CM4620-202

A Pharmacodynamic and Pharmacokinetic Study of CM4620 Injectable Emulsion in Patients with Acute Pancreatitis

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FOR QUALIFIED INVESTIGATORS AND THEIR IRB ONLY

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Confidentiality Statement

PRINCIPAL INVESTIGATOR STATEMENT OF AGREEMENT

I, the undersigned Principal Investigator, have read and understood the foregoing protocol and its appendices.

I have read, understood and signed the Statement of Investigator Form FDA-1572 that outlines my responsibilities as Principal Investigator.

I have read and understood the provisions of Title 21 of the Code of Federal Regulations Part 312, Subpart D regarding responsibilities of Sponsors and Investigators; and Part 50 regarding protection of human patients and informed consent.

I promise to abide by all applicable laws and regulations, and agree that, in all cases, the most restrictive regulation related to a given aspect of research involving protection of human patients will be followed. In the event I have a question regarding my obligations during the conduct of this protocol, I have ready access to these aforementioned regulations, as either my personal copy, or available on file from the Chairperson of the IRB or CalciMedica, and,

I am authorized to enter into this commitment to conduct the study outlined in this protocol, and my signature below signifies that I agree to conduct the study as outlined herein.

_____

Printed Name of Principal Investigator

_____

Signature of Principal Investigator

_____

Date

SPONSOR APPROVAL AND SIGNATURE PAGE

26-Sep-2018

Sudarshan Hebbar M.D.
Chief Medical Officer

Date

26 Sept 2018

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Chief Scientific Officer

Date

SYNOPSIS

Protocol Number:	CM4620-202
Protocol Title:	A Pharmacodynamic and Pharmacokinetic Study of CM4620 Injectable Emulsion (CM4620-IE) in Patients with Acute Pancreatitis
Sponsor:	CalciMedica, Inc. 505 Coast Blvd. South, Suite 202 La Jolla, CA 92037 USA
Study Phase:	2
Planned Number of Patients and Sites:	Approximately 5 patients with acute pancreatitis will be dosed at 1 site.
CM4620-IE Dose and Route of Administration:	A single dose of CM4620-IE at ≤ 2.08 mg/kg will be administered on Day 1 in 5 patients. If necessary, up to an additional 4 patients may be treated at a different dose of CM4620-IE as determined by the obtained PK and PD data. All doses of CM4620-IE will be administered intravenously (IV) over 4 hours.
Objectives:	*Primary*: • To assess the change in IL-2 production by stimulated T-lymphocytes ex vivo after a single dose of CM4620-IE in patients with acute pancreatitis *Secondary*: • To assess the safety and tolerability of a single dose of CM4620-IE in patients with acute pancreatitis • To determine the pharmacokinetic profile of CM4620-IE after a single dose in patients with acute pancreatitis • To assess changes in circulating levels of IL-6.
Inclusion Criteria:	Patients must meet all of the following criteria to be enrolled in the study: 1. Diagnosis of acute pancreatitis established by the presence of abdominal pain consistent with acute pancreatitis, and 1 of the following 2 criteria: a. Serum lipase and/or serum amylase > 3 times the upper limit of normal (ULN); b. Characteristic findings of acute pancreatitis on abdominal imaging; 2. Adults ≥ 18 years of age; 3. A female patient of child-bearing potential who is sexually active with a male partner must be willing to practice acceptable methods of birth

