free of respiratory failure at Day 28	Full analysis set
Percent change from baseline in C-reactive protein	Full analysis set
Change from baseline in ferritin	Full analysis set
Change from baseline in absolute lymphocyte counts	Full analysis set
All-cause mortality at Day 90	Full analysis set
Proportion of subjects alive and discharged from the intensive care unit (ICU) at Days 14 and 28	Full analysis set
Time from randomization to first occurrence of respiratory failure or death on study due to any cause	Full analysis set
Number of days alive and free of respiratory failure from randomization to 28 days after randomization	Full analysis set
Number of days with respiratory failure from randomization to 28 days after randomization	Full analysis set
Number of days hospitalized from randomization to 28 days after randomization	Full analysis set
Number of days in ICU from randomization to 90 days after randomization	Full analysis set
Number of days alive outside of hospital from randomization to 28 days after randomization	Full analysis set
Number of days alive outside of hospital from randomization to 90 days after randomization	Full analysis set

Relative change from baseline in oxygenation index (SpO_2/FiO_2)	Full analysis set
Time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale through Day 28	Full analysis set
Time to $SpO_2 > 94\%$ on room air	Full analysis set
Other data	
Disposition, demography and baseline characteristics: subject characteristics, medical history, relevant surgical history, concomitant medications, oxygen therapy and ventilator history, history of substance abuse, SARS-CoV-2 infection comorbidities and risk factors/lifestyle events	Full analysis set
PK data	PK analysis set
PD data	PK analysis set as appropriate

2.1.1 Full analysis set (Intention-to-treat (ITT) population)

The full analysis set (FAS) will include all subjects who are randomized and will be used for all efficacy analyses. Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Subjects who were randomized but did not subsequently go on to receive study treatment will be included in the analysis in the treatment arm to which they were randomized, following the "intent-to-treat" principle.

2.1.2 Per-protocol analysis set

The per-protocol analysis set (PPAS) will be a subset of the ITT population including only subjects without important detected protocol deviations affecting the efficacy endpoints. Subjects will be summarized according to the actual treatment received. The primary efficacy endpoint of the study will also be summarized for this population.

2.1.3 Safety analysis set

The safety analysis set (SAF) is based on the treatment subjects actually received. In this study, the treatment is either acalabrutinib + BSC or BSC only. If a subject receives at least 1 dose of acalabrutinib, the subject is considered as acalabrutinib-treated, regardless which arm the subject was randomized to. Subjects who do not receive any acalabrutinib will be summarized in the BSC group.

2.1.4 PK analysis set

The PK analysis set (PKAS) will include all subjects who receive ≥1 dose of acalabrutinib and had ≥1 post-dose evaluable PK data point for acalabrutinib or ACP-5862. The population will be defined by AstraZeneca, the pharmacokineticist and the statistician prior to any analyses being performed.

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2.2 Deviations

The following general categories will be considered important protocol deviations and will be programmatically derived from the eCRF data and entered into the Clinical Trial Management System (CTMS) by the monitor. These will be listed and discussed in the Clinical Study Report (CSR) as appropriate:

- Subjects randomized to the acalabrutinib + BSC arm but who did not receive any doses of acalabrutinib (Deviation 1)

- Subjects who deviate from key eligibility criteria per the CSP (Deviation 2)
  Inclusion criteria: 1, 3, 4
  Exclusion criteria: 1

- Subjects developed discontinuation criteria but have not been withdrawn from treatment (Deviation 3):

  o Pregnancy

Subjects who receive the wrong treatment at any time will be included in the SAF as described in Section 2.1. During the study, decisions on how to handle errors in treatment dispensing (with regard to continuation/discontinuation of study treatment or, if applicable, analytically) will be made on an individual basis with written instruction from the Global Study Lead and/or Statistician.

The important protocol deviations will be listed and summarized by randomized treatment group. None of the deviations will lead to subjects being excluded from the analysis sets described in section 2.1 (with the exception of the PK analysis set, if the deviation is considered to impact upon PK, and the PPAS).

The need for additional sensitivity analysis due to protocol deviations will be determined following review of the protocol deviations ahead of database lock and will be documented prior to the primary analysis being conducted.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Efficacy variables

3.1.1 Alive and free of respiratory failure at Day 14

The primary endpoint is the proportion of subjects who are 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:

- o Endotracheal intubation and mechanical ventilation;
- o Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates >20L/min with fraction of delivered oxygen ≥50%);
- o Non-invasive positive pressure ventilation or continuous positive airway pressure;
- o Extracorporeal membrane oxygenation.

Only the subject's survival status and respiratory-failure status on Day 14 will be considered for this endpoint. No visit window will be used for this endpoint. If they experience respiratory failure after randomization but recover by Day 14, per the definition above, they will be considered alive and free of respiratory failure at Day 14.

For the FAS analysis, subjects who withdraw or are lost to follow up prior to Day 14, thus survival status and respiratory status at Day 14 cannot be assessed, will be included in the denominator of this analysis as though they had died or had a respiratory failure.

For the PPAS analysis, subjects who withdraw or are lost to follow up prior to Day 14, thus survival status and respiratory status at Day 14 cannot be assessed, will be excluded from this analysis, hence the percentage for each treatment group will be calculated as:

$$\frac{\text{Number of subjects alive and free of respiratory failure at Day 14}}{\text{Number of subjects who have died or are still in the study at Day 14}} \times 100\%$$

To avoid a biased estimate of the proportion at interim analyses, the subjects included in this analysis (based on the FAS and PPAS definitions) will be restricted to subjects who reached Day 14 (or would have reached Day 14 had they not died, withdrawn or been lost to follow up) at the time the analysis. This will be considered the full analysis set evaluable at Day 14.

3.1.2 Alive and free of respiratory failure at Day 28

This is defined as the proportion of subjects who are alive and free of respiratory failure at Day 28. Respiratory failure is defined the same as specified in Section 3.1.1 above.

Only the subject's survival status and respiratory-failure status on Day 28 will be considered for this endpoint. No visit window will be used for this endpoint. If they experience respiratory failure after randomization but recover by Day 28, per the definition above, they will be considered alive and free of respiratory failure at Day 28.

For the FAS analysis, subjects who are lost to follow up prior to Day 28, thus survival status and respiratory status at Day 28 cannot be assessed, will be included in the denominator of this analysis as though they had died or had a respiratory failure.

For the PPAS analysis, subjects who are lost to follow up prior to Day 28, thus survival status and respiratory status at Day 28 cannot be assessed, will be excluded from this analysis, hence the percentage for each treatment group will be calculated as:

$$\frac{\text{Number of subjects alive and free of respiratory failure at Day 28}}{\text{Number of subjects who have died or are still in the study at Day 28}} \times 100\%$$

To avoid a biased estimate of the proportion at interim analyses, the subjects included in this analysis (based on the FAS and PPAS definitions) will be restricted to subjects who reached Day 28 (or would have reached Day 28 had they not died, withdrawn or been lost to follow up) at the time the analysis. This will be considered the full analysis set evaluable at Day 28.

3.1.3   Percent change from baseline in C-reactive protein

This is defined as the percent change from baseline in C-reactive protein (CRP) at Days 3, 5, 7, 10, 14 and 28. For this endpoint, baseline is defined as the observation on the date of randomization (Day 1). If no result was obtained on the date of randomization, the last result prior to the date of randomization will be used. Details on visit windows are provided in Section 4.1.

3.1.4   Change from baseline in ferritin

This is defined as the change from baseline in ferritin at Days 3, 5, 7, 10, 14 and 28. For this endpoint, baseline is defined as the observation on the date of randomization (Day 1). If no result was obtained on the date of randomization, the last result prior to the date of randomization will be used. Details on visit windows are provided in Section 4.1.

The percent change from baseline at these timepoints will also be derived.

3.1.5   Change from baseline in absolute lymphocyte counts

This is defined as the change from baseline in absolute lymphocyte counts at Days 3, 5, 7, 10, 14 and 28. For this endpoint, baseline is defined as the observation on the date of randomization (Day 1). If no result was obtained on the date of randomization, the last result prior to the date of randomization will be used. Details on visit windows are provided in Section 4.1.

The percent change from baseline at these timepoints will also be derived.

3.1.6   All-cause mortality at Day 90

This is defined as the proportion of subjects who have died due to any cause by Day 90.

If a subject is not known to have already died, they (or a caregiver/relative) will be contacted at Day 90 (± 7 days) to confirm survival status. If a subject is lost to follow-up or has

withdrawn consent to be followed-up at this timepoint, the survival status of the subject may be obtained by site personnel by checking publicly available resources (as applicable under local laws).

Subjects alive at Day 90 will be censored at Day 90 and subjects lost to follow-up (i.e. with unknown survival status at Day 90) will be censored at the last time known to be alive.

3.1.7   Alive and discharged from the ICU at Days 14 and 28

This is defined as the proportion of subjects alive and discharged from the ICU at Day 14 and the proportion of subjects alive and discharged from the ICU at Day 28.

For a subject to be considered discharged from the ICU, they must not be in ICU on Day 14 (or Day 28), regardless of whether or not ICU-standard care is reported as not clinically indicated in the CHCSS eCRF.

Only the subject's survival status and ICU status on Day 14 (or Day 28) will be considered for this endpoint. No visit window will be used for this endpoint. If they are admitted to ICU after randomization but are discharged by Day 14 (or Day 28), they will be considered alive and discharged from the ICU at Day 14 (or Day 28).

For the FAS analysis, subjects who withdraw or are lost to follow up prior to Day 14 (or Day 28), thus survival status and respiratory status at Day 14 (or Day 28) cannot be assessed, will be included in the denominator of this analysis as though they had died or had a respiratory failure.

For the PPAS analysis, subjects who withdraw or are lost to follow up prior to Day 14 (or Day 28), thus survival status and respiratory status at Day 14 (or Day 28) cannot be assessed, will be excluded from this analysis, hence the percentage for each treatment group will be calculated as:

$$\frac{\text{Number of subjects alive and free of respiratory failure at Day 14 (or Day 28)}}{\text{Number of subjects who have died or are still in the study at Day 14 (or Day 28)}} \times 100\%$$

To avoid biased estimates of the proportions at interim analyses should they be generated, the subjects included in this analysis (based on the FAS and PPAS definitions) will be restricted to subjects who reached Day 14 (or Day 28) (or would have reached Day 14 (or Day 28) had they not died, withdrawn or been lost to follow up) at the time the analysis. This will be considered the full analysis set evaluable at Day 14 (or Day 28).

