CONFIDENTIAL

Statistical Analysis Plan (SAP)

Sponsor:	*CalciMedica through EMAS*
Study code:	*CM4620-201*
Study title:	*An Open-Label, Dose-Response Study of CM4620 Injectable Emulsion in Patients with Acute Pancreatitis and Accompanying Systemic Inflammatory Response Syndrome (SIRS)*
Date:	*Draft 1 – 03OCT2018* *Final_draft – 01MAR2019* *FINAL – 03MAR2019*

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1 LIST OF ABBREVIATIONS

AE – Adverse Event

ALB - Albumin

ATC – Anatomical-Therapeutic-Chemical

CF – Clean File

CRF – Case Report Form

CSP – Clinical study protocol

FAS – Full Analysis Set

HCT - Hematocrit

MedDRA – Medical Dictionary for Regulatory Affairs

PPS – Per Protocol Set

SAE – Serious Adverse Event

SAP – Statistical Analysis Plan

SAS – Statistical Analysis System

SD – Standard Deviation

2 INTRODUCTION

This Statistical Analysis Plan (SAP) gives details regarding the statistical analyses and data presentation outlined in the final Clinical study protocol (CSP) for the study *CM4620-201.* Any changes from the final CSP are given in Section 8. This needs to be approved and signed prior to database lock.

3 CLINICAL STUDY DETAILS

3.1 Clinical Study Objectives

3.1.1 Primary objective

To assess the safety and tolerability of CM4620-IE in patients with acute pancreatitis and accompanying SIRS

3.1.2 Primary endpoint

The primary endpoints of the study are related to safety, these include Adverse Events (AEs), Vital Signs (VS) and safety laboratory measures

3.1.3 Secondary objectives

To assess the efficacy of CM4620-IE in patients with acute pancreatitis and accompanying SIRS

To determine the pharmacokinetic profile of CM4620-IE in patients with acute pancreatitis and accompanying SIRS

3.1.4 Secondary endpoints

The secondary efficacy endpoints are:

- CTSI Score categorized into Mild, Moderate and Severe
- Balthazar score
- Pancreatic Parenchymal Necrosis
    - < 30%
    - 30-50%
    - > 50%
- PASS score
- Tolerating Solid Food
    - Time to tolerating solid food
    - Arithmetic mean of time to tolerate 50% solid food
- Biomarker measurements including, but not limited to:
    - ANC/ALC (Absolute neutrophils count / Absolute Lymphocytes count)
    - C-Reactive Protein (CRP)
    - D-Dimer

  - Procalcitonin
  - Il-6
  - Il-8
- SIRS
  - Time to resolution of SIRS
  - The number of days alive and free from SIRS
  - Total SIRS score
- Any Organ Failure (LISTINGS)
- Respiratory Failure (LISTINGS)
- Renal Failure (LISTINGS)
- Cardiovascular Failure (LISTINGS)
- Sequential Organ Failure Assessment (SOFA):
  - Respiration Score
  - Coagulation Score
  - Liver Score
  - Cardiovascular Score
  - Central Nervous System Score
  - Renal Score
  - SOFA total Score
- Modified Sequential Organ Failure Assessment (MSOFA):
  - Modified total SOFA Score
- Severity as defined by Revised Atlantic Classification of Acute Pancreatitis
- Severity as defined by Determinant Based Classification of Acute Pancreatitis
- APACHE II score
- Pain Numeric Rating Scale (PNRS) score
- Critical-Care Pain Observation Tool (CPOT) score
- Overall Survival (Listings)
- Number of hospitalized days
  - Total Days
  - Days in Intensive Care

3.2 Clinical Study Design

This open-label, dose-response study will evaluate the safety and efficacy of CM4620-IE in patients with acute pancreatitis and accompanying SIRS. The study will consist of two phases. The first phase will consist of 2 cohorts that will be enrolled concurrently. Cohort 1 will consist of 4 female patients who will be randomized 3:1 to receive CM4620-IE plus supportive care versus supportive care alone. Cohort 2 will consist of 4 male patients who will be randomized

3:1 to receive CM4620-IE plus supportive care versus supportive care alone. Planned doses for patients in both cohorts who are randomized to receive CM4620-IE are 1.0 mg/kg on Day 1 and 1.4 mg/kg on Days 2-4. The first infusion of CM4620-IE must be started within 6 (up to 8) hours of the patient or LAR providing informed consent and should be administered IV over 4 hours. Subsequent infusions will be started every 24 hours (± 1 hour) from the start of the first infusion.