	control for 365 days after the last dose of CM4620-IE; 4. A male patient who is sexually active with a female partner of childbearing potential must be willing to practice acceptable methods of birth control for 365 days after the last dose of CM4620-IE and must not donate sperm for 365 days; 5. Willing and able to, or have a legal authorized representative (LAR) who is willing and able to, provide informed consent to participate, and cooperate with all aspects of the protocol.
Exclusion Criteria:	Patients with any of the following conditions or characteristics must be excluded from enrolling in the study: 1. Any concurrent clinical condition that a study physician believes could potentially pose an unacceptable health risk to the patient while involved in the study or may limit expected survival to < 6 months; 2. Suspected presence of cholangitis in the judgment of the treating investigator; 3. Any malignancy being treated with chemotherapy or immunotherapy; 4. Any autoimmune disease being treated with immunosuppressive medication or immunotherapy (Section 5.3 for list of prohibited medications); 5. History of: a. Chronic pancreatitis, pancreatic necrosectomy, or pancreatic enzyme replacement therapy; b. Biopsy proven cirrhosis, portal hypertension, hepatic failure/hepatic encephalopathy; c. Known hepatitis B or C, or HIV; d. History of organ or hematologic transplant; e. Myocardial infarction, revascularization, cardiovascular accident (CVA) in the 30 days prior to Day 1; 6. Current renal replacement therapy; 7. Current known abuse of cocaine or methamphetamine; 8. Known to be pregnant or are nursing; 9. Participated in another study of an investigational drug or therapeutic medical device in the 30 days prior to Day 1; 10. History of allergy to eggs or known hypersensitivity to any components of CM4620-IE; 11. Prior treatment with CM4620-IE.

Study Design:	This open-label study will evaluate the pharmacodynamic and pharmacokinetic profile of CM4620-IE in patients with acute pancreatitis. The first five (5) patients will receive ≤ 2.08 mg/kg of CM4620-IE by continuous IV infusion on Day 1. If necessary, up to an additional 4 patients may be treated at a different dose of CM4620-IE as determined by the obtained PK and PD data. The infusion of CM4620-IE will start within 12 hours from the time the patient or LAR provides informed consent. The decision to enroll additional patients will be made after CalciMedica reviews the available pharmacodynamic, pharmacokinetic, safety and tolerability data from the first 5 patients enrolled and discusses the data with the Principal Investigator. A study physician or appropriately trained delegate will perform in all patients enrolled in the study who remain hospitalized, selected safety assessments daily through Day 10 and every 48 hours from Day 12 until Day 30, or until discharge if occurring earlier. Patients discharged prior to Day 30 will be asked to return for a blood draw and SAE evaluation. Those patients who do not return will be contacted on Day 30 (± 2 days) to capture SAEs and any readmissions to the hospital. Patients will also be contacted on Day 90 (± 7 days) to assess mortality. It is recommended that all patients in the study should receive supportive care consistent with the 2013 International Association of Pancreatology (IAP)/American Pancreatic Association (APA) evidence-based guidelines for the management of acute pancreatitis, and local standard of care (SOC) for the management of other medical conditions. Fluid resuscitation should be provided to all patients as recommended in the guidelines; lactated Ringer's solution may be the preferred replacement fluid for patients with acute pancreatitis.
Safety Assessments:	Safety assessments will consist of: • Limited physical examinations • Vital sign measurements • Clinical laboratory measurements • Specified concomitant medications • Incidence, intensity and relationship of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Pharmacodynamic Assessment:	Blood samples for the measurement of IL-2 production by stimulated T-lymphocytes will be obtained prior to the administration of CM4620-IE, and after completion of CM4620-IE administration. Serum or plasma samples will also be collected at these times for the measurement of IL-6 levels.

Pharmacokinetic Assessments:	Plasma samples for bioanalytical assessment of CM4620 concentration will be obtained after the completion of CM4620-IE administration.
Statistical Considerations	This study is not powered for analysis of study data with inferential statistics. All data will be summarized using descriptive statistics only. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard of deviation, coefficient of variation and or geometric mean. Categorical data will be summarized with number and proportion of patients.