3.1.8   Time to first occurrence of respiratory failure or death

This is defined as the time (in days) from randomization to the first occurrence of respiratory failure or death (due to any cause) on study (up to Day 28), whichever occurs first.

If a subject does not have an event (i.e., does not experience respiratory failure or death) on or before Day 28 and does not withdraw or become lost to follow up from the study prior to Day

28, the data will be censored at Day 28. If a subject does not have an event but withdraws from the study or is lost to follow up prior to Day 28, the data will be censored at the last date known that the subject was alive and free of respiratory failure up to Day 28.

Subjects with respiratory failure at baseline (defined as respiratory failure on the date of randomization (Day 1)) will not be included in any analyses of time to first occurrence of respiratory failure or death.

3.1.9 Days alive and free of respiratory failure over the course of 28 days

This is defined as the total number of days alive and free of respiratory failure from randomization to Day 28.

For a day to count as 'alive and free of respiratory failure', the subject must be free of respiratory failure for the entire day. All days from the start date to the stop date inclusive of each respiratory failure will count as respiratory failure days. If a subject dies on Day 1, the number of days alive and free of respiratory failure is zero. If a subject is alive on Day 28 and has not experienced respiratory failure at any point over the 28-day period, the number of days alive and free of respiratory failure is 28 days.

The following rules will be applied for missing data:

- If a subject has been discharged from hospital and is known to be alive at Day 28, and there is no evidence that respiratory failure has occurred during this period, the number of days from being discharged to Day 28 will be counted as days alive and free of respiratory failure. If a subject has been discharged from hospital but dies prior to Day 28 and there is no evidence that respiratory failure has occurred during this period, the number of days from being discharged to the last date known to be alive will be counted as days alive and free of respiratory failure.

- If a subject has been discharged from hospital but dies prior to Day 28 and there is evidence of respiratory failure during this period, the number of days from being discharged to the last date known to be free of respiratory failure will be counted as days alive and free of respiratory failure.

- If a subject withdraws from the study or is lost to follow up prior to Day 28, the days with unknown survival/respiratory failure status will be considered as follow:

    o If the subject is discharged from hospital at the time they withdraw from the study or are lost to follow up, days from last known status to Day 28 (or date last known to be alive if death is known, whichever occurs first) will be counted as days alive and free of respiratory failure.

    o If a subject is in hospital and is not experiencing respiratory failure at the time they withdraw from the study, days from last known status to Day 28 (or date

last known to be alive if death is known, whichever occurs first) will be counted as days alive and free of respiratory failure.

- o If the subject is in hospital and is experiencing respiratory failure at the time they withdraw from the study, days from last known status to Day 28 will be assumed as experiencing respiratory failure.

3.1.10 Days with respiratory failure over the course of 28 days

This is defined as the number of days with respiratory failure from randomization to Day 28.

The number of days with respiratory failure over the course of 28 days includes all respiratory failures within this 28-day period. All days from the start date to the stop date inclusive of each respiratory failure will count as respiratory failure days.

The following rules will be applied for missing data and deaths:

- Unless stated otherwise, if a subject dies (due to any cause) prior to Day 28, the number of days from death to Day 28 will be counted as days with respiratory failure.

- If a subject has been discharged from hospital and is known to be alive at Day 28, and there is no evidence that respiratory failure has occurred during this period, the number of days from being discharged to Day 28 will be assumed free of respiratory failure.

- If a subject has been discharged from hospital but dies prior to Day 28 and there is no evidence that respiratory failure has occurred during this period, the number of days from being discharged to the last date known to be alive will be assumed free of respiratory failure. The number of days from death to Day 28 will be counted as days with respiratory failure.

- If a subject has been discharged from hospital but dies prior to Day 28 and there is evidence of respiratory failure during this period, the number of days from being discharged to the last date known to be free of respiratory failure will be assumed free of respiratory failure. The number of days from the start of respiratory failure to Day 28 will be counted as days with respiratory failure.

- If a subject withdraws from the study or is lost to follow up prior to Day 28, the days with unknown respiratory failure status will be considered as follow:

  - o If the subject is discharged from hospital at the time they withdraw from the study or are lost to follow up, days from last known status to Day 28 (or date last known to be alive if death is known, whichever occurs first) will be assumed free of respiratory failure.

  - o If a subject is in hospital and is not experiencing respiratory failure at the time they withdraw from the study, days from last known status to Day 28 (or date

last known to be alive if death is known, whichever occurs first) will be assumed free of respiratory failure.

- o If the subject is in hospital and is experiencing respiratory failure at the time they withdraw from the study, days from last known status to Day 28 will be counted as days with respiratory failure.

3.1.11   Days hospitalized over the course of 28 days

This is defined as the number of days hospitalized from randomization to Day 28.

For a day to be counted as a hospitalized day in this endpoint, the investigator must confirm that hospitalization is clinically indicated. This information is recorded in the CHCSS eCRF each day the subject is hospitalized.

The number of days hospitalized over the course of 28 days includes any readmissions to hospital within this 28-day period. All days from the start date to the stop date inclusive of each hospital admission will count as hospitalized days.

The following rules will be applied for missing data and deaths:

- Unless stated otherwise, if a subject dies (due to any cause) prior to Day 28, the number of days from death to Day 28 will be counted as days hospitalized.

- If a subject withdraws from the study or is lost to follow up prior to Day 28, the days with hospitalization status will be considered as follow:

  - o If the subject is discharged from hospital at the time they withdraw from the study or are lost to follow up, days from last known status to Day 28 (or date last known to be alive if death is known, whichever occurs first) will be assumed free of hospitalization.

  - o If the subject is in hospital at the time they withdraw from the study, days from last known status to Day 28 will be counted as days hospitalized.

3.1.12   Days in ICU over the course of 90 days

This is defined as the number of days in ICU (length of stay) from randomization to Day 90.

For a day to be counted as an ICU day in this endpoint, the investigator must confirm that the subject is receiving ICU-standard care (or equivalent) and that ICU is clinically indicated. This information is recorded in the CHCSS eCRF each day the subject is receiving ICU-standard case. The number of days in ICU over the course of 90 days includes any readmissions to the ICU within this 90-day period. All days from the start date to the stop date inclusive of each ICU stay will count as ICU days.

The following rules will be applied for missing data and deaths:

- Unless stated otherwise, if a subject dies (due to any cause) prior to Day 90, the number of days from death to Day 90 will be counted as ICU days.

- If a subject has been discharged from hospital they will be assumed free of ICU.

- If a subject has been discharged from hospital but dies prior to Day 90 and there is no evidence of ICU admission during this period, the number of days from being discharged to the last date known to be alive will be assumed free of ICU. The number of days from death to Day 90 will be counted as ICU days.

- If a subject has been discharged from hospital but dies prior to Day 90 and there is evidence of ICU admission during this period, the number of days from being discharged to the last date known to be free of ICU will be assumed free of ICU. The number of days from ICU admission to Day 90 will be counted as ICU days.

- If a subject withdraws from the study or is lost to follow up prior to Day 90, the days with unknown ICU status will be considered as follow:

  o If the subject is not in ICU at the time they withdraw from the study or are lost to follow up, days from last known status to Day 90 (or date last known to be alive if death is known, whichever occurs first) will be assumed free of ICU.

  o If a subject is in ICU at the time they withdraw from the study, days from last known status to Day 90 (or date last known to be alive if death is known, whichever occurs first) will be counted as ICU days.

3.1.13   Days alive outside of hospital over the course of 28 days

This is defined as the number of days alive outside of hospital from randomization to Day 28.

For a day to be counted as outside of hospital, the subject must not be in hospital. If the subject is in hospital but hospitalization is recorded as not clinically indicated, this day will still be considered as a day in hospital and therefore will not be counted in this endpoint.

The following rules will be applied for missing data:

- If a subject withdraws from the study or is lost to follow up prior to Day 28, the days with unknown survival/hospitalization status will be considered as follow:

  o If the subject is discharged from hospital when they withdraw from the study or are lost to follow up, days from last known status to Day 28 (or date last known to be alive if death is known, whichever occurs first) will be counted as days alive and outside of hospital.

o If a subject is in hospital at the time they withdraw from the study, days from last known status to Day 28 will be assumed hospitalized days.

3.1.14 Days alive outside of hospital over the course of 90 days

This is defined as the number of days alive outside of hospital from randomization to Day 90.

For a day to be counted as outside of hospital, the subject must not be in hospital. If the subject is in hospital but hospitalization is recorded as not clinically indicated, this day will still be considered as a day in hospital and therefore will not be counted in this endpoint.

The following rules will be applied for missing data:

- If a subject withdraws from the study or is lost to follow up prior to Day 90, the days with unknown survival/hospitalization status will be considered as follow:

    o If the subject is discharged from hospital when they withdraw from the study or are lost to follow up, days from last known status to Day 90 (or date last known to be alive if death is known, whichever occurs first) will be counted as days alive and outside of hospital.

    o If a subject is in hospital at the time they withdraw from the study, days from last known status to Day 90 will be assumed hospitalized days.

3.1.15 Relative change from baseline in oxygenation index

This is defined as the percentage change from baseline in oxygenation index (SpO_2/FiO_2) to Days 3, 5, 7 and 10. For this endpoint, baseline is defined as the observation on the date of randomization (Day 1) only.

Oxygenation index is calculated as

SpO_2 [%] / FiO_2 [decimal]

It will be calculated for baseline and each post-baseline assessment using the SpO_2 (oxygen saturation) value and the FiO_2 (fraction of inspired oxygen) value collected or derived on the VS and OXYGEN or VENTUSE eCRF pages, respectively. Details on these variables and visit windows are provided in Section 3.2.6 and Section 4.1, respectively.

3.1.16 Time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale through Day 28

This is defined as the time (in days) from randomization to the date of first demonstrated clinical improvement of at least 2 points (i.e., a decline of two points) on the following 9-point category ordinal scale through Day 28:

0. *Uninfected, no clinical or virological evidence of infection
1. Ambulatory, no limitation of activities

2. Ambulatory, limitation of activities
3. Hospitalized – mild disease, no oxygen therapy
4. Hospitalized – mild disease, oxygen by mask or nasal prongs
5. Hospitalized – severe disease, non-invasive ventilation or high flow oxygen
6. Hospitalised – severe disease, intubation and mechanical ventilation
7. Hospitalized – severe disease, ventilation and additional organ support, such as pressors, renal replacement therapy, extracorporeal membrane oxygenation
8. Death

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

This information will be collected in the OSCI pages in the eCRF as per the SoA in the CSP.

