AstraZeneca

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

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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
BMI	Body Mass Index
BP	Blood Pressure
BSC	Best supportive care
CI	Confidence Interval
CRP	C-reactive Protein
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for AEs
CTMS	Clinical Trial Management System
ECG	Electrocardiogram
ECHO	Echocardiogram
ECI	Events of Clinical Interest
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EES	Efficacy Evaluable Set
ICU	Intensive Care Unit
iDMC	Independent Data Monitoring Committee

IPD	Important Protocol Deviation
KM	Kaplan-Meier
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mSOFA	Modified Sequential Organ Failure Assessment
NG	Nasogastric
[redacted]	[redacted]
P/F	PaO_2/FiO_2
PK	Pharmacokinetic
PKS	Pharmacokinetic Analysis Set
PT	Preferred Term
SAE	Serious Adverse Event
SAS	Safety Analysis Set
SD	Standard Deviation
SOC	System Organ Class
SoA	Schedule of Activities
TEAE	Treatment Emergent Adverse Event
WHO-DD	World Health Organization-Drug Dictionary

AMENDMENT HISTORY

Date	Brief description of change
	N/A

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 1 of the CSP.

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

1.1 Study Objectives

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

Table 1 Objectives and Endpoints

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

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

Objective	Endpoint/Variable
Secondary Objective	**Secondary Endpoints/Variables**
• To evaluate the preliminary efficacy of adding acalabrutinib suspension to BSC for treatment of participants with COVID-19	• Proportion of participants alive and free of respiratory failure at Days 14 and 28 • Percent change from baseline in CRP (time frame: baseline, Days 3, 5, 7, 14, 28) • Time to improvement defined as time to clinical improvement of ≥ 2 points (from first dose date) on a 9-point category ordinal scale, live discharge from the hospital, or considered fit for discharge (a score of 0, 1, or 2 on the ordinal scale), whichever comes first, by Day 28
Exploratory Objectives	**Exploratory Endpoints/Variables**
[redacted]	[redacted]
[redacted]	[redacted]

1.2 Study Design

Approximately 20 participants will be included to ensure at least 16 participants are evaluable. participants will receive acalabrutinib suspension (ie, acalabrutinib 100 mg suspension in COCA-COLA® delivered via NG tube) bid for 14 days (a maximum of 28 doses). In addition to receiving best supportive care (SOC).

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

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

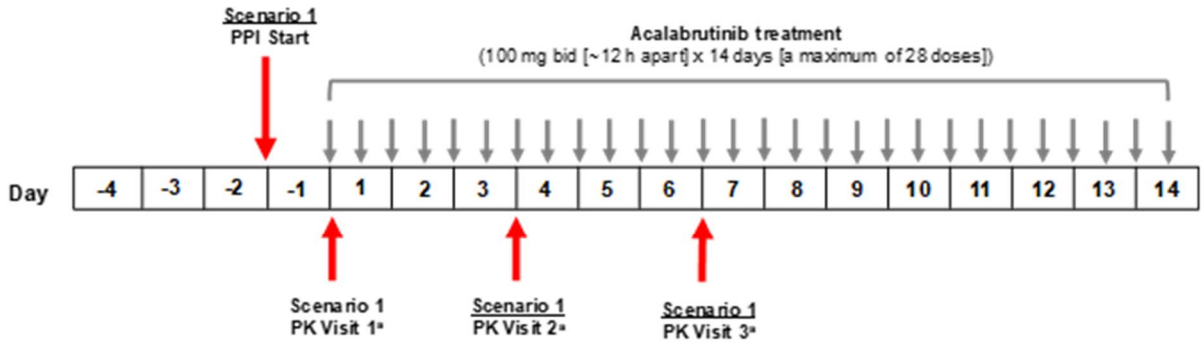
Table 2 PK Visit and Description

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

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

The study design is illustrated in Figure 1.