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LIST OF TERMS AND ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AP	Acute Pancreatitis
APACHE II	Acute Physiology and Chronic Health Evaluation II
AST	Aspartate transaminase
ATP	Adenosine triphosphate
BUN	Blood urea nitrogen
CCK	Cholecystokinin
CECT	Contrast Enhanced Computed Tomography
CGMO	Current Good Manufacturing Practice
CPOT	Critical Care Pain Observation Tool
CRF	Case report form
CRAC	Calcium release-activated calcium
CTSI	Computed Tomography Severity Index
CV	Cardiovascular
ECG	Electrocardiogram
EDTA	Edetate disodium salt dehydrate
ER	Endoplasmic reticulum
ERCP	Endoscopic retrograde cholangiopancreatography
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GFR	Glomerular filtration rate
HED	Human equivalent dose
hr(s)	Hour(s)
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent to Treat
kg	Kilogram
L	Liter
LAR	Legal authorized representative
MAD	Multiple ascending dose
mg	milligram

Abbreviation	Definition
MPO	Myeloperoxidase
NOAEL	No observable adverse effect level
PNRS	Pain numeric rating scale
PEEP	Positive end-expiratory pressure
PK	Pharmacokinetic
PP	Per protocol
QTcF	QT corrected for HR using Fridericia's method
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	Standard of care
SOCE	Store-operated calcium entry
SOFA	Sequential organ failure assessment
SOP	Standard operating procedures
VTBI	Volume to be infused
WBC	White blood cell
µg	microgram

1 INTRODUCTION

1.1 Acute Pancreatitis

Acute pancreatitis (AP) is an acute inflammatory process of the pancreas with varying involvement of local tissues and/or more remote organ systems. Due to the dynamic nature of the disease, it leads to wide-ranging outcomes that evolve rapidly in any given patient with little predictability. There is no prescribed order of events that the disease course follows, beyond the basic concept of an early (usually <1-2 weeks) and a late (>1-2 weeks) phase, with the former characterised by varying degrees of pancreatic, and potentially systemic, inflammation, and the latter by a compensatory immunosuppressive phase that can make patients susceptible to infection.

Due to the evolving nature of AP, the severity may change during the course of the disease. The Atlanta classification of 2012 defines three degrees of severity: mild acute pancreatitis, moderately severe AP, and severe acute pancreatitis (Banks 2013). Terminology that is important in this classification includes transient organ failure, persistent organ failure, and local or systemic complications. Transient organ failure is organ failure that is present for < 48 hours. Persistent organ failure is defined as organ failure that persists for ≥ 48 hours. Local complications include peripancreatic fluid collections and acute necrotic collections, while systemic complications can be related to exacerbations of underlying co-morbidities. Severe acute pancreatitis is defined by the presence of persistent organ failure, moderately severe acute pancreatitis by either or transient organ failure or local or systemic complications, and mild acute pancreatitis by none of these features. A new international classification, referred to as the 'determinant-based classification of severity', has been proposed as an alternative to the Atlanta classification (Dellinger 2012). This classification is based on the actual local and systemic determinants of severity, rather than a description of events that are correlated with severity. The derivation of a classification based on the above principles results in four categories of severity: mild, moderate, severe, and critical. The determinant-based classification approach to severity has elicited a great deal of interest; nevertheless, the Atlanta classification remains the standard against which severity of AP is assessed.

AP can be subdivided into two histopathological subtypes: interstitial oedematous pancreatitis and necrotising pancreatitis. In the majority of cases, AP comprises clinically of a mild transitory form of oedematous-interstitial inflammation, which is self-limiting and resolves spontaneously. However, 15–20% of patients with AP will develop the more severe form of the disease (Whitcomb 2006). Necrotising pancreatitis most commonly manifests as necrosis involving both the pancreas and peripancreatic tissues and, less commonly, as necrosis of only the peripancreatic tissue, and rarely of the pancreatic parenchyma alone. Patients with peripancreatic necrosis alone have increased morbidity and intervention rates compared to patients with interstitial oedematous pancreatitis (Singh 2011). Repeated attacks of AP can result in chronic pancreatitis, which increases the risk of developing pancreatic cancer by up to 100-fold (Petersen 2006).

Gallstones and alcohol misuse are long-established risk factors for AP. The next most common cause is thought to be endoscopic procedures, e.g. endoscopic retrograde cholangiopancreatography (ERCP). Other causes include surgery or trauma, metabolic problems, infections, hereditary

factors and drugs. A small residual group has no obvious cause and is labelled ‘‘idiopathic.’’ However, many of these may be due to unidentified microlithiasis (cholesterol crystals, biliary sludge, or small stones). Smoking is an independent risk factor, and its effects could be synergistic with those of alcohol (Lindkvist 2008; Tolstrup 2009).