Baseline ordinal scale score is defined as the result obtained on the date of randomization (Day 1) only.

If a subject does not have an event (i.e., does not demonstrate clinical improvement of at least 2 points) on or before Day 28 and does not withdraw or become lost to follow up from the study prior to Day 28, the data will be censored at Day 28. If a subject does not have an event but withdraws from the study or is lost to follow up prior to Day 28, the data will be censored at the last date known that the subject has not demonstrated clinical improvement of at least 2 points up to Day 28.

If a subject does not have an event and dies before Day 28, they will be censored at Day 28.

The following additional exploratory efficacy endpoints that utilise the category ordinal scale will be analysed:

3.1.16.1   Time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale, live discharge from hospital, or considered fit for discharge, whichever comes first through Day 28

This is defined as the time (in days) from randomization to the earliest date at which any of the following criteria are met:

- First demonstrated clinical improvement of at least 2 points (i.e., a decline of two points) on the following 9-point category ordinal scale
- Live discharge from hospital
- The date the subject is considered fit for discharge (a score of 0, 1 or 2 on the ordinal scale)

The first demonstrated clinical improvement of at least 2 points and observing a score of 0, 1 or 2 (i.e. the subject is considered fit for discharge) will be determined using the same ordinal scale described in Section 3.1.16. The date of live discharge from hospital will be captured in the CHCSS page in the eCRF.

If a subject does not have an event (i.e., does not demonstrate clinical improvement of at least 2 points or is not discharged from the hospital or is not considered fit for discharge) on or before Day 28 and does not withdraw or become lost to follow up from the study prior to Day 28, the data will be censored at Day 28. If a subject does not have an event but withdraws from the study or is lost to follow up prior to Day 28, the data will be censored at the last date known that the subject did not demonstrate any of the three above criteria up to Day 28.

If a subject does not have an event and dies before Day 28, they will be censored at Day 28.

3.1.16.2   Time to recovery (from randomization) through Day 28

This is defined as the time (in days) from randomization to recovery, where the date of recovery is defined as the earliest date any of the categories in the following 3-point scale are met:

1. Hospitalized not requiring supplemental oxygen, not requiring medical care
2. Not hospitalized but limitations on activities
3. Not hospitalized and no limitations

Table 5 outlines how the 3-point scale will be derived from the information collected from the 9-point category ordinal scale (Section 3.1.16) and hospitalization details.

Table 5   Derivation of the 3-point scale

3-point scale	Derivation from 9-point category scale and hospitalization details
(1) Hospitalized not requiring supplemental oxygen, not requiring medical care	Hospitalized with a score of 0, 1, 2 or 3 and "Is hospitalization clinically indicated" answered No in the eCRF.
(2) Not hospitalized but limitations on activities	Discharged from hospital with a score of 2
(3) Not hospitalized and no limitations	Discharged from hospital with a score of 0 or 1

If a subject does not have an event (i.e., does not meet any of the criteria specified in the 3-point scale) on or before Day 28 and does not withdraw or become lost to follow up from the study prior to Day 28, the data will be censored at Day 28. If a subject does not have an event but withdraws from the study or is lost to follow up prior to Day 28, the data will be censored at the last date known that the subject did not meet any of the criteria specified in the 3-point scale up to Day 28.

If a subject does not have an event and dies before Day 28, they will be censored at Day 28.

3.1.17 Time to $SpO_2 > 94\%$ on room air

This is defined as the time (in days) from randomization to the first occurrence that $SpO_2 > 94\%$ on room air through Day 28. SpO_2 will be captured on the VS module in the eCRF.

Baseline SpO_2 is defined as the result obtained on the date of randomization (Day 1). Subjects with $SpO_2 > 94\%$ on room air at baseline will not be included in any analyses of time to $SpO_2 > 94\%$ on room air.

If a subject does not experience an event (i.e., does not have $SpO_2 > 94\%$ on room air) on or before Day 28 and does not withdraw or become lost to follow up from the study prior to Day 28, the data will be censored at Day 28. If a subject does not have an event but withdraws from the study or is lost to follow up prior to Day 28, the data will be censored at the last date known that the subject did not have $SpO_2 > 94\%$ up to Day 28.

If a subject does not have an event and dies before Day 28, they will be censored at Day 28.

3.2 Safety variables

The safety of acalabrutinib in subjects with COVID-19 when administered with BSC is a primary endpoint and will be assessed by type, frequency, severity, and relationship to study treatment of any treatment-emergent adverse events (TEAEs) or abnormalities of laboratory tests, serious adverse events (SAEs), or adverse events leading to discontinuation of study treatment.

3.2.1 Adverse events

After the signing of the ICF, all SAEs must be reported. After the first dose of study treatment, all AEs/SAEs, irrespective of attribution of causality, must be reported. AE reporting, irrespective of seriousness, ends 28 ($\pm$ 3) days after the last dose of study treatments(s) for those on acalabrutinib + BSC (Arm 1) and 38 ($\pm$ 3) days from randomization for those on BSC only (Arm 2).

The following are NOT considered an AE:
- **Pre-existing condition that has not worsened:** A pre-existing condition (documented on the medical history eCRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Diagnostic testing and procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported. If a test or procedure is done to rule out a diagnosis, the sign or symptom leading to the test/procedure should be the event term, and the event term should only be updated to the diagnosis if/when the diagnosis is confirmed. Testing and procedures performed solely as screening measures (e.g., routine screening mammography or colonoscopy) should not be reported as AEs or SAEs.

- **Abnormal laboratory results:** Abnormal laboratory results are not AEs unless they are clinically significant. For example, a clinically significant laboratory result is one that requires treatment (for example a blood transfusion for low haemoglobin) or requires a change in study drug (e.g., lowering the dose or withholding study drug while the laboratory finding resolves or stabilizes).

- **Progression of underlying disease:** Progression of underlying disease unequivocally related to COVID-19 pneumonia (such as worsening of respiratory status or complications associated with pneumonia) will not be reported as an AE if it is clearly consistent with the suspected progression of the underlying disease. Clinical symptoms of progression may be reported as AEs if the symptoms cannot be determined as exclusively due to the progression of the underlying disease, or if they do not fit the expected pattern of progression for the disease under study.

Events will be defined as treatment-emergent if they onset, or worsen (by investigator report of a change in intensity), during the treatment period as defined in the CSP. The Medical Dictionary for Regulatory Activities (MedDRA) (version 23.0) will be used to code the AEs. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for AEs (CTCAE) version 5.0. The CTCAE grade will be assigned by the investigator as follows:

- Grade 1: Mild AE

- Grade 2: Moderate AE

- Grade 3: Severe AE

- Grade 4: Life-threatening or disabling AE

- Grade 5: Death related to AE

For events with varying severity, the worst reported grade will be used.

Missing start and stop dates for AEs will be handled using the rules described in Section 4.1.

3.2.2   Exposure, dose intensity and treatment compliance

Study drug exposure and dosing information will be collected for acalabrutinib-treated subjects.

Intended treatment duration

Intended treatment duration [days] is defined as the number of days a subject is intended to be on treatment.

A subject is expected to receive 20 doses of acalabrutinib, with each dose taken approximately 12 hours apart. One dose is therefore considered a duration of 0.5 days dosing. Therefore, depending on the timing of the subject's first dose, they can adhere to the dosing schedule and receive 20 doses over two time periods:

- Over the course of 10 days (bid, AM and PM), or

- Over the course of 11 days (one on Day 1 (PM), bid on Day 2-10 (AM and PM), one on Day 11 (AM).

Since doses are approximately 12 hours (0.5 days) apart, the total intended treatment duration in both of the above scenarios is 10 days:

- 0.5 days × 2 doses × 10 days = 10 days

- (0.5 days × 1 dose) + (0.5 days × 2 doses × 9 days) + (0.5 days × 1 dose) = 10 days

Hence,

Intended treatment duration (days) = 10 days

Actual treatment duration

Actual treatment duration (days) is defined as the total number of days a subject is on treatment. It is calculated as:

Actual treatment duration (days) = Date of last dose > 0mg – Date of first dose + 1

Dose reductions or increases are permitted, and the calculation of actual treatment duration makes no adjustment for any dose modifications that may have occurred.

Average daily dose

The average daily dose (mg) is the average dose a subject received on a given day. It is calculated as

Average daily dose (mg) = total dose received (mg) / Actual treatment duration (days)

Percentage of Intended Dose

Percentage of intended dose (PID) is the percentage of the actual dose delivered relative to the intended dose. PID is calculated as:

PID= 100% * d/D, where:

- d is the total dose received (mg), and

- D is the total dose of the drug that would be delivered, if there were no modifications to dose or schedule: 2000mg

If a subject overdoses, the start and stop date of the overdose and the dose received will be included in the above derivations of actual treatment duration, average daily dose and PID.

3.2.3 Laboratory assessments

Laboratory tests will be performed as specified in the SoA in the CSP.

The baseline laboratory result is defined as the result obtained on the date of randomization (Day 1). If no result was obtained on the date of randomization, the last result prior to the date of randomization will be used.

Visit windows and how to handle multiple records will be described in Section 4.1.

Change or percentage change from baseline in hematology and clinical chemistry variables, as well as CRP, ferritin and ALC will be calculated for each post-baseline assessment recorded in the eCRF.

Laboratory abnormalities will be defined based on laboratory normal ranges (universal normal ranges for central laboratory tests), and absolute values will be classified as low (below range), normal (within range or limits of range), or high (above range).

Laboratory parameters will also be classified using the National Cancer Institute Common Terminology Criteria (CTC) version 5.0 into CTC grades.

The denominator used in laboratory abnormality summaries will include only evaluable subjects (i.e., those who had sufficient data to have the possibility of an abnormality). For example:

- If an abnormality criterion involves a change from baseline, evaluable subjects would have both a baseline and at least 1 post-baseline value recorded

- If an abnormality criterion does not consider changes from baseline to be evaluable, the subject need only have 1 post-baseline value recorded

3.2.4 Physical examinations and chest imaging, electrocardiograms and echocardiograms

Physical examinations and chest imaging, electrocardiograms and echocardiograms will be performed as per SoA and as described in Section 8.1.5 of the CSP.