Figure 1 Study Design



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

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

Note: PK Visit 2 can occur as early as Day 2 (if participant has been on a PPI for ≥ 4 consecutive days prior to receiving the third acalabrutinib dose), and up to Day 4 (if participant initiated PPI treatment 24 hours prior to receiving the first dose of acalabrutinib on Day 1). See table 3 for more information.
bid = twice daily; PK = pharmacokinetic(s); PPI = proton-pump inhibitor.

1.3 Number of Subjects

Approximately 20 participants will be enrolled to have at least 16 evaluable participants. No formal power calculation is used for sample size determination. The sample size is chosen based on desire to gain adequate information while exposing as few patients as possible to the study procedure.

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 3.

The analysis populations are defined in Table .

Table 3 Populations for Analysis

Population/Analysis set	Description
PK Analysis Set (PKS)	The PK Analysis Set will include all participants who received ≥ 1 dose of acalabrutinib and had ≥ 1 post-dose evaluable PK data point for acalabrutinib. The population will be defined by AstraZeneca, the pharmacokinetics, and the statistician prior to any analyses being performed.
Safety Analysis Set (SAS)	The Safety Analysis Set will include all participants who received ≥ 1 dose of study intervention
Efficacy Evaluable Set (EES)	The Efficacy Evaluable Set will include all participants who received ≥ 1 dose of study intervention
[redacted]	[redacted]

PK = pharmacokinetic; [redacted]; PPI = proton-pump inhibitor.

2.2 Deviations

Protocol deviation is defined in a separate protocol deviation list. The important protocol deviations will be listed and summarized. 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).

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.

In addition to the above, other study deviations captured from the eCRF module for inclusion/exclusion criteria will be tabulated and listed. Any other deviations from monitoring notes or reports will be reported in an appendix to the CSR.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Pharmacokinetic Variables

The PK of acalabrutinib and its active metabolite ACP-5862 in subjects with COVID-19 when administered with BSC is a primary endpoint and will be assessed by following PK parameters:

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

All PK parameters include in the protocol are listed in the Table 4 below, and are defined as appropriate for study design.

Table 4. Non-Compartmental Pharmacokinetic Parameters to be Calculated

Parameter	Label in TFLs	Definition	Method of Determination
AUC_{0-t}	AUC0-t	Area under the concentration-time curve from time 0 to the time of the last observed non-zero concentration	Calculated using the Linear Trapezoidal with Linear Interpolation Method
AUC_{0-inf}	AUC0-inf	Area under the concentration-time curve from time 0 extrapolated to infinity	$AUC_{0-inf} = AUC_{0-t} + (C_{last}/K_{el})$ where C_{last} is the last observed non-zero concentration
$AUC_{\%extrap}$	AUC%extrap	Percent of AUC0-inf extrapolated	$\%AUC_{extrap} = (1 - AUC_{0-t}/AUC_{0-inf}) \times 100$
C_{max}	Cmax	Maximum observed concentration	Taken directly from bioanalytical data
T_{max}	Tmax	Time to reach C_{max}; if the maximum value occurs at more than one timepoint, T_{max} is defined as the first timepoint with this value	Taken from clinical database as the difference in the time of the blood draw associated with C_{max} and the time of study drug administration
T_{last}	Tlast	Time of the last measurable non-zero concentration	Taken from the clinical database as the difference in the time of the blood draw associated with the last measurable concentration and the time of study drug administration
K_{el}	Kel	Apparent first order terminal elimination rate constant	Calculated by linear least-squares regression analysis from a semi-log plot of the plasma concentration-time curve, using the maximum number of points in the terminal log linear phase (e.g., 3 or more non-zero plasma concentrations)
t½	t1/2	Apparent first order terminal elimination half-life	$t1/2 = 0.693/K_{el}$
CL/F	CL/F	Apparent total plasma clearance after oral (extravascular) administration (calculated for acalabrutinib only)	$CL/F = Dose/(AUC_{0-inf})$