The second phase will consist of 2 cohorts. Cohort 3 will consist of 8 female patients who will be randomized 3:1 to receive CM4620-IE plus supportive care versus supportive care alone. Cohort 4 will consist of 8 male patients who will be randomized 3:1 to receive CM4620-IE plus supportive care versus supportive care alone. Planned doses for patients in both cohorts who are randomized to receive CM4620-IE are 2.08 mg/kg of CM4620-IE on Days 1 and 2, and 1.6 mg/kg on Days 3 and 4. The first infusion of CM4620-IE must be started within 6 (up to 8) hours of the patient or LAR providing informed consent and will be administered intravenously IV over 4 hours. Subsequent infusions will be started every 24 hours (± 1 hour) from the start of the first infusion.

The decision to start Cohort 3 will be made after CalciMedica reviews the available efficacy, safety and tolerability data from Cohort 1 and discusses with the Principal Investigators. The decision to start Cohort 4 in the second phase of the study will be made after CalciMedica reviews the available efficacy, safety and tolerability data from Cohort 2 and discusses with the Principal Investigators.

For all 4 cohorts, a study physician or appropriately trained delegate will perform all assessments daily through Day 10, or until discharge if occurring earlier. After Day 10, and starting on Day 12, serious adverse events (SAEs) will be captured every 48 hours until Day 30 (± 2 days), or until discharge if occurring earlier. Patients discharged prior to Day 30 will be contacted on Day 30 (± 2 days) to capture SAEs and any re-admissions to the hospital. Patients will also be contacted on Day 90 (± 7 days) to assess mortality.

3.3 Number of Subjects

24 randomized subjects

3.4 Methods of Assigning Subject to IMP

Patients will be randomized 3:1 to receive CM4620-IE in addition to supportive care consistent with the 2013 IAP/APA evidence-based guidelines for the management of acute pancreatitis versus supportive care alone. Randomization will be stratified by sex. CalciMedica or its designee will prepare the randomization schedule prior to the start of the study

3.5 Blinding

Not applicable

4 STATISTICAL AND ANALYTICAL PLANS

4.1 General

All endpoints below will be presented by:

1) All cohorts

If there will be some exploratory hypothesis testing performed a 5% significance level will be used.

4.2 Sample Size Justification

This open-label study will enroll 24 patients. The sample size was selected based on practical considerations to initially evaluate the safety, efficacy and pharmacokinetic profile of CM4620-IE in patients with acute pancreatitis and accompanying SIRS. This study is not powered for analysis of study data with inferential statistics

4.3 Definition of Analysis Sets

4.3.1 Full Analysis Set

The **Full Analysis Set** (FAS) consists of all randomized patients who receive any amount of CM4620-IE or supportive care. Patients will be analyzed according to treatment they actually received.

4.3.2 Per Protocol Set

No Per Protocol Set will be used.

4.4 Definition of Baseline

Baseline measurement is defined as the latest measurement prior to first dose of IMP including Apache II score.

4.5 Summary Statistics

In general, all data collected will be presented with summary statistics and given in patient data listings. Summary statistics will include at least number of patients, mean, standard deviation, median, minimum and maximum for continuous data and frequency and percentage for categorical data. Table with summary statistics will be divided by treatment group and dose group, and visit where applicable. Patient data listings will be sorted by treatment, subject and timing of assessments.

For confidence intervals for proportions will the Clopper-Pearson exact formula be used.

4.6 Significance Level

If applicable will 5% significance level be used.

4.7 Multiple Comparisons/Multiplicity

No adjustment for multiple comparison/multiplicity will be performed, all significant statistical findings, must be reviewed for medical relevance.

4.8 Handling of Drop-outs, Missing Data and Outliers

Outliers will be included in summary tables and listings, and will not be handled separately in any analyses. No imputation of missing data will be performed (however, will data entered in unscheduled visit be placed to the nearest applicable visit with missing values).