A 12-lead electrocardiogram (ECG) will be done at screening, Day 10, and as clinically indicated after study entry. All ECGs will be obtained in triplicate. Each ECG will define heart rhythm, P wave duration, PR interval, RR interval, QRS duration, QT interval, QTc and overall evaluation. Baseline is defined, after taking the average of the triplicates, as the averaged triplicate on the date of randomization (Day 1). If no result was obtained on the date of randomization, the latest result prior to the date of randomization is used.

The left ventricular ejection fraction (LVEF) will be reported when echocardiograms (ECHO) are conducted. The LVEF % will also be reported.

Abnormalities recorded at screening or baseline for ECG or ECHO results will be recorded as a concurrent condition. Abnormalities first recorded during the treatment period will be recorded as AEs unless unequivocally related to the disease under study.

3.2.5 Vital signs and arterial blood gases

The vital signs to be collected are blood pressure, respiratory rate, oxygen saturation [SpO_2], pulse, and body temperature, as per the SoA in the CSP.

The oxygen saturation of the blood will be assessed using standard pulse oximetry or by arterial blood gas for those subjects who have an arterial blood gas obtained.

The vital sign and blood oxygen measurements are: systolic BP (mmHg), diastolic BP (mmHg), MAP (mmHg), pulse rate (bpm), respiratory rate (breaths/min), body temperature and oxygen saturation (%). MAP will be calculated as:

diastolic BP + 1/3 (systolic BP- diastolic BP).

For all vital signs except oxygen saturation, baseline is defined as the result obtained on the date of randomization (Day 1). If no result was obtained on the date of randomization, the last result prior to the date of randomization will be used.

For oxygen saturation, baseline is defined as the result obtained on the date of randomization (Day 1) only.

Vital sign measurements taken at unscheduled visits will not be used in the summaries of vital signs. However, any vital sign measurements taken at unscheduled visits that are regarded as abnormal or clinically significant will be presented as such.

3.2.6 Oxygen treatment, ventilator use and mSOFA score

If a subject requires oxygen supplementation, data will be recorded, including method of oxygen supplementation and maximum daily flow rate. Fraction of inspired oxygen [FiO_2] will be reported or derived.

For subjects using a nasal cannula or simple mask, the maximum daily flow rate will be entered into the OXYGEN or VENTUSE eCRF and FiO_2 will be derived as per the conversion guidelines in Section 8.3. Note that the conversion is different depending on whether the subject is on a simple mask or nasal cannula. If FiO_2 is entered when a simple mask is selected as the method of oxygen, the value entered in the database will be used instead of deriving the value. For subjects on high-flow oxygen therapy or using other types of masks, FiO_2 will be entered directly into the OXYGEN eCRF page. For subjects on high-flow oxygen therapy or using other types of masks, FiO_2 will be entered directly into the OXYGEN

eCRF page. For subjects on mechanical ventilation, FiO_2 will be entered directly into the VENTUSE eCRF page.

Since FiO_2 is only collected on days that oxygen or mechanical ventilation is used, FiO_2 will be imputed for days that no oxygen or mechanical ventilation is reported. If a subject has no oxygen or mechanical ventilation reported on a given day (method of oxygen (MOXDEL) is blank in the OXYGEN form and type of assisted ventilation (ASSVENTT) is blank in the VENTUSE form) then FiO_2 will be imputed as 21%.

If a subject requires mechanical ventilation, data will be recorded regarding whether ventilator weaning was attempted. For subjects on mechanical ventilation the following ventilator settings will be recorded: tidal volume, FiO_2, peak airway pressure over the last 24 hours, plateau pressure, positive end expiratory pressure, and respiratory rate. Predicted body weight will be recorded assessment of tidal volume. The data will be recorded daily, and the worst value of the day will be entered in the eCRF.

For subjects on mechanical ventilation, an arterial blood gas (pH, oxygen, carbon dioxide, oxygen saturation and bicarbonate), if available, will be recorded daily.

For subjects admitted to ICU, the modification Sequential Organ Failure Assessment (mSOFA) score will be calculated. For each of the following routine assessments, the worst value of the day will be recorded in the eCRF: oxygen saturation by pulse oximetry (SpO_2)/FiO_2 (mmHg), platelet count, bilirubin, vasopressor use (μg/kg/min, mmHg), and creatinine (or urine output).

For oxygen, mechanical ventilation and mSOFA variables, baseline is defined as the result obtained on the date of randomization (Day 1) only.

3.3 Pharmacokinetic variables

The PK of acalabrutinib and its active metabolite (ACP-5862) in subjects with COVID-19 when administered with BSC is a secondary endpoint. The PK will be assessed by summarizing the plasma concentrations for both analytes at the specified time points. Additionally, PK parameters for acalabrutinib and ACP-5862 (such as, maximum observed concentration (C_{max}) and AUC) may be estimated, as considered appropriate.

Pharmacokinetic concentration data will be collected as per the SoA in the CSP. Plasma concentrations of study drug and/or metabolite are used as supplied by the analytical laboratory for PK analysis.

3.4 Exploratory pharmacodynamic and correlative variables

CCI

CCI
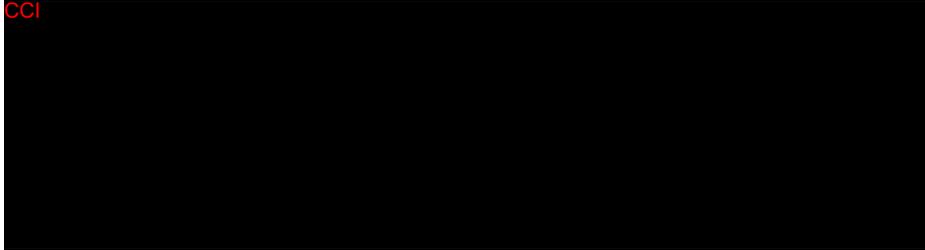
3.5 Other variables

3.5.1 Baseline characteristics

Baseline characteristics that will be collected or derived are:

- Demographics: Age (years), sex, race and ethnicity

- Subject characteristics: Weight, height and body mass index (BMI), where BMI (kg/m^2) = Weight/Height^2

- Medical history: Name of past and/or concomitant diseases (verbatim and coded using the MedDRA dictionary version 23.0), start and stop dates

- Relevant surgical history: Surgical procedure (verbatim and coded using the MedDRA dictionary version 23.0)

- Pregnancy status for applicable subjects only: test date and result (positive or negative)

- History of substance abuse: cigarettes (former/current/never), vaping (former/current/never), recreational inhaled drugs (former/current/never), alcohol (former/current/never)

- SARS-CoV-2 infection comorbidities: infection comorbidities prior to admission, subcategory, comorbidity start and stop date

- SARS-CoV-2 infection risk factors/lifestyle events: infection risk factor, infection risk factor start and stop date

- SARS-CoV-2 infection signs and symptoms: infection signs or symptoms, clinical event start and stop date

- Respiratory failure status at baseline (with vs without), as defined in Table 1, where baseline is defined as the result obtained on the date of randomization (Day 1)

- Intensity of oxygen treatment and mechanical ventilation at baseline: most extreme oxygen treatment or mechanical ventilation, flow rate

- Intensity of oxygen treatment and mechanical ventilation prior to baseline: most extreme oxygen treatment or mechanical ventilation, flow rate, duration of treatment

3.5.2   Prior and concomitant medications and procedures

All therapies (drug and non-drug), including herbal preparations, whether prescribed or over-the-counter, that are used during the study will be recorded on the eCRF. Details include generic and/or brand names of the medications, World Health Organisation Drug Dictionary (WHO-DD) encoding (B3 format), reason for use, route, dose, dosing frequency, and start and end dates. Procedures performed during the study will be recorded on the eCRF and details include the procedure name, WHO-DD encoding (B3 format), reason for the procedure, and start and end dates.

Prior therapies are defined as those taken prior to study treatment with a stop date prior to the first dose of study treatment (acalabrutinib + BSC subjects) or prior to randomization (BSC only subjects). For subjects on acalabrutinib + BSC, concomitant therapies and procedures are defined as those with a stop date on or after the first dose date of study treatment. Start date may be before or after first dose. For subjects on BSC only, concomitant therapies and procedures are defined as those with a stop date on or after randomization. Start date may be before or after randomization.

Best supportive care medication will be collected as a concomitant medication with therapy reason as 'disease under study'.

Missing start and stop dates for medications and procedures will be handled using the rules described in Section 4.1.

Medications received prior to or concomitantly will be coded using the WHO Drug Dictionary Anatomical Therapeutic Chemical (ATC) classification codes. Concomitant medications will be summarized for the FAS by ATC classification codes. Subjects with the same concomitant medication/procedure multiple times will be counted once per medication/procedure. A medication/procedure that can be classified into more than one chemical and/or therapeutic subgroup will be presented in each subgroup.

4.   ANALYSIS METHODS

4.1   General principles

All statistical analyses will be performed by AZ statistical programming group. Any deviations from the analyses presented in this SAP will be detailed in the clinical study report. All outputs will be produced using SAS® version 9.4 or a later version in accordance with AZ standards.

The below mentioned general principles will be followed throughout the study:

- Demography and baseline characteristics data will be summarised using the FAS.

- All efficacy data will be summarised and analysed using the FAS, unless otherwise specified.

- Safety data will be summarized using the SAF.

- PK data will be summarized using the PKAS.

- CCI

- Descriptive statistics will be used for all variables, as appropriate.

- Stratification factors age ($\geq$ 65 vs < 65 years) and comorbidities (present vs absent) as recorded at randomization in the IRT system will be used for any summaries or analyses using the FAS that are presented by stratification factor. For summaries or analyses by stratification factor performed using the PPAS, the true stratification results (captured in the eCRF) will be used.

- Continuous variables will be summarised by the number of observations (n), mean, standard deviation (SD), median, minimum and maximum and will be based on non-missing observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean and median will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database.

- Categorical variables will be summarized by frequency counts and percentages and include the number of subjects with present data and the number of subjects with missing (not present) data. Unless stated otherwise, percentages will be calculated based on the population total for each treatment group. Percentages will be presented to one decimal place.

- For the PK and PD summaries the reported results will be summarized using appropriate significant figures rather than decimal places.