Parameter	Label in TFLs	Definition	Method of Determination
V_z/F	Vz/F	Apparent volume of distribution during the terminal elimination phase after oral (extravascular) administration (calculated for acalabrutinib only)	$V_z/F = Dose/(AUC_{0\text{-}inf} \times K_{el})$

Pharmacokinetic concentration data will be collected as per the schedule of activities (SoA) in clinical study protocol (CSP). PK analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times will be used. Nominal sampling times and best fit of the regression will be used for any interim PK parameter calculations. Plasma concentrations of study drug and its metabolite are used as supplied by the analytical laboratory for PK analysis. The units of concentration and resulting PK parameters will be presented as they are received for the analytical laboratory unless otherwise specified in the PK order form.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.1, or higher and/or SAS® Version 9.3 or higher. PK parameters will not be calculated for profiles with less than 3 consecutive postdose time points with quantifiable concentrations. The data from profiles with insufficient data to calculated the PK parameters will be included in the listing of concentrations but excluded from the concentration summaries for the affected analyte and treatment.

For the calculation of PK parameters, plasma concentrations below the limit of quantitation (BLQ) prior to the first quantifiable concentration will be set to zero and plasma concentrations BLQ after the first quantifiable concentration will be treated as missing.

If an entire concentration-time profile is not quantifiable, the profile will be excluded from the PKS.

The C_{max} and t_{max} will be derived directly from the plasma concentration-time profiles. In the case where multiple peaks of equal magnitude are present, the earliest t_{max} will be reported.

K_{el} will be calculated by log-linear regression of the terminal portion of the concentration-time profiles for the derivation of regression-based parameters where there are sufficient data. The AUCs will be calculated using 'Linear up/Log down' method. Where appropriate, the AUC_{last} will be extrapolated to infinity using Kel to obtain AUC_{inf}. The CL/F will be determined from the ratio of dose/AUC_{inf}. The Vz/F will be determined from the ratio of CL/F/Kel. The MR parameters will be calculated after molar conversion. If t½ is estimated over less than three half-lives, the Kel related values will be flagged in the data listings but will be excluded from summary and PK statistical analysis.

An Rsq adj value of ≥0.8 indicate good fit of the log-linear regression. Any Kel with a Rsq_adj of <0.8 be flagged in the data listings along with the regression-based parameters and discussed in the CSR. The Kel and related PK parameters will be excluded from summary and PK statistical analysis.

The minimum requirement for the calculation of AUCs will be the inclusion of at least 3 consecutive quantifiable concentrations. Where there are only 3 quantifiable concentrations at least one of these should follow the peak concentration. Where $\%AUC_{extrap}$ is >10%, AUC_{inf} and derived parameter values will be flagged and excluded from descriptive and inferential statistics and discussed in the CSR.

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 (± 3) days after the last dose of study treatments.

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) (using the latest or current MedDRA version) 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. 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. The intended and actual treatment duration [days], the average daily dose (mg), relative dose intensity (%) and treatment compliance (%) will be reported according to table 5.

By subject exposure listing will be provided.

Table 5 Definition of Exposure Variables

Parameters	Definition
Intended treatment duration	Date of last dose (> 0mg) - date of first dose + 1
Actual treatment duration	Intended treatment duration (days) – total duration of interruptions (days)
Average daily dose	total dose received (mg) / Actual treatment duration (days)
Relative dose intensity[RDI]	100% × d/D where d is the actual cumulative dose [mg] delivered up to the actual last day of dosing for the drug, and D is the total dose of the drug that would be delivered: Actual treatment duration [days] × 100 [mg] ×2
Treatment compliance	100 × [1- (total number of days of study drug interruption / actual treatment duration)].

3.2.3 Laboratory assessments

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

For the derivation of baseline and post-baseline visit values, the rules described in Section 4.1 considering definition of baseline, and how to handle multiple records will be used.