4.9 Adjustment for Covariates

Not applicable

4.10 Multicenter Studies

No adjustment for sites will be performed.

4.11 Examination of Subgroups

Gender and HCT/ALB will be used as subgroups for all secondary endpoints.

4.12 Blind Review

Not applicable.

5 SUBJECTS

5.1 Subject Disposition

The number of subjects that entered the study, withdrawn subjects, completed subjects and the number of subjects at each visit will be summarized by treatment.

5.2 Baseline Characteristics and Demographics

All baseline and demographic data will be presented using summary statistics.

6 TREATMENT INFORMATION AND EXTENT OF EXPOSURE

6.1 Active Treatment

The number of subjects on each IP will be tabulated with start time, stop time and duration of application will be tabulated using listings and summary statistics.

6.2 Prior and Concomitant Medications

Prior and concomitant medication data will be listed and tabulated by ATC code. Prior and concomitant medications will be coded according to the World Health Organization (WHO Drug Dictionary) classification system.

7 STATISTICAL METHODOLOGY

All parameters will be presented by treatment and visit using summary statistics. Additional statistical analyses are specified below.

7.1 Primary endpoint(s)

7.1.1 Definition

The adverse event will be coded using MeDRA dictionary.

Absolute and percent change from baseline will be calculated for both the vital signs and laboratory parameters.

7.1.2 Analysis

The adverse events will be analyzed using frequencies and percent divided by SOC, and PT code using the TESS approach.

The vital signs will be presented using summary statistics by visit.

Safety laboratory parameters will be presented using shift tables.

7.1.3 Presentation

The adverse events will be present using frequency tables.

7.2 Secondary Endpoints – CTSI and mCTSI

7.2.1 Definition

Balthazar score is classified according to the table below

Grade	CT Finding Balthazar	Points
A	Normal Pancreas	0
B	Enlargement of Pancreas	1
C	Inflammatory changes in pancreas and peripancreatic fat	2

D	Ill-defined single peripancreatic fluid collection	3
E	Two or more poorly defined peripancreatic fluid collections	4

Pancreatic Parenchymal Necrosis is classified as:

Pancreatic Necrosis	Points
None	0
<30%	2
30-50%	4
>50%	6

The CTSI score is the sum of the Balthazar and Pancreatic Necrosis scores:

- 0-3: mild acute pancreatitis
- 4-6: moderate acute pancreatitis
- 7-10: severe acute pancreatitis

Change for the category of the severity of acute pancreatitis by CTSI score will be calculated from baseline to day 5 and later dates as necessary.

7.2.2 Analysis

No statistical test will be performed on these variables.

7.2.3 Presentation

Each individual scale will be presented both by using summary statistics in tables and frequency tables.

The total scores will be presented using summary statistics.

7.3 Secondary Endpoints - PASS score

7.3.1 Definition

The definition of the PASS score is in accordance with the description below:

Calculated every 12 hours from 1st vital signs taken in the Emergency Department

Organ Failure Score: # Organs x 100 for each system

Organ Failure Definition: Modified Marshall Scoring System (adapted from Banks et al[4])

	Score				
Organ system	0	1	2	3	4
Respiratory (PaO_2/FiO_2)	>400	301–400	201–300	101–200	≤101
Renal					
Serum creatinine, μmol/L	≤134	134–169	170–310	311–439	>439
Serum creatinine, mg/dL	<1.4	1.4–1.8	1.9–3.6	3.6–4.9	>4.9
Cardiovascular (systolic blood pressure, mmHg)[b]	>90	<90, fluid responsive	<90, not fluid responsive	<90, pH <7.3	<90, pH <7.2

[a]A score of 2 or more in any system defines the presence of organ failure
[b]Off inotropic support

- Mechanical ventilation counts as respiratory organ failure
- New onset dialysis included as renal failure

SIRS (Systemic Inflammatory Response Syndrome): # SIRS Criteria satisfied x 25 for each criteria. (See below)

- Heart Rate > 90 beats per minute
- Temperature > 38 Celsius or < 36 Celsius
- White blood cell count < 4000 or > 12000
- Respiration > 20/minute