- Baseline is defined as the result obtained on the day of randomization (Day 1). If no result was obtained, the latest result prior to the day of randomization is used. Applies to:

    o Baseline for all laboratory assessments

- o Baseline for vital signs except oxygen saturation (SpO_2)

    - o Baseline ECG assessment

- Baseline is defined as the result obtained on the day of randomization (Day 1) only. Applies to:
    - o Respiratory failure status at baseline
    - o Baseline oxygen saturation (SpO2)
    - o Baseline for all oxygen and mechanical ventilation assessments
    - o Baseline ordinal scale score
    - o Baseline mSOFA score
- For all summaries, change from baseline variables will be calculated as the post-baseline value minus the value at baseline. The percentage change from baseline will be calculated as ((post-baseline value – baseline value)/baseline value) x 100.

- Unless stated otherwise, visit windows will apply as follows:

    - o Day 1 (date of randomization): No window unless specified above (where latest result prior to date of randomization can be used)

    - o Day 2-10 or discharge (whichever occurs first): no visit window. Note: if a subject is discharged prior to Day 7 they will visit the site for an assessment 2 to 4 days after discharge. Assessments should match those for Day 10.

    - o Day 14: ±2 days

    - o Day 28: ±3 days

    - o Arm 1 Safety follow-up at 28 days after last dose of acalabrutinib: ±3 days

    - o Arm 2 Safety follow-up (for AEs, concomitant medications and survival assessment) at 38 days after randomization: ±3 days

    - o Long-term follow-up 90 days after randomization: ±7 days

    - o Observations recorded on the date closest to the scheduled assessment day (as long as this is within the visit window) will be used as the scheduled assessment. Any observations recorded outside of the visit window will be considered unscheduled visit observations and will not be included in visit-based summaries at a treatment-group level. If multiple observations are recorded per day, or observations within a visit window are equidistant from the target day, the worst assessment reported will be used as the scheduled assessment. For laboratory and vital signs assessments, this is the maximum reported value.

o   Visit-based summaries will include: Baseline (Day 1), Day 2-10, Day 14 and
    Day 28 where applicable, as per SoA.

o   For listings at a subject level, all values will be included (regardless of whether
    they appear in a corresponding visit-based summary) when deriving a patient
    level statistic such as a maximum.

No imputation of values for missing data will be performed except for missing or partial start
and end dates for AEs and concomitant medication (CM) (Table 6). If the data cut-
off/snapshot date or the subject's date of death is prior to the date imputed based on the rules
outlined below, then the earliest of these dates will be imputed.

**Table 6   Imputation rules for missing or partial AE and concomitant medication
dates**

Form		Imputation	
		Acalabrutinib + BSC	**BSC alone**
	Start date		
	Missing		
AE and CM	AE/CM ended before first dose date/ randomization date	Impute 1st January with year being the same year as CM/AE end date	
	AE/CM ended after first dose date/ randomization date	Impute date of first dose	Impute date of randomization
	Partial		
AE and CM	Missing day	Impute 1st of the month unless AE/CM start month is the same month as the first dose, then impute date of first dose. Check start date is prior to end date.	Impute 1st of the month unless AE/CM start month is the same month as randomization, then impute date of randomization. Check start date is prior to end date.
	Missing day and month	Impute 1st January unless AE/CM start year is the same year as the first dose, then impute date of first dose. Check start date is prior to end date. If end date is now prior to start	Impute 1st January unless AE/CM start year is the same year as randomization, then impute date of randomization. Check start date is prior to end date. If end date is now prior to start date, impute 1st

		date, impute 1st January as the start day and month.	January as the start day and month.
	End date		
	Missing		
AE and CM	CM flag ongoing takes any value (yes, no or missing) and CM start date is prior, on or after first dose date/ randomization AE stop date missing	Impute min (date of death, data cut-off/snapshot date)	
	Partial		
CM	Missing day	Impute the last day of the month unless month is the same as month of last dose, then impute date of last dose.	Impute the last day of the month unless month is the same as month of randomization date + 10 days, then impute randomization date + 10 days.
	Missing day and month	Impute date of last dose + 28 days + 3 days	Impute date of randomization + 38 days + 3 days

4.2 Analysis methods

4.2.1 Disposition of subjects

The number and percentage of subjects who were enrolled to the study, randomized, randomized and received treatment, randomized and did not receive treatment, completed treatment, discontinued prematurely from treatment, completed the study, withdrew from the study, and reasons for withdrawal from the study will be summarized by treatment group and overall for all subjects.

The following will be presented by treatment group and as a total:

- Number and percentage of subjects in each analysis set

- Number and percentage of subjects in each country and center (using the FAS)

- Number and percentage of subjects in each combination of the stratification factors: age ($\geq$ 65 vs < 65 years) and comorbidities (present vs absent) as recorded at randomization in the IRT system (using the FAS)

The stratification factors as recorded at randomization in the IRT system will be compared to those entered into the clinical database and discrepancies will be summarized.

4.2.2 Protocol deviations

Important protocol deviations are defined in Section 2.2 and will be listed by treatment group and summarized separately by treatment group for all subjects randomized to treatment.

The number and percentage of subjects with any IPD will be summarized for each IPD category. Subjects with more than one deviation in the same IPD category will be counted once for that IPD category. Any subjects who have deviations in more than one IPD category will be counted once in the overall summary.

4.2.3 Demographic and other baseline characteristics

Demographic and other baseline characteristics will be listed for all subjects and summarized by treatment group and overall for the FAS using the rules for summarizing continuous and categorical variables described in Section 4.1.

In addition to being summarized as continuous variables, age and BMI will be summarized as the following categorical variable: age group (<65, ≥ 65 years, as well as categories of <20, $\geq 20 - < 35$, $\geq 35 - < 50$, $\geq 50 - < 65$, $\geq 65 - < 75$, ≥ 75 years.) and BMI group (Underweight [<18.5], Normal [$18.5 - <25.0$], Overweight [$25.0 - <30.0$] and Obese [$>=30.0$].

The number and percentage of subjects with comorbidities for each treatment group will also be presented, as well as the number of comorbidities (e.g. the number and percentage of subjects in each treatment group with 1, 2, 3, etc. comorbidities) and type.

The number and percentage of subjects with signs and symptoms at screening for each treatment group will be presented overall and by onset time relative to randomization.

The most extreme oxygen treatment or mechanical ventilation received at baseline will also be summarized (most extreme to least extreme: ECMO, invasive ventilation, non-invasive ventilation). If the subject's most extreme treatment is oxygen (no mechanical ventilation was received), maximum oxygen flow rate will be summarized. This will be repeated for prior to baseline, and in addition the duration of any oxygen treatment or mechanical ventilation will be summarized continuously and categorically.

Medical history and surgical history are coded using MedDRA (version 23.0) and will be summarized by System Organ Class (SOC) and Preferred Term (PT).

4.2.4 Prior and concomitant medications and procedures

The following summaries will be produced:

- Summary of prior medications
- Summary of concomitant medications – including best supportive care

- Summary of best supportive care – past
- Summary of best supportive care - current

All concomitant and other treatment data will be listed for all subjects in the FAS. Missing coding terms should be listed and summarised as "Not coded".

4.3 Analysis of efficacy

The efficacy analyses described in this section are primary or secondary endpoints and will be performed for subjects in the FAS by treatment group (unless stated otherwise).

4.3.1 Primary endpoint

4.3.1.1 Alive and free of respiratory failure at Day 14

The primary endpoint is the proportion of subjects who are alive and free of respiratory failure at Day 14, where respiratory failure is defined in Section 3.1.1.

The point estimate and its 95% confidence interval (CI; using Wald method with continuity correction) will be calculated for each treatment group. The Cochran-Mantel-Haenszel $\chi2$ test, stratified by age ($\geq$ 65 vs < 65 years) and comorbidities (present vs absent), will be used to compare the proportion of subjects who are alive and free of respiratory failure at Day 14 between the two treatment groups. An unstratified analysis ($\chi2$ test) will also be performed. Finally, the difference in the proportion of subjects who are alive and free of respiratory failure at Day 14 will also be provided with 95% CIs.

This primary endpoint will also be summarized (point estimate and 95% CI Wald method with continuity correction as above) by the following subgroups:

- the predefined age categories defined in Section 4.2.3

- country

- sex

- race

- ethnicity

- comorbidities (present vs absent)

- history of substance abuse (former/current/never)

- concomitant antiviral use (yes vs no)

- respiratory failure status at baseline (with vs without)

Categories within subgroups may be combined if a category has an insufficient number of subjects, this will be documented in the CSR.

The number and percentage of subjects who experienced respiratory failure but were free of respiratory failure at Day 14 will be summarized by treatment group. This summary will also include summary statistics for the number of respiratory failures that occurred.

All analyses described in this section will be primarily conducted in the FAS but will be repeated for the PPAS.

The proportion for each group, and the difference in proportions, as well as the 95% CIs, will also be reported in the FAS but excluding subjects who have withdrawn or have been lost to follow-up on or prior to Day 14.

The method for handling subjects that withdraw or are lost to follow up prior to Day 14 is detailed in Section 3.1.1.

Additional sensitivity analyses and subgroup analyses (such as by concomitant medication usage) of the primary endpoint may be performed as appropriate.

4.3.2 Secondary endpoints

4.3.2.1 Alive and free of respiratory failure at Day 28

The point estimate and its 95% confidence interval (CI; using Wald method with continuity correction) will be calculated for each treatment group. Summaries of the subgroups specified in Section 4.3.1.1 will also be produced. Analyses may be repeated for the PPAS, using the definition of the PPAS in Section 3.1.2.

The proportion for each group, and the difference in proportions, as well as the 95% CIs, will also be reported in the FAS but excluding subjects who have withdrawn or have been lost to follow-up prior to Day 28.

The number and percentage of subjects who experienced respiratory failure but were free of respiratory failure at Day 28 will be summarized by treatment group. This summary will also include summary statistics for the number of respiratory failures that occurred.

The method for handling subjects that withdraw or are lost to follow up prior to Day 28 is detailed in Section 3.1.2.

4.3.2.2 Percent change from baseline in C-reactive protein

Summary statistics (n, mean, median, SD, minimum, and maximum) and the percent change from baseline to each scheduled study assessment will be presented by treatment group.

Box plots of absolute value over time and a line graph of the mean change (and SD) from baseline to each scheduled study assessment may be presented for each treatment group.