There are currently two primary aims in the initial treatment of patients with AP. The first aim is to provide supportive therapy, and to treat specific complications that may occur. The second aim is to limit the severity of pancreatic inflammation, necrosis, and SIRS (Werner 2005).

There is currently no approved pharmaceutical treatment for AP, regardless of the severity of the disease (Lankisch 2015). Fluid resuscitation is at the cornerstone of early treatment of AP (Lankisch 2015). Analgesics, usually opioids, are administered initially to manage the abdominal pain. Enteral feeding can also be used and is preferred over exclusive parenteral nutrition. Thus, patients are generally managed with supportive care, including fluid replacement, painkillers, oxygen, feeding via a tube or into a vein, and antibiotics. Severely ill patients with organ failure are managed aggressively using a variety of different treatment strategies.

1.2 Pathophysiology of Acute Pancreatitis

The exocrine pancreas is a highly specialised secretory organ capable of synthesizing, storing and releasing large quantities of digestive enzyme precursors into the small intestine, essential for the breakdown of food. Homeostasis of the functional cellular unit, the acinar cell, is therefore paramount for the smooth running of physiological processes; disruption can lead to severe damage of the pancreas, resulting in premature activation of zymogens, vacuolization and necrotic cell death, features typical of AP.

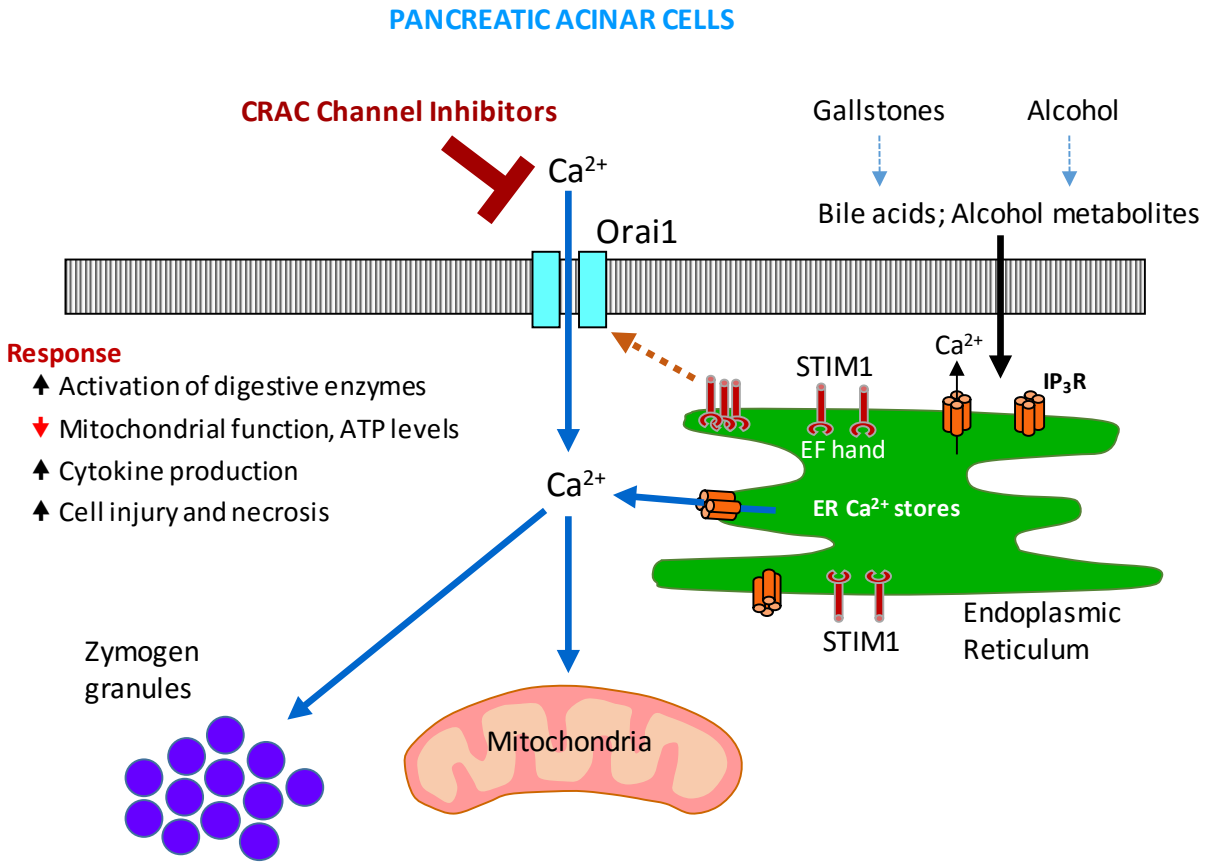
The pancreatic acinar cells are responsible for synthesizing digestive proenzymes such as trypsinogen, which, when secreted with pancreatic fluids, become activated in the gut to help digest food. This secretory process is regulated through cytosolic calcium levels in the pancreatic acinar cells. At physiological concentrations, the neurotransmitter acetylcholine and the hormone cholecystokinin (CCK) evoke repetitive short-lasting increases in cytosolic Ca^{2+} in pancreatic acinar cells, provided by Ca^{2+} release from internal stores such as the endoplasmic reticulum (ER) (Petersen 2011). Repetitive release of Ca^{2+} from internal stores triggers activation of store operated calcium entry (SOCE) through Calcium Release-Activated Calcium (CRAC) channels to replenish the stores from interstitial fluid and activates mitochondria to produce adenosine triphosphate (ATP) (Petersen 2011; Gerasimenko 2013). Both Ca^{2+} and ATP are required for the secretion of the digestive proenzymes and the accompanying fluid needed to wash the secreted proteases out of the duct system and into the gut (Petersen 2011).