Take the most extreme value within each 12 hour window
Take the WBC from the most recent prior CBC if none available in a given 12 hour window

Abdominal Pain Score: Abdominal pain (0-10) x 5

- Highest numerical value in each 12 hour window

Morphine Equivalent Dose Score: Morphine Equivalent Dose x 5

- For consistency will be using IV MED (typical MED is for oral)
- Common conversions: (easiest to convert to IV)
- Morphine IV to PO is 1 to 3 (ie morphine 10 mg IV = 30 mg PO)
- Dilaudid IV to PO is 1 to 4 (ie dilaudid 1.5 mg IV = 7.5 mg PO)
- Dilaudid IV to Morphine IV is 1:7
- Note: 1 po MED = 30 mg oral morphine
- (refer to tables for more specific conversion)

	Parenteral	Oral
Morphine	10	30
Buprenorphine	0.3	0.4 (sl)
Codeine	100	200
Fentanyl	0.1	NA
Hydrocodone	NA	30
Hydromorphone	1.5	7.5
Meperidine	100	300
Oxycodone	10	20
Oxymorphone	1	10
Tramadol	100	120

Equianalgesic dose conversions. For calculation of Pancreatitis Activity Score:

1 MED (morphine equivalent dose) = 1 mg parenteral morphine = 3 mg oral morphine.

Tolerating Solid Diet Score: (yes=0, no=1) x 40

- Retrospective analysis: based on change in diet order
- Prospective analysis: tolerating at least 50% of solid meal without increase abdominal pain or vomiting

Then calculate the total score including absolute and percent change from baseline

7.3.2 Analysis

No analyses will be performed

7.3.3 Presentation

The PASS score will be presented using summary statistics and presented in tables and graphs. The graphs will be the mean value at each visit including the 2-standard error of the mean.

7.4 Secondary Endpoints – Solid food

7.4.1 Definition

The definition of tolerating solid food is that at least 50% is tolerated. Then will the time to first occurrence of tolerating solid food be calculated as date of tolerating solid food – date of randomization +1.

At each visit will tolerating solid food be coded into yes or no.

7.4.2 Analysis

No analyses will be performed

7.4.3 Presentation

The variable tolerating food as yes/no will be presented using frequency tables.

The variable tolerating food as percentage will be presented using summary statistics.

7.5 Secondary Endpoints - Biomarker

7.5.1 Definition

The following biomarkers will be used in the analyses.

ANC/ALC (Absolute neutrophils count / Absolute Lymphocytes count)

C-Reactive Protein (CRP)

D-Dimer

Procalcitonin

Il-6

Il-8

Absolute and percent change will be calculated for each biomarker.

7.5.2 Analysis

No statistical tests will be performed.

7.5.3 Presentation

All biomarkers will be presented using summary statistics and graphs showing both the mean, absolute and percent change over time.

7.6 Secondary Endpoints - SIRS

7.6.1 Definition

SIRS consist of 4 components; temperature of < 36°C or > 38°C, heart rate > 90 beats per minute, respiratory rate >20 breaths per minute or $PaCO_2$ < 32 mmHg and white blood cells (WBC) > 12,000 mm^3, <4000mm^3 or > 10% immature band forms. SIRS is present if two or more of the 4 components are identified. If any of the 4 components are missing, that component will not contribute to the SIRS evaluation.

The total SIRS score is the sum of all SIRS components at each time point

Time to resolution of SIRS will be defined as time from randomization to first sign of resolution of SIRS.

The number of days alive and free from SIRS

7.6.2 Analysis

No statistical tests will be performed.

7.6.3 Presentation

The total score of SIRS will be presented using summary statistics.

7.7 Secondary Endpoints – Organ failure

7.7.1 Definition

Respiratory Failure

The presence of respiratory failure will be assessed on Days 1-10.

Respiratory failure is defined as PaO2/FiO2 ≤300, either determined by ABG or calculated from the SpO2/FiO2 or the use of non-invasive or invasive mechanical ventilation (respiratory support).