A by-subject listing will also be presented.

4.3.2.3   Change from baseline in ferritin

Summary statistics (n, mean, median, SD, minimum, and maximum) and the change and percent change from baseline to each scheduled study assessment will be presented by treatment group.

Box plots of absolute value over time and a line graph of the mean change (and SD) from baseline to each scheduled study assessment may be presented for each treatment group.

A by-subject listing will also be presented.

4.3.2.4   Change from baseline in absolute lymphocyte count

Summary statistics (n, mean, median, SD, minimum, and maximum) and the change and percent change from baseline to each scheduled study assessment will be presented by treatment group.

Box plots of absolute value over time and a line graph of the mean change (and SD) from baseline to each scheduled study assessment may be presented for each treatment group.

A by-subject listing will also be presented.

4.3.2.5   All-cause mortality at Day 90

The number and percentage of subjects who have died (all-cause and 'related to disease under investigation' as recorded in the DEATH eCRF), those still alive, those with unknown survival status (lost to follow-up), those who have withdrawn consent and those censored for any other reason at Day 90 will be summarized by treatment group.

Kaplan-Meier (KM) plots and summary statistics will be presented for survival time by treatment group. The proportion of subjects alive at Day 90 will be defined as the KM estimate of overall survival at 90 days. This will be presented, along with its 95% CI. The computation of the CI will be based on a log-log transformation.

The method for handling subjects that withdraw or are lost to follow up prior to Day 90 is detailed in Section 3.1.6.

Subgroup analyses on COVID-related deaths may be performed as appropriate.

4.3.2.6   Alive and discharged from the ICU at Days 14 and 28

A summary of the number and percentage of subjects alive and discharged from the ICU at Day 14 will be presented. This will be repeated for Day 28. Analyses may be repeated for the PPAS, using the definition of the PPAS in Section 3.1.7.

The method for handling subjects that withdraw or are lost to follow up prior to Day 14 (or Day 28) is detailed in Section 3.1.7.

4.3.2.7 Time to first occurrence of respiratory failure or death

Time from randomization to first occurrence of respiratory failure or death (due to any cause) on study (up to Day 28), whichever occurs first, will be analyzed using the KM method by treatment group.

KM plots and summary statistics will be presented for time to first occurrence of respiratory failure or death by treatment group.

The HR and its 95% CI will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron), stratified by age (<65 vs ≥65 years) and comorbidities (present vs absent) and the CI calculated using a profile likelihood approach. Summary statistics will include the lower and upper quartile and median survival time with 95% CI.

The method for handling subjects that withdraw or are lost to follow up is detailed in Section 3.1.8.

4.3.2.8 Days alive and free of respiratory failure over the course of 28 days

Summary statistics (n, mean, median, SD, minimum, and maximum) of the number of days alive and free of respiratory failure over 28 days will be presented by treatment group. In addition, the number and percentage of subjects in the following categories will be presented, 0 days, 1-6 days, 7-14 days, 15-21 days, and 22-28 days.

The method for handling subjects that withdraw or are lost to follow up prior to Day 28 is detailed in Section 3.1.9.

4.3.2.9 Days with respiratory failure over the course of 28 days

Summary statistics (n, mean, median, SD, minimum, and maximum) of the number of days with respiratory failure over 28 days will be presented by treatment group. In addition, the number and percentage of subjects in the following categories will be presented, 0 days, 1-6 days, 7-14 days, 15-21 days, and 22-28 days.

A bar chart of the number of days with respiratory failure for each subject within the treatment group will be produced, i.e., showing graphically the distribution of the number of days with respiratory failure for each treatment group.

The proportion of subjects who experienced respiratory failure or died over the course of 28 days will also be summarized by treatment group. Subjects with respiratory failure on the day of randomization will be excluded from this summary.

Furthermore, the proportion of subjects who required invasive ventilation or ECMO or died over the course of 28 days will be summarized by treatment group.

The method for handling deaths and subjects that withdraw or are lost to follow up prior to Day 28 is detailed in Section 3.1.10.

4.3.2.10   Days hospitalized over the course of 28 days

Summary statistics (n, mean, median, SD, minimum, and maximum) of the number of days hospitalized over 28 days will be presented by treatment group. In addition, the number and percentage of subjects in the following categories will be presented, 0 days, 1-6 days, 7-14 days, 15-21 days, and 22-28 days.

A bar chart of the number of days hospitalized for each subject within the treatment group will be produced, i.e., showing graphically the distribution of the number of days hospitalized for each treatment group.

The method for handling deaths and subjects that withdraw or are lost to follow up prior to Day 28 is detailed in Section 3.1.113.1.8.

4.3.2.11   Days in ICU over the course of 90 days

Summary statistics (n, mean, SD, median, minimum and maximum) for the length of stay (days) in ICU over 90 days will be presented by treatment group. In addition, the number and percentage of subjects in the following categories will be presented, 0 days, 1-6 days, 7-14 days, 15-21 days, 22-28 days and >28 days.

A bar chart of the number of days in ICU for each subject within the treatment group will be produced, i.e., showing graphically the distribution of the number of days in ICU for each treatment group.

The method for handling deaths and subjects that withdraw or are lost to follow up prior to Day 90 is detailed in Section 3.1.12.

4.3.2.12   Days alive outside of hospital over the course of 28 days

Summary statistics (n, mean, SD, median, minimum and maximum) of the days alive outside of hospital over 90 days will be presented by treatment group.

The method for handling subjects that withdraw or are lost to follow up prior to Day 28 is detailed in Section 3.1.13.

4.3.2.13   Days alive outside of hospital over the course of 90 days

Summary statistics (n, mean, SD, median, minimum and maximum) of the days alive outside of hospital over 90 days will be presented by treatment group.

The method for handling subjects that withdraw or are lost to follow up prior to Day 90 is detailed in Section 3.1.14.

4.3.2.14   Relative change from baseline in oxygenation index

Summary statistics (n, mean, median, SD, minimum, and maximum) and the percent change from baseline to each scheduled study assessment will be presented by treatment group.

Box plots of absolute value over time and a line graph of the mean change (and SD) from baseline to each scheduled study assessment may be presented for each treatment group.

A by-subject listing will also be presented.

4.3.2.15 Time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale through Day 28

Time from randomization to the date of first demonstrated clinical improvement of at least 2 points on a 9-point category ordinal scale through Day 28 will be portrayed using the KM method by treatment group.

Alongside summary statistics, a KM plot of the cumulative improvement rate over time will be presented by treatment group.

The HR and its 95% CI will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron), stratified by age (<65 vs ≥65 years) and comorbidities (present vs absent). The CI will be calculated using a profile likelihood approach. Summary statistics will include the lower and upper quartile and median time to clinical improvement with the 95% CI.

The method for handling subjects that withdraw or are lost to follow up or die is detailed in Section 3.1.16.

In addition to the above, for each treatment group, ordinal scale scores will be presented by day and the change in the score from baseline to each post-baseline assessment will be summarized.

Additional sensitivity analyses may be performed as appropriate.

Time to clinical improvement of at least 2 points (from randomization) on a 9-point category ordinal scale, live discharge from hospital, or considered fit for discharge, whichever comes first) through Day 28

Time from randomization to the date of first demonstrated clinical improvement of at least 2 points on a 9-point category ordinal scale, live discharge from hospital, or considered fit for discharge, whichever comes first, through Day 28 will be portrayed using the KM method by treatment group.

Alongside summary statistics, a KM plot of the cumulative improvement rate over time will be presented by treatment group.

The HR and its 95% CI will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron), stratified by age (<65 vs ≥65 years) and comorbidities (present vs absent). The CI will be calculated using a profile likelihood approach. Summary statistics will include the lower and upper quartile and median time to clinical improvement with the 95% CI.

The method for handling subjects that withdraw or are lost to follow up or die is detailed in Section 3.1.16.1.

Additional sensitivity analyses may be performed as appropriate.

Time to recovery (from randomization) through Day 28

Time from randomization to the date of recovery through Day 28 will be portrayed using the KM method by treatment group.

Alongside summary statistics, a KM plot of the cumulative recovery rate over time will be presented by treatment group.

The HR and its 95% CI will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron), stratified by age (<65 vs ≥65 years) and comorbidities (present vs absent). The CI will be calculated using a profile likelihood approach. Summary statistics will include the lower and upper quartile and median time to clinical improvement with the 95% CI.

The method for handling subjects that withdraw or are lost to follow up or die is detailed in Section 3.1.16.2.

Additional sensitivity analyses may be performed as appropriate.

4.3.2.16   Time to $SpO_2 > 94\%$ on room air

Time from randomization to $SpO_2 > 94\%$ on room air through Day 28 will be portrayed using the KM method by treatment group.

Alongside summary statistics, a KM plot of the cumulative $SpO_2 > 94\%$ rate over time will be presented by treatment group.

The HR and its 95% CI will be estimated from a stratified Cox Proportional Hazards model (with ties = Efron), stratified by age (<65 vs ≥65 years) and comorbidities (present vs absent). The CI will be calculated using a profile likelihood approach. Summary statistics will include the lower and upper quartile and median time to clinical improvement with the 95% CI.

The method for handling subjects that withdraw or are lost to follow up or die is detailed in Section 3.1.17.

Additional sensitivity analyses may be performed as appropriate.

4.4   Analysis of safety

This section describes safety analyses to be conducted. All of the analyses in this section will be based on the safety population and will be performed for all safety variables specified below. All analyses of safety data will employ descriptive statistics. Formal statistical analysis (with generation of a p-value) will not be performed for these endpoints.

4.4.1 Adverse events

Verbatim descriptions of AEs will be mapped per version 23.0 of the MedDRA thesaurus terms and graded per National Cancer Institute (NCI) CTCAE, v5.0 or higher. Unless stated otherwise, only treatment-emergent adverse events (TEAEs) will be presented in the summaries. For acalabrutinib + BSC subjects, TEAEs are AEs starting or ongoing AEs worsening after the first dose of study treatment and AEs with start date up to the last dose of study treatment plus 28 (±3) days; for BSC only subjects, TEAEs are AEs starting or ongoing AEs worsening after date of randomization and AEs with start date up to 38 (± 3) days after randomization. . In the case a subject's actual treatment received is different than their randomized treatment, TEAEs are AEs starting on or after the date of randomization up to the later of 38 (± 3) days after randomization or the last dose of study treatment plus 28 (±3) days. When programmatically assigning the AEs as treatment emergent, the upper window will be used.