The triggers of AP, such as gallstones and alcohol, lead to massive and sustained release Ca^{2+} from ER stores, resulting in maintenance of high cytosolic Ca^{2+} levels and a Ca^{2+} depleted state of the stores (Muallem 1988). The sustained cytosolic Ca^{2+} elevation is due to excessive Ca^{2+} entry into the cells from the interstitial fluid following depletion of ER Ca^{2+} stores. Mechanistically, when the ER stores are depleted of Ca^{2+} the acinar cell attempts to refill the stores with Ca^{2+} entering through a plasma membrane CRAC channel, with Orai1 being the key

Ca^{2+}-conducting component of the channel complex (Lur 2009). The opening of the Orai1 channel is activated by STIM1 in response to ER Ca^{2+} store depletion (Gerasimenko 2013).

The massive release of ER Ca^{2+} followed by the sustained elevation in cytosolic Ca^{2+} causes the digestive enzymes to be activated inappropriately within the acinar cells, resulting in autodigestion (i.e., digestion of the pancreas and surrounding tissue), necrosis (Phillip 2014), and the characteristic features of AP. Elevated cytosolic Ca^{2+} also results in lower production of ATP by mitochondria, which limits the cell's ability to handle stress and the high intracellular Ca^{2+} load, further promoting necrosis (Criddle 2016). Figure 1 shows the sequence of events leading to AP following activation of CRAC channels.

Figure 1. Schema showing the activation of CRAC channels found on pancreatic acinar cells triggering a series of events which lead to acute pancreatitis.



1.3 Overview of CM4620

CM4620 is a potent and selective inhibitor of CRAC channels. CRAC channels are composed of the pore-forming plasma membrane protein Orai1 and the calcium-sensing ER gating-protein STIM1. Low levels of calcium within the ER cause the STIM1 protein to oligomerize and move to locations closely apposed to Orai1. When STIM1 binds to Orai1, the Orai1 Ca^{2+} pore opens, permitting entry of extracellular calcium into the cell through the CRAC channel. This process is referred to as SOCE and evidence suggests that SOCE through CRAC channels plays a critical role in the degradation and necrosis of pancreatic acinar cells in patients with AP.