Renal Failure

- An increase in serum creatinine ≥300% if the baseline creatinine is known from prior to the hospitalization for acute pancreatitis, or
- A serum creatinine ≥1.9 mg/dL, or
- The initiation of renal replacement therapy

For patients with pre-existing chronic kidney disease, organ failure will be defined as:

- An increase in serum creatinine ≥300% if the baseline creatinine is known from prior to the hospitalization for acute pancreatitis, or
- An increase of serum creatinine to a level >4.0 mg/dl, or

- The initiation of renal replacement therapy

Cardiovascular Failure

The presence of cardiovascular failure will be assessed on Days 1-10. For the cardiovascular system, organ failure will be defined as:

- A systolic blood pressure <90 mmHg that is not fluid responsive, or
- The use of either vasopressor or inotropic support

Any Organ Failure

If the patient meets the conditions for at least one type of organ failure (respiratory failure, renal failure or cardiovascular failure), they have a diagnosis of Organ Failure. If they meet the conditions for more than one organ failure they also have a diagnosis of multiple organ failure. Patients free from all types or organ failure or without data to support diagnosis of organ failure, do not have organ failure

Transient organ failure

Patients with transient organ failure are identified by organ failure lasting less than 48 hours. Persistent organ failure is documented for greater or equal to 48 hours. New persistent Organ Failure is only applicable for patients without Organ Failure at baseline.

7.7.2 Analysis

No statistical tests will be performed.

7.7.3 Presentation

All organ failure variables will only be presented in listings together with the definition variables.

7.8 Secondary Endpoints – SOFA score

7.8.1 Definition

The total SOFA score will be calculated using all including parts:

Respiration Score, Coagulation Score, Liver Score, Cardiovascular Score, Central Nervous System Score, Renal Score in accordance to:

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

The Modified Sequential Organ Failure Assessment (MSOFA) total score will be calculated excluding the Central Nervous System Score.

Absolute and percent changes for each including item and total score will be calculated.

7.8.2 Analysis

No statistical tests will be performed.

7.8.3 Presentation

All including item and total scores will be presented using summary statistics.

7.9 Secondary Endpoints - Revised Atlantic Classification of Acute Pancreatitis

7.9.1 Definition

Revised Atlanta Classification of Acute Pancreatitis, is determined by transient or persistent organ failure (Section 7.7), and local or systemic complications (systemic complications is defined as exacerbation of pre-existing comorbidity).

Grades of Severity	
Mild	No organ failure No local or systemic complications
Moderately Severe	Organ failure that resolves within 48 hours and/or Local or systemic complications without organ failure
Severe	Persistent Organ Failure

7.9.2 Analysis

No statistical tests will be performed.

7.9.3 Presentation

The Revised Atlantic Classification of Acute Pancreatitis will be presented using frequency tables.

7.10 Secondary Endpoints - Determinant Based Classification of Acute Pancreatitis

7.10.1 Definition

Severity as defined by Determinant Based Classification of Acute Pancreatitis will be provided by CalciMedica in excel format in accordance to by subject:

	Mild AP	Moderate AP	Severe AP	Critical AP
(Peri)pancreatic necrosis	No	Sterile	Infected	Infected
	And	And/Or	Or	And
Organ Failure	No	Transient	Persistent	Persistent

The Excel file will have information regarding: Randomization number, outcome of (Peri)pancreatic necrosis. Organ failure will be captured in accordance with section 7.7.

7.10.2 Analysis

No statistical tests will be performed.

7.10.3 Presentation

The Determinant Based Classification of Acute Pancreatitis will be presented using frequency tables.

7.11 Secondary Endpoints - Pain Numeric Rating Scale (PNRS)

7.11.1 Definition

The mean daily Pain Numeric Rating Scale (PNRS) score will be calculated using.

Pain Numeric Rating Scale

1. On a scale of 0 to 10, with 0 being no pain at all and 10 being the worst pain imaginable, how would you rate your pain RIGHT NOW.

0	1	2	3	4	5	6	7	8	9	10
No Pain										**Worst Pain Imaginable**

The absolute and percent change from baseline will be calculated.

7.11.2 Analysis

No statistical tests will be performed.