The following summaries will be provided:

- A summary of the number and percentage of subjects reporting any TEAE, TEAEs with outcome of death, at least one TEAE of CTCAE grade 3 or higher, at least one serious TEAE, at least one TEAE possibly related to study drug, and at least one TEAE leading to discontinuation of study drug by treatment group.

- A summary of the number of TEAEs, TEAEs with outcome of deaths, TEAEs with CTCAE grade 3 or higher, serious TEAEs, TEAEs possibly related to study drug, and TEAEs leading to discontinuation of study drug by treatment group.

- A summary of the number and percentage of subjects reporting a TEAE by treatment group, SOC and PT.

- A summary of the number and percentage of subjects reporting the most common TEAEs (occurring in at least 5% of overall subjects) by treatment group , SOC and PT.

- A summary of the number and percentage of subjects reporting a TEAE by treatment group, maximum CTCAE grade, SOC and PT. This will include a subset of grade 3 or higher.

- A summary of the number and percentage of subjects reporting a TEAE possibly related to study drug by SOC and PT.

- A summary of the number and percentage of subjects reporting a TEAE leading to discontinuation of study drug by SOC and PT.

For the most common TEAEs, all events that occur in at least 5% of subjects overall will be summarized by preferred term, by decreasing frequency. This cut-off may be modified after review of the data. When applying a cut-off (e.g., 5%), the raw percentage should be

compared to the cut-off, no rounding should be applied first (i.e., an AE with frequency 4.9% will not appear if the cut-off is 5%).

The following by-subject listings will be provided:

- A listing of all AEs (including non-treatment-emergent events and any collected but are not, by definition, AEs since they are related to disease under study), by treatment group, and including center, E-code, AE (SOC, PT, verbatim term), date of onset, date of resolution, duration, CTCAE grade, seriousness, action taken, outcome, relationship to study treatment and time from last dose to start of AE.

4.4.1.1 Deaths, serious adverse events (SAEs), and other significant adverse events

The following summaries will be provided:

- A summary of the number and percentage of total deaths, deaths related to the disease under investigation (as determined by the investigator), deaths after the end of safety follow-up (28 (±3) days after last dose for acalabrutinib + BSC subjects, 38 (±3) days after randomization for BSC only subjects) by treatment group

- A summary of the number and percentage of subjects reporting a treatment-emergent SAE by treatment group, SOC and PT.

- A summary of the number of treatment-emergent SAEs by treatment group, SOC and PT.

- A summary of the number and percentage of subjects reporting a treatment-emergent SAE leading to discontinuation of study drug by SOC and PT.

- A summary of the number and percentage of subjects with a treatment-emergent SAE with an outcome of death by treatment group and PT.

Adverse events of special interest (AESI) for acalabrutinib include ventricular arrhythmias (e.g., ventricular extrasystoles, ventricular tachycardia, ventricular arrhythmia, ventricular fibrillation). AESI preferred terms are listed in Section 8.1. These events will be summarized similarly as follows:

- A summary of the number and percentage of subjects reporting an AESI by treatment group, CTCAE grade, group term and PT.

- A summary of the number and percentage of subjects reporting an AESI possibly related to study drug by group term and PT.

- A summary of the number and percentage of subjects reporting an AESI leading to discontinuation of study drug by group term and PT.

A list of AESI PTs will also be provided.

Events of clinical interest (ECIs) are provided in Section 8.1. ECIs will be reported for the duration of study treatment and during any protocol-specified follow-up period. These events will be summarized similarly to AESIs by treatment group and a list of ECI PTs will be provided.

The following by-subject listings will be presented:

- A by-subject listing of key information for serious adverse events (SAEs).
- A by-subject listing of key information for AESIs and ECIs.
- A by-subject listing of deaths, including the date of death, the primary and secondary cause of death, whether an autopsy was performed and whether the death was related to the disease under study.
- A by-subject listing of key information for AEs leading to discontinuation of study treatment.

The following subject narratives will be provided:

- Narratives of SAEs with an outcome of death.
- Narratives of SAEs, possibly related to study drug.
- Narratives of discontinuation of investigational product due to AEs.
- Narratives of AESIs.
- Narratives of any other medically-relevant AE that does not fall into the above categories.

No formal statistical tests will be performed to compare AE rates between treatment groups.

4.4.2   Exposure, dose intensity and treatment compliance

Study drug exposure will be listed and summarized for acalabrutinib-treated subjects in the SAF. The following summaries will be produced:

- Actual treatment duration

- Summary statistics (n, mean, median, SD, minimum, and maximum) of PID

- Calculated average daily dose

4.4.3   Laboratory assessments

For the following continuous laboratory parameters, summary statistics (n, mean, median, SD, minimum, and maximum) of the laboratory results (converted to SI units) and the change from baseline at each scheduled post-baseline assessment will be presented by treatment group:

- Efficacy laboratory parameters: CRP, ALC, ferritin

- Fibrinogen

- PT

- aPTT

- INR

- D-dimer

- Procalcitonin

- Cardiac troponin

Selected laboratory parameters (including categorical parameters) may be analysed with shift tables (defined by the normal ranges) of baseline to minimum post-baseline value (low, medium, high) and of baseline to maximum post-baseline value (low, normal, high) by treatment group may be presented. For laboratory parameters classified using CTC grades, shift tables for selected laboratory parameters may also be produced showing baseline CTC grade to maximum post-baseline CTC grade by treatment group.

By-subject listings of haematology and clinical chemistry parameters will be presented. Unscheduled laboratory results will not be included in the by-visit summaries but will be included in listings, as well as any out of range or shift tables of worst postbaseline data.

Liver function abnormality by Hy's law and frequencies of abnormal treatment emergent uric acid will be summarized.

4.4.4 Vital signs

Summary statistics (n, mean, median, SD, minimum, and maximum) for each of the vital signs and the change from baseline at each scheduled post-baseline assessment will be presented by treatment group.

A by-subject listing of all vital sign parameters will be presented; abnormal vital signs will be flagged.

4.4.5 Physical examinations and chest imaging, electrocardiograms and echocardiograms

By-subject listings of all physical examination and weight data will be presented.

If there is a sufficient number of subjects with post-baseline assessments ($\geq$10 subjects per treatment group), a shift table of the number and percentage of subjects with normal or abnormal ECG evaluations may be presented from baseline to the most extreme post-baseline evaluation.

By-subject listings of all ECG parameters will be presented along with the heart rhythm and overall evaluation of ECGs at all visits.

By-subject listings of ECHO overall evaluation, abnormalities and LVEF will be presented.

4.4.6 Oxygen treatment, ventilator use and mSOFA

Oxygen treatment and ventilator use data will be used to assess primary and secondary efficacy endpoints of the study.

The number and percentage of subjects requiring oxygen treatment or mechanical ventilation at each timepoint will be presented by treatment group. Oxygen flow rate and method of mechanical ventilation at baseline will also be presented by treatment group. Change from baseline in oxygen flow rate to each post-baseline flow rate and to the maximum post-baseline flow rate will be summarized.

For subjects requiring oxygen treatment, by-subject listings will be presented.

For subjects requiring mechanical ventilation, by-subject listings will be presented on the data collected, as listed in Section 3.2.6.

By-subject listings of mSOFA scores and sub-scores may be presented.

4.5 Analysis of pharmacokinetics

Plasma concentrations of study drug and/or metabolite will be grouped, tabulated, summarized and plotted, as appropriate. Plasma concentrations will be listed for each subject by nominal time point, as warranted by the data. Additionally, the data will also be displayed graphically, as appropriate.

The PK parameters for acalabrutinib and ACP-5862 (such as, AUC and Cmax) may be estimated using a population PK approach, if warranted by the data, and reported separately from the Clinical Study Report (CSR).

Potential correlations of exposure with safety and efficacy outcomes or biomarker measurements may be explored as warranted by the data.

4.6 Analysis of exploratory variables and pharmacodynamics

CCI
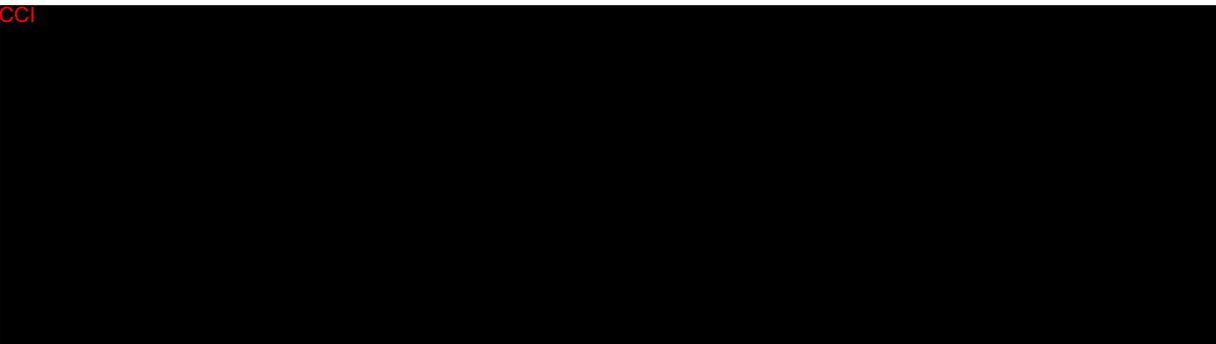
CCI

5. INTERIM ANALYSES

A DMC will conduct a planned interim safety review and a planned efficacy interim analysis before the primary analysis of the study data. Details are provided in Section 6.

6. DATA MONITORING COMMITTEE

This study will have a DMC. The details of the roles and responsibilities of the DMC are provided in the DMC charter. The DMC will be responsible for oversight of participant safety and monitoring the balance of risks and benefits in the study. To fulfil this, the study will use a DMC to conduct a planned interim safety review and a planned efficacy interim analysis before the primary analysis of the study data.

The first DMC review is an interim safety review which will take place after the first 30 subjects have been randomized into the study and have had 28 days of follow-up from randomization.

The second DMC review is a planned interim analysis of the primary efficacy endpoint, which will take place when the last subject randomized has had 14 (± 2) days of follow up after randomization. At the time of the interim analysis of the primary efficacy endpoint, accumulated safety data will also be reviewed by the DMC.