Change or percentage change from baseline in hematology and clinical chemistry variables, as well as ferritin and CRP 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). Physical examinations and chest imaging, electrocardiograms and echocardiograms

3.2.4 Physical examination and chest imaging, electrocardiograms and echocardiograms

Physical examinations and chest imaging, electrocardiograms and echocardiograms will be performed as per SoA.

A 12-lead electrocardiogram (ECG) will be done at screening, as clinically indicated, Day 14 or discharge. Baseline is defined, after taking the average of the triplicates, as the latest non-missing averaged triplicate prior to the first study drug.

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, oximetry, pulse, and body temperature, as per the SoA in the CSP.

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

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 blood oxygen-haemoglobin saturation (%). MAP will be calculated as:

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

If multiple vital sign measurements are taken per day, the measurement closest to 08:00 each day will be used. 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 on high-flow oxygen therapy, FiO_2 will be entered directly into the OXYGEN eCRF page. For subjects not on high-flow oxygen therapy, the maximum daily flow rate will be entered into the OXYGEN eCRF and FiO_2 will be derived as per the conversion guidelines in Section 9.2. Note that the conversion is different depending on whether the subject is on a mask or nasal cannula.

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. If more than one value is obtained for the arterial blood gases, the value closest to 08:00 will be used.

Assuming that PAO_2 (the partial pressure of alveolar oxygen) is obtained from the alveolar gas equation: $PAO_2 = (FiO_2 \times (760-47)) - (PaCO_2/0.8)$ then alveolar to arterial (AA) gradient will be calculated as: AA gradient = $PAO_2 - PaO_2$.

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 laboratory values, the last available (if within 48 hours) will be used. On days when laboratory results are unavailable, values will be extrapolated from the previously available values.

3.3 Efficacy Variables

The efficacy of acalabrutinib in subjects with COVID-19 when administered with BSC is a secondary endpoint and will be assessed by following variables:

3.3.1 Alive and free of respiratory failure at Day 14 (Day 28)

For the purpose of this study, respiratory failure is defined based on resource utilization of any of the following modalities:

- Endotracheal intubation and mechanical ventilation
- Oxygen delivered by high-flow nasal cannula (heated, humidified, oxygen delivered via reinforced nasal cannula at flow rates > 20 L/min with fraction of delivered oxygen ≥ 0.5)
- Noninvasive positive pressure ventilation or continuous positive airway pressure
- Extracorporeal membrane oxygenation

Only the subject's survival status and respiratory-failure status on Day 14 will be considered for this endpoint. If they experience respiratory failure after first dosed but recover by Day 14, per the definition above, they will be considered alive and free of respiratory failure at Day 14.

Subjects who 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.

Similar analysis will be applied for alive and free of respiratory failure at Day 28.

3.3.2 Percent change from baseline in C-reactive protein

This is defined as the percent change from baseline in C-reactive protein (CRP) at Day 1 to Day 14 and Day 28 after first dose. For this endpoint, baseline is defined as the last observation prior to first dose.

3.3.3 Time to 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

This is defined as the time (in days) from first dose date to the earliest date at which any of the following **event** 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 (CSP Table 8)
- Live discharge from hospital
- The date the subject is considered fit for discharge (a score of 0, 1 or 2 on the ordinal scale)

If a subject does not have an event on or before Day 28 and does not withdraw/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/ 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 within 28 days.

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

3.4 Exploratory [redacted]

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), defined as the following:
    - Without respiratory failure at baseline: subjects do not require oxygen delivered by high-flow nasal cannula or require oxygen delivered by high-flow nasal cannula with flow rate $\leq$ 20 L/min and $FiO_2 < 0.5$
    - With respiratory failure at baseline: subjects require oxygen delivered by high-flow nasal cannula with
        - 20 L/min < flow rate <30 L/min and
        - $0.5 \leq FiO_2 < 0.6$

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. Concomitant therapies and procedures are defined as those with a stop date on or after the first dose date of study treatment.