The potential for CM4620 to inhibit CRAC channels was investigated by measuring the electrophysiological current (I_{CRAC}) associated with calcium entry through CRAC channels in HEK293 cells stably expressing recombinant human Orai1/STIM1. Cellular recordings were performed using the whole-cell patch clamp method. Measurements of I_{CRAC} were made after the addition of extracellular 10 mM calcium chloride and subsequent administration of CM4620 at concentrations of 0.001, 0.01, 0.1, and 1 μM. CM4620 was able to inhibit I_{CRAC} in a concentration-dependent manner, producing a mean 50% inhibition (IC_{50}) value of 119 nM. Rapid and complete inhibition was achieved at 1 μM of CM4620. Evaluations were performed to further elucidate the site of action of CM4620. A mutation in Orai1 (Orai1-V102C) is known to produce constitutively active CRAC channels without the need for STIM1. In this evaluation, successive concentrations of CM4620 produced nearly complete inhibition of the STIM1-independent I_{CRAC}, indicating that Orai1 is a major site of action of the compound.

1.4 Pre-Clinical Development of CM4620

1.4.1 Pre-Clinical Safety and Toxicology Studies

Safety pharmacology studies conducted in rats indicated no CM4620-induced adverse effects on central nervous or respiratory systems. Dose-limiting adverse clinical and cardiovascular effects were noted in a single telemetered cynomolgus monkey dosed at 25 mg/kg IV with CM4620-IE. Cardiovascular data at lower doses (1, 3 and 10 mg/kg) showed transient, non-dose-related, slight-to-moderate increases in systolic/diastolic arterial blood pressures and negative chronotropic effects (mild and non-adverse) at all doses and in placebo treated animals.

Repeat-dose toxicity studies conducted in both rats and monkeys showed no observable adverse effect levels (NOAELs) of 25 mg/kg/day and 3 mg/kg/day, respectively. In vitro genetic toxicity studies were negative in the Ames bacterial reverse mutation assay and weakly positive/equivocal in a micronucleus assay conducted in human peripheral blood lymphocytes. A subsequent in vivo micronucleus study conducted in rats involving two different endpoints (bone marrow micronucleus and liver Comet assays) showed no evidence of DNA reactivity. Based on the results of the complete battery of genotoxicity testing, the weight of evidence indicates that CM4620 is neither mutagenic nor clastogenic. Hemolysis testing concluded that CM4620 placebo was compatible with human plasma and non-hemolytic in human blood. Specific local tolerance studies to examine irritation/inflammation at the injection site were not performed, but no evidence of compound-related or vehicle-related local irritation was observed in the repeat-

dose toxicity studies in rat and monkey. Finally, in vitro 3T3 results indicated that CM4620 is potentially phototoxic, so appropriate precautions are being taken in clinical trials.

1.4.2 Preclinical Efficacy Studies

Non-clinical studies conducted in murine and human pancreatic acinar cells to date have demonstrated that by acting on CRAC channels in pancreatic acinar cells, CM4620 can protect these cells from pancreatitis-induced cell death and can reduce biochemical, immunological and histopathologic consequences when administered early in the course of the disease. CM4620 caused marked reductions in serum amylase activity, pancreatic trypsin activity, myeloperoxidase (MPO) activity (a marker of neutrophil infiltration) in the pancreas and lung, and led to a significant reduction in pancreatic histopathology scores. Importantly, the non-clinical findings provide proof of concept that CM4620 has the potential to be effective in the treatment of AP regardless of the cause and support the administration of CM4620 as an IV infusion to humans. Additional non-clinical evidence supports the position that the effects of CM4620 on the pancreas are complimented by its ability to reduce inflammatory responses that can manifest clinically as SIRS.