The two DMC reviews may be combined if the study is fully enrolled at the time of the first DMC review. The DMC may support any health authority interactions or internal discussions based on their review. The study team will remain blinded to the data that the DMC will review until database lock for the primary analysis of the study, which will occur when all randomized subjects have been followed for 38 (± 3) days from randomization.

In addition to the two formal reviews, the DMC will review all fatal events on an ongoing basis. Further details will be provided in a separate DMC charter.

To maintain the overall type I error of the study at the 2-sided 0.05 level, at the interim analysis, the primary efficacy endpoint (the proportion of subjects who are alive and free of respiratory failure at Day 14) will be tested at the 2-sided 0.0001 level. At the primary analysis for the study, this primary efficacy endpoint will be tested at the 2-sided 0.0499 level.

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

Details on the outputs that will be provided to the DMC are listed in Section 8.2.

7.   CHANGES OF ANALYSIS FROM PROTOCOL

N/A

8.   APPENDIX

8.1   AESI and ECI definitions

Adverse Event of Special Interest (AESI)

The following preferred terms for the ventricular arrhythmias AESI include:

- Torsade de pointes
- Ventricular arrhythmia
- Ventricular extrasystoles
- Ventricular fibrillation
- Ventricular flutter
- Ventricular tachyarrhythmia
- Ventricular tachycardia

Events of Clinical Interest

The Events of Clinical Interest (ECIs) are from the acalabrutinib program with extended
dosing of acalabrutinib in patients with haematologic malignancies.

Category	Subcategory	Definition
Cardiac events		• SOC Cardiac disorders
	Atrial fibrillation	• PT Atrial fibrillation • PT Atrial flutter
	Ventricular tachyarrhythmias	• PT Torsade de pointes • PT Ventricular fibrillation • PT Ventricular flutter • PT Ventricular tachyarrhythmia • PT Ventricular tachycardia
Cytopenias – Anemia		• SMQ Haematopoietic erythropenia [narrow + broad]
Cytopenias – Leukopenia		• SMQ Haematopoietic leukopenia [narrow + broad]
	Neutropenia	• PT Band Neutrophil count decreased • PT Band neutrophil percentage decreased • PT Cyclic neutropenia • PT Febrile Neutropenia • PT Idiopathic neutropenia • PT Neutropenia • PT Neutropenic infection • PT Neutropenic sepsis • PT Neutrophil count decreased • PT Neutrophil percentage decreased
	Other leukopenia	• SMQ Haematopoietic leukopenia [narrow + broad] excluding PTs for neutropenia above

Cytopenias - Thrombocytopenia		• SMQ Haematopoietic thrombocytopenia [narrow + broad]
Hemorrhage		• SMQ Haemorrhage terms (excl. laboratory terms)
	Major hemorrhage	• As per Acerta definition (see below)
Hepatotoxicity		• SMQ [narrow] Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions • SMQ [narrow] Hepatitis, non-infectious • SMQ [narrow] Liver related investigations signs
Hypertension		• SMQ Hypertension [narrow]
Infections		• SOC Infections and infestations
Interstitial lung disease/Pneumonitis		• SMQ [narrow] Interstitial lung disease
Second primary malignancies[a]		• SMQ Malignant tumours (including Haematological malignant tumours SMQ and Non-haemoatological malignant tumours SMQ) • SMQ Malignant lymphomas [narrow] SMQ Myelodysplastic syndrome [narrow]
	Second primary malignancies (excluding non melanoma skin)	• The above excluding PTs mapping to HLT Skin neoplasms malignant and unspecified (excluding melanoma)
Tumor lysis syndrome[b]		• PT Tumour lysis syndrome

MedDRA version 23.0
HLT=High-Level Term; PT=Preferred Term; SOC=System Organ Classes; SMQ=Standardized MedDRA Queries.
[a] Only flagged as an ECI if malignancy is reported in the subject's medical history and is ongoing.
[b] Only flagged as an ECI if tumor lysis syndrome is reported in the subject's medical history and is ongoing.

Major Hemorrhage

Major hemorrhage is defined as any hemorrhagic event that is serious, or Grade ≥ 3 in severity, or that is a CNS hemorrhage (any severity grade).

Search Strategy:

    I.   Use standardized MedDRA query:
        o   Haemorrhage terms (excluding laboratory terms) (SMQ) [20000039]

    II.   Identify Major Events that are a subset of the Haemorrhage SMQ:
        o   Grade $\geq$3 AE
        o   Any serious adverse event
        o   All grades of CNS hemorrhage

<div align="center">

CNS Hemorrhage Preferred Terms (MedDRA Version 23.0)

</div>

• Acute haemorrhagic leukoencephalitis

- Basal ganglia haematoma
- Basal ganglia haemorrhage
- Basilar artery perforation
- Brain contusion
- Brain stem haematoma
- Brain stem haemorrhage
- Brain stem microhaemorrhage
- Central nervous system haemorrhage
- Cerebellar haematoma
- Cerebellar haemorrhage
- Cerebellar microhaemorrhage
- Cerebral aneurysm perforation
- Cerebral aneurysm ruptured syphilitic
- Cerebral arteriovenous malformation haemorrhagic
- Cerebral artery perforation
- Cerebral cyst haemorrhage
- Cerebral haematoma
- Cerebral haemorrhage
- Cerebral haemorrhage foetal
- Cerebral microhaemorrhage
- Encephalitis haemorrhagic
- Epidural haemorrhage
- Extradural haematoma
- Haemorrhage intracranial
- Haemorrhagic cerebral infarction
- Haemorrhagic stroke
- Haemorrhagic transformation stroke
- Intracerebral haematoma evacuation
- Intracranial haematoma
- Intracranial tumour haemorrhage
- Intraventricular haemorrhage
- Meningorrhagia
- Ocular retrobulbar haemorrhage
- Optic disc haemorrhage
- Optic nerve sheath haemorrhage
- Pituitary haemorrhage
- Putamen haemorrhage
- Retinal aneurysm rupture
- Retinal haemorrhage
- Retinopathy haemorrhagic
- Ruptured cerebral aneurysm
- Spinal cord haematoma
- Spinal cord haemorrhage

- Spinal epidural haematoma
- Spinal epidural haemorrhage
- Spinal subarachnoid haemorrhage
- Spinal subdural haematoma
- Spinal subdural haemorrhage
- Subarachnoid haematoma
- Subarachnoid haemorrhage
- Subdural haematoma
- Subdural haematoma evacuation
- Subdural haemorrhage
- Subgaleal haematoma
- Subgaleal haemorrhage
- Subretinal haematoma
- Thalamus haemorrhage
- Traumatic intracranial haematoma
- Traumatic intracranial haemorrhage

8.2 DMC outputs for review meeting

The outputs that will be produced for the DMC reviews are provided in Table 7.

Table 7   **DMC review outputs**

Output	Analysis set
Disposition, recruitment, stratification factors, demographic and subject characteristics, medical history, concomitant medications/ BSC, signs and symptoms at screening, duration of hospitalization, respiratory failure status at baseline, intensity of oxygen treatment and mechanical ventilation at baseline. The above will be summarized as detailed in Section 4.2.1, 4.2.3 and 4.2.4.	Full analysis set
Duration of exposure, average daily dose, percentage of intended dose. The above will be summarized as detailed in Section 4.4.2.	Safety analysis set (acalabrutinib-treated subjects only)
Subjects on oxygen treatment, mechanical ventilation, or either, over the course of the study. The above will be summarized as detailed in Section 4.4.6.	Safety analysis set
Adverse events: TEAEs, TEAEs leading to discontinuation of study drug, AEs possibly related to study drug, SAEs. The above will be summarized as detailed in Section 4.4.1.	Safety analysis set
Listing of deaths	Full analysis set
Proportion of subjects alive and free of respiratory failure at Day 14 and Day 28 (summary statistics only for the first DMC interim safety review). Stratified and unstratified analysis of the proportion of subjects alive and free of respiratory failure at Day 14 (testing with odds ratios and p-values provided for the DMC interim efficacy review). Proportion of subjects who experienced respiratory failure of died over the course of 28 days. Proportion of subjects who required invasive ventilation or ECMO or died over the course of 28 days.	Full analysis set

8.3   Fraction of Inspired Oxygen (FiO$_2$)

For all supplemental oxygen delivery devices, the patient is not just breathing the direct oxygen, but rather is breathing a **combination** of room air plus the oxygen from the supplemental device. Different devices deliver to the patient more or less of a % of what is coming in from the tank.

Fraction of Inspired Oxygen (FiO$_2$) for a nasal canula and a simple mask are given in the tables below. For other oxygen delivery systems, such as masks, tents, there is more oxygen that "blows by" or is lost, therefore higher flow rate setting on the oxygen tank are needed to achieve the same FiO$_2$. A tracheostomy would require different calculations as well.

Example: with a **nasal cannula**, we assume that the fraction of oxygen that is inspired (above the normal atmospheric level or 20%) increases by 4% for every additional liter of oxygen flow administered.

For a Nasal Cannula: FiO$_2$ (%) = (Flow Rate (L/min) × 4) + 20

Oxygen tank **FLOW RATE** in liters / min	FiO$_2$ -- Fraction of Inspired Oxygen value (%)
1 L / min	24
2 L / min	28
3 L / min	32
4 L / min	36
5 L / min	40
6 L / min	44

For a Simple Mask:
If Flow Rate < 10 L/min: FiO$_2$ (%) = Max[(Flow Rate (L/min) × 6) − 1, 24]
If Flow Rate ≥ 10 L/min: FiO$_2$ (%) = Flow Rate (L/min) × 6

Oxygen tank **FLOW RATE** in liters / min	FiO$_2$ -- Fraction of Inspired Oxygen value (%)
6 L / min	35
7 L / min	41
8 L / min	47
9 L / min	53
10 L / min	60

9.   REFERENCES

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Document Name: d822fc00001-sap-ed-4		
Document Title:	Statistical Analysis Plan Edition 4	
Document ID:	Doc ID-004288154	
Version Label:	4.0 CURRENT LATEST APPROVED	
Server Date **(dd-MMM-yyyy HH:mm 'UTC'Z)**	**Signed by**	**Meaning of Signature**
06-Oct-2020 21:25 UTC	PPD ACERTA	Content Approval
07-Oct-2020 08:14 UTC	PPD	Author Approval

Notes: (1) Document details as stored in ANGEL, an AstraZeneca document management system.