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 SAS 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, baseline characteristics and safety data will be summarised using the SAS. All efficacy data will be summarised and analysed using the EES, unless otherwise specified. PK data will be summarized using the PKS. Exploratory [redacted]
- 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. The SD will be reported to two more decimal places than the raw data.

- 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. Percentages will be presented to one decimal place.

- For the PK [redacted] summaries the reported results will be summarized using appropriate significant figures rather than decimal places.

- Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of study drug.

- 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) × 100.

- Visit windows will apply as follows:

    - Days 1-14 or discharge: no visit window. Note: if a subject is discharged prior to Day 14 they will visit the site for an assessment 2 to 4 days after discharge. Assessments should match those for Day 14.
    - Day 20: ±3 days
    - Day 28: ±3 days
    - Safety follow-up at 28 days after last dose of acalabrutinib: ±3 days
    - 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 for ventilator use, the observations closest to 08:00 will be used as the scheduled assessment. If multiple observations are recorded per day for other assessments, the worst assessment reported will be used as the scheduled assessment.
    - For summaries 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) (Section 9.3). 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 in Section 9.3, then the earliest of these dates will be imputed.

4.2 Analysis Methods for Disposition, Demographic, Baseline Characteristics, Prior and Concomitant Medications/Procedures

4.2.1 Disposition of subjects

The number and percentage of subjects who were enrolled to the study, received treatment, enrolled 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 for all subjects.

The number and percentage of subjects in each analysis set, and in each center (using SAS) will also be presented.

4.2.2 Protocol deviations

Important protocol deviations are defined in Section 2.2 and will be listed for all subjects received study 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 in SAS using the rules for summarizing continuous and categorical variables described in Section 4.1.

In addition to being summarized as continuous variables, age, weight, and BMI will be summarized as the following categorical variable: age group (<65, ≥65 years, as well as categories of <20, ≥20 - < 35, ≥35 - < 50, ≥50 - <65, ≥ 65 - <75, ≥75 years.), weight group (<70, ≥70 – ≤90, >90 kg) 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 will also be presented, as well as the number of comorbidities (e.g. the number and percentage of subjects with 1, 2, 3, etc. comorbidities).

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 or procedures

The following summaries will be produced for all subjects in SAS:

- Summary of prior medications or procedures
- Summary of concomitant medications or procedures

All concomitant and other treatment data will be listed for all subjects in the SAS.

Missing coding terms should be listed and summarised as "Not coded".

4.3 Analysis of Pharmacokinetics

The PK analyses will be performed at AZ Research & Development.

The plasma concentrations of acalabrutinib and ACP-5862 will be listed for all subjects and summarized by analyte, and nominal sample time for all subjects in the PKS. Summary statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum will be calculated for all nominal concentration timepoints.

Excluded subjects will be included in the concentration listings, but will be excluded from the summary statistics and noted as such in the tables.

All BLQ values will be presented as “BLQ” in the concentration listings and footnoted accordingly. For the calculation of summary statistics, plasma acalabrutinib and ACP-5862 concentrations BLQ will be treated as zero prior to the first quantifiable concentration and as missing elsewhere.

Mean and individual concentration-time profiles for plasma acalabrutinib and ACP-5862 will be presented on linear and semi-log scales. Linear mean plots will be presented with and without SD.

Plasma acalabrutinib and ACP-5862 PK parameters will be listed and summarized by analyte and treatment for all subjects in the PKS. Summary statistics (n, arithmetic mean, SD, CV%, SEM, minimum, median, maximum, geometric mean [Geom Mean] and geometric CV% [Geom CV%]) will be calculated for plasma acalabrutinib and ACP-5862 PK parameters. Excluded subjects will be listed in the PK parameter tables, but will be excluded from the summary statistics and noted as such in the tables.

Individual plasma concentrations of acalabrutinib and ACP-5862 will be presented with the same level of precision as received from the bioanalytical laboratory. Individual PK parameters will be reported to 3 significant figures for individual parameters, with the exception of T_{max}, T_{last}, and t½, which will be presented with 2 decimal places, and C_{max}, which will be presented in the same precision as the bioanalytical data.