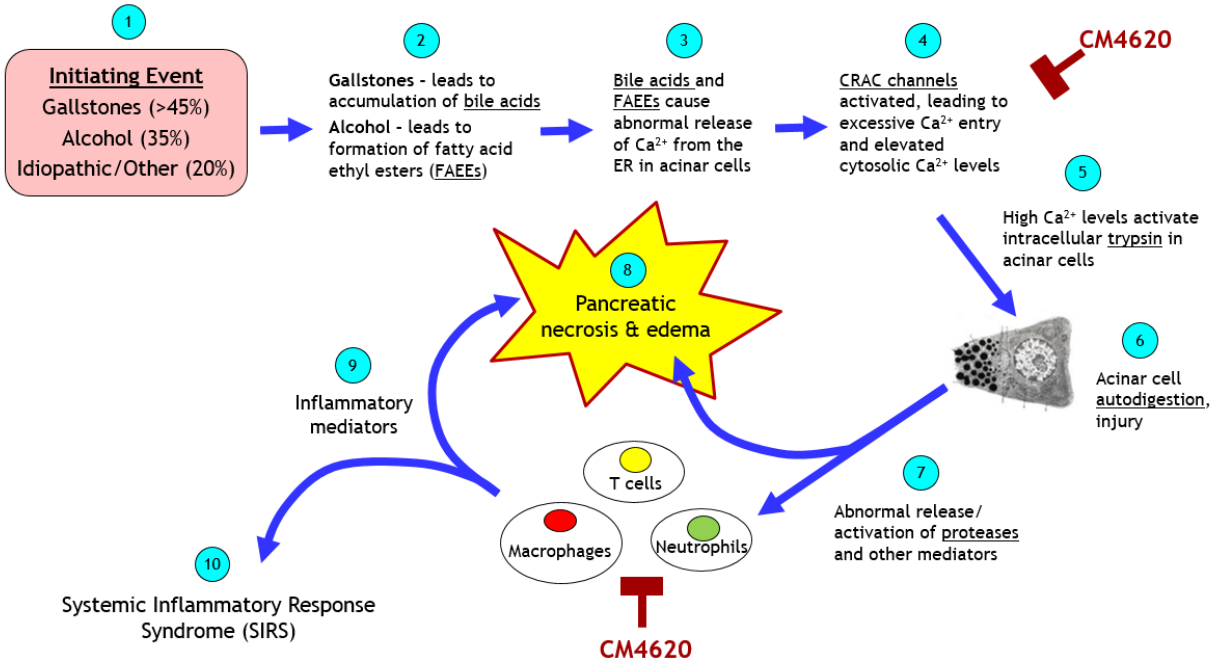
The protection offered by CM4620 in vitro has been confirmed in three diverse in vivo models representative of gallstone-, alcohol-, or hyper-stimulation–induced acute pancreatitis (TLCS-induced, fatty acid ethyl ester [FAEE]-induced and caerulein-induced pancreatitis models, respectively). Trypsin activity within pancreatic tissue, myeloperoxidase activity within pancreatic and lung tissue, and histopathological indices of pancreatic damage, such as edema, inflammatory cell infiltration, vacuolization, and necrosis, were all markedly reduced following single 5-20 mg/kg intraperitoneal (IP) doses of CM4620 in the mouse (caerulein-induced acute pancreatitis), two 5 or 20 mg/kg IP doses of CM4620 in the mouse (TLCS-induced and FAEE-induced pancreatitis models) or one 4-hour IV infusion of CM4620 Nano-emulsion (the intended clinical dosage form, route of administration and infusion duration) at doses of 5-20 mg/kg in the rat (caerulein-induced pancreatitis model). The timing of CM4620 administration relative to induction of pancreatitis was investigated in the TLCS-induced and FAEE-induced pancreatitis models and the results suggest that CM4620 may be more effective in minimizing pancreatic injury and subsequent downstream events if it is administered early in the course of disease, although later administration retains effectiveness in halting disease progression (Wen 2015).