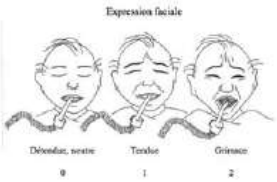
7.11.3 Presentation

The PNRS will be presented using summary statistics with graphs over time presenting the mean, absolute and percent change.

7.12 Secondary Endpoints - Critical-Care Pain Observation Tool (CPOT)

7.12.1 Definition

Critical-Care Pain Observation Tool (CPOT) total score will be calculated from each individual item along with absolute and percent change.

Indicator	Score		Description
Facial expression  Caroline Arbour, RN, B.Sc., PhD(student) School of Nursing, McGill University	Relaxed, neutral	0	No muscle tension observed
	Tense	1	Presence of frowning, brow lowering, orbit tightening and levator contraction or any other change (e.g. opening eyes or tearing during nociceptive procedures)
	Grimacing	2	All previous facial movements plus eyelid tightly closed (the patient may present with mouth open or biting the endotracheal tube)
Body movements	Absence of movements or normal position	0	Does not move at all (doesn't necessarily mean absence of pain) or normal position (movements not aimed toward the pain site or not made for the purpose of protection)
	Protection	1	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements
	Restlessness/Agitation	2	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed
Compliance with the ventilator (intubated patients)	Tolerating ventilator or movement	0	Alarms not activated, easy ventilation
	Coughing but tolerating	1	Coughing, alarms may be activated but stop spontaneously
	Fighting ventilator	2	Asynchrony: blocking ventilation, alarms frequently activated
OR **Vocalization (extubated patients)**	Talking in normal tone or no sound	0	Talking in normal tone or no sound
	Sighing, moaning	1	Sighing, moaning
	Crying out, sobbing	2	Crying out, sobbing
Muscle tension Evaluation by passive flexion and extension of upper limbs when patient is at rest or evaluation when patient is being turned	Relaxed	0	No resistance to passive movements
	Tense, rigid	1	Resistance to passive movements
	Very tense or rigid	2	Strong resistance to passive movements or incapacity to complete them
TOTAL	___ / **8**		

7.12.2 Analysis

No statistical tests will be performed.

7.12.3 Presentation

The CPOT will be presented using summary statistics with graphs over time presenting the mean, absolute and percent change.

7.13 Secondary Endpoints - Overall Survival

7.13.1 Definition

Overall Survival will be defined as 90 days survival. If a patient is alive at day 90 such patient will be censored. The overall survival time will be the time from randomization to either death or censored date (could be lost to follow up or day 90).

The incidence of death will be calculated.

7.13.2 Analysis

No statistical tests will be performed.

7.13.3 Presentation

The incidence of death will be presented using listings.

7.14 Secondary Endpoints – Hospitalization days

7.14.1 Definition

Total time in hospital is defined as (datetime of discharge from hospital – datetime of randomization). The time in intensive care unit will be calculated as time of first ICU visit until discharge from ICU unit. If no endpoint is recorded, time in hospital/ICU will be set to 30 days. If the patient died in hospital/ICU, the date of death (time 00:00 imputed if missing) will be used to calculate time in hospital/ICU.

7.14.2 Analysis

No statistical tests will be performed.

7.14.3 Presentation

Both the total number of hospital days and number of days at ICU will be presented using summary statistics.

7.15 Discontinuation

Patients who discontinue from IMP treatment will be tabulated. The reason for discontinuation will be given. For discontinuation due to AE, the AEs will be given.

7.16 Interim Analysis

Not applicable

8 CHANGES FROM THE CSP

9 STATISTICAL DELIVERABLES

The following documents will be delivered:

- SAP
- Statistical analyses and summary tables

10 SOFTWARE

All statistical analyses will be performed using SAS Version 9.4 (SAS institute, Cary, NC).

11 APPROVAL

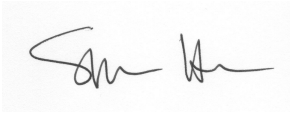
Issued by:

_____ _____

Fredrik Hansson, Director Biometrics — Date (dd-Mmm-yyyy)

CTC Representative

Approved by:



04-Apr-2019

_____ _____

Sudarshan Hebbar — Date (dd-Mmm-yyyy)

CalciMedica Representative