The level of precision for each concentration and PK parameter statistic will be as follows:

- minimum/maximum with the same precision as in individual data
- arithmetic mean, median and geometric mean with one more level of precision than minimum/maximum
- SD with one more level of precision than mean/median
- n will be presented as an integer
- CV% and geometric CV% will be presented to 1 decimal place.

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

4.4 Analysis of Efficacy

The efficacy analyses described in this section are secondary endpoints. Formal statistical analysis (with generation of a p-value) will not be performed for efficacy endpoints.

4.4.1 Alive and free of respiratory failure at Day 14 (and 28)

The first efficacy endpoint is the proportion of subjects who are alive and free of respiratory failure at Day 14, where respiratory failure is defined in Section 3.3.1.

The point estimate and its 90% confidence interval (CI; using Wald method with continuity correction) will be calculated and summarized. The difference in the proportion of subjects who are alive and free of respiratory failure at Day 14 with its 90% Cis will be included in this summary. The number and percentage of subjects who experienced respiratory failure but were free of respiratory failure at Day 14 will also be included in above summary.

For those wo have respiratory failure, summary statistics for the number of respiratory failures that occurred will be summarized.

This efficacy endpoint will also be summarized (point estimate and 90% CI Wald method with continuity correction as above) by the following subgroups:

- age (predefined age categories defined in Section 4.2.3)

- sex
- race
- ethnicity
- comorbidities (present vs absent)
- history of substance abuse (former/current/never)
- Concomitant antiviral use (yes vs no)
- Respiratory failure at baseline (with vs without, defined in Section 4.2.3)

The method for handling subjects that withdraw/ are lost to follow up prior to Day 14 is detailed in Section 3.3.1.

Similar analysis will be conducted for Day 28.

4.4.2 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.

Box plots of absolute value over time and percent change from baseline to each scheduled study assessment may be presented.

A by-subject listing will also be presented.

4.4.3 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

This efficacy endpoint will be portrayed using the KM method. Alongside summary statistics, a KM plot of the cumulative improvement rate over time will be presented.

The HR and its 90% CI will be estimated from a Cox Proportional Hazards model (with ties = Efron), The CI calculated using a profile likelihood approach. Summary statistics will include the lower and upper quartile and median time to clinical improvement with the 90% CI.

The method for handling subjects that withdraw/ are lost to follow up or die is detailed in Section 3.3.3.

Additional sensitivity analyses may be performed as appropriate.

4.5 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.

4.5.1 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) (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) will be presented in the summaries. 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.
- 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.
- A summary of the number and percentage of subjects reporting a TEAE by 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 SOC and PT.
- A summary of the number and percentage of subjects reporting a TEAE by CTCAE grade, SOC and PT.
- A summary of the number and percentage of subjects reporting a TEAE with CTCAE grade 3 or higher by SOC and PT.
- 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), by 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.

4.5.1.1 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.

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

- A summary of the primary cause 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 PTs are listed in Section 9.1. These events will be summarized as follows:

- A summary of the number and percentage of subjects reporting an AESI by 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 SOC and PT.

A list of AESI PTs will also be provided.

Events of clinical interest (ECIs) are provided in Section 9.1. These events will be summarized similarly to AESIs 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 SAEs with an outcome of death.
- 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 with an outcome other than death.
- 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.

4.5.2 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 using the definition of exposure variables in Table 5 in Section 3.2.3:

- Intended treatment duration
- Actual treatment duration
- Summary statistics (n, mean, median, SD, minimum, and maximum) of RDI
- The number and percentage of dose interruptions, dose increases, and reasons for dose interruptions and dose increases
- Calculated average daily dose
- Treatment compliance

4.5.3 Laboratory assessments

For the following continuous laboratory parameters, summary statistics (n, mean, median, SD, minimum, and maximum) of the laboratory results (conventional units and System

International (SI) units) and the change from baseline at each scheduled post-baseline assessment will be presented:

- Fibrinogen
- PT
- aPTT
- INR
- D-dimer
- CRP
- Procalcitonin
- Cardiac troponin
- BNP

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) 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 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.

4.5.4 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.

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

4.5.5 Physical examinations and chest imaging, electrocardiograms and echocardiograms

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

By-subject listings of chest imaging (when clinically indicated) findings will be presented.

If there is a sufficient number of subjects with post-baseline assessments (≥10 subjects), 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.

4.5.6 Oxygen treatment, ventilator use and mSOFA

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

The number and percentage of subjects requiring oxygen treatment or mechanical ventilation at each timepoint will be presented. The method of oxygen or mechanical ventilation, as well as the number and percentage of subjects who go from oxygen treatment to mechanical ventilation, will also 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.

4.6 Analysis of exploratory variables and [redacted]

[redacted]

5. INTERIM ANALYSES

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

6. INDEPENDENT DATA MONITORING COMMITTEE

This study will not have iDMC.

7. SAFETY REVIEW COMMITTEE

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

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

The SRC will consist of the AstraZeneca Study Physician or delegate, Principal Investigator or equivalent delegate from active investigational sites, and Global Safety Physician or delegate. Other attendees may also be invited as appropriate.
Details on the process of ongoing evaluation of safety data by the SRC and the committee composition is described further in the SRC charter.

8. CHANGES OF ANALYSIS FROM PROTOCOL

N/A

9. APPENDIX

9.1 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
- Suspected transmission of an infectious agent via product

Events of Clinical Interest

The Events of Clinical Interest (ECIs) have been identified based on preclinical findings, emerging data from clinical studies relating to acalabrutinib, and [redacted] The adverse events (AEs) selected for dedicated analysis were evaluated using Standardized MedDRA Queries (SMQs), where available, by System Organ Classes (SOCs), or by Sponsor-defined baskets of MedDRA Adverse Event Grouped Terms.

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		• 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		• PT Tumour lysis syndrome

MedDRA version 23.0
HLT=High-Level Term; PT=Preferred Term; SOC=System Organ Classes; SMQ=Standardized MedDRA Queries.

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 version 23.0 query:
   - Haemorrhage terms (excluding laboratory terms) (SMQ) [20000039]

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

CNS Hemorrhage Preferred Terms (MedDRA Version 23.0)

- 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

9.2 Fraction of Inspired Oxygen (FiO2)

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 (FiO2) for a nasal canula and a Venturi 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 FiO2. 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: FiO2 = (Flow Rate (L/min) × 0.04) + 0.2

Oxygen tank **FLOW RATE** in liters / min	**FiO2** -- Fraction of Inspired Oxygen value
0 (no oxygen, just room air)	0.2
1 L / min	0.24
2 L / min	0.28
3 L / min	0.32
4 L / min	0.36
5 L / min	0.4
6 L / min	0.44

For a Venturi Mask:

Oxygen tank **FLOW RATE** in liters / min	**FiO2** -- Fraction of Inspired Oxygen value
< 2 L / min	0.2
2 L / min ≤ Flow Rate < 4 L / min	0.24
4 L / min ≤ Flow Rate < 6 L / min	0.28
6 L / min ≤ Flow Rate < 8 L / min	0.31
8 L / min ≤ Flow Rate < 10 L / min	0.35
10 L / min ≤ Flow Rate < 15 L / min	0.4
≥ 15 L / min	0.6

9.3 Imputation rules for missing or partial AE on concomitant medication

Imputation rules for missing or partial AE on concomitant medication dates

Form		Imputation
	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
	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.
	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.
	End date	
	Missing	
AE and CM	CM flag ongoing= 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.
	Missing day and month	Impute date of last dose + 28 days + 3 days

10. REFERENCES

SIGNATURE PAGE

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