The potential for CM4620 to reduce SIRS through an inhibitory effect on immune cells has been investigated in vitro, ex vivo and as part of in vivo pancreatitis models. In vitro, CM4620 inhibited human neutrophil function and inhibited release of key inflammatory cytokines (IL-2, IFNγ and IL-17) in human lymphocytes (IC_{50} 4-138 nM). Results from ex vivo pharmacodynamic analyses in blood demonstrated that CM4620 was able to significantly reduce stimulated IL-2 secretion from T cells, and presumably other lymphocytes, in a dose-dependent manner in Sprague Dawley rats and cynomolgus monkeys after 14 days of oral dosing. Further, the effects of CM4620 on myeloperoxidase activity in the lung of mice in TLCS-induced and FAEE-induced pancreatitis models and rats in the caerulein-induced pancreatitis model were assessed. Myeloperoxidase activity is a measure of neutrophil infiltration and when seen in the lung in these models it is indicative of a systemic inflammatory process analogous to SIRS in humans.

Two IP doses of CM4620 at 20 mg/kg in mice or one 4-hour infusion of CM4620 Nano-emulsion at 5 mg/kg in rats were able to substantially reduce lung myeloperoxidase activity (80% reduction in the mouse TLCS model, 73% reduction in the rat caerulein model). Lastly, in the IV infusion study in rats, CM4620 significantly reduced IL-6 and TNFα mRNA levels in both pancreas and lung, as well as that of myeloperoxidase.

Figure 2 highlights the potential role of CM4620 in treating acute pancreatitis through its effects on both the acinar cell and the immune system:

Figure 2. Sites of action of CM4620 in treating acute pancreatitis



1.5 Clinical Development of CM4620-IE

CalciMedica has conducted two Phase 1 studies of CM4620-IE in healthy subjects: a single ascending dose (SAD) study (CM4620-101) and a multiple ascending dose (MAD) study (CM4620-102). In CM4620-101 (Table 1), 32 healthy subjects were enrolled in five groups and randomized in a 3:1 ratio to receive a single dose of active versus placebo. The dose levels for each group are noted in Table 1. The dose volume of the emulsion was fixed at 1.3 mL/kg for all subjects in the SAD study groups, and CM4620-IE or placebo was administered via a 4-hour IV infusion.

Table 1 SAD (CM4620-101)

Group	Active Treatment	Number of Active Treatment Subjects	Number of Placebo Treatment Subjects	IV Dose Volume (mL/kg)
1	0.1 mg/kg	6	2	1.3
2	0.24 mg/kg	3	1	1.3
3	0.48 mg/kg	3	1	1.3
4	1.0 mg/kg	6	2	1.3
5	2.1 mg/kg	6	2	1.3

Of the 32 enrolled subjects, there were no serious adverse events (SAE) or adverse events (AE) classified as moderate or severe in intensity. There were three clinical AEs that were all classified as mild in intensity. Two of the AEs were considered possibly related and one was considered unlikely or unrelated to study treatment. In each case, no action was taken with respect to study treatment because of the AEs. No laboratory abnormalities were observed that were considered clinically significant. There were vehicle-related increases in serum triglyceride and cholesterol levels noted in some subjects that returned to baseline within 24 hours. There was no evidence of any sustained treatment-related increase in systolic or diastolic blood pressure. In addition, cardiac function, monitored by continuous electrocardiographic recording and serial biomarker testing, showed no evidence of any treatment-related effect on heart rate, QTcF, cardiac troponin-T or B-type natriuretic peptide levels.

In the SAD study (CM4620-101), interim non-compartmental pharmacokinetic (PK) analysis indicates that CM4620 likely distributes to three compartments. Plasma concentrations of compound rise steadily during the 4-hour infusion, with T_{max} achieved at the end of infusion (4 hours). After the end of infusion, there is a rapid and prominent distribution phase followed by a prolonged period of residual drug levels. The terminal elimination phase has not yet been fully characterized as it appears to be much longer than was anticipated based on pre-clinical PK data in mouse, rat, dog and monkey. Plasma concentrations during the terminal phase are approximately 5% of C_{max} values and, as indicated above, to date there have been no clinically significant AEs reported during this phase. Plasma exposures, defined by $AUC_{0\text{-}24h}$, appear to be dose-proportional and reached a maximum of 6710 ng*h/mL in Group 5, which is 4.3-fold below the mean AUC_{24h} in monkey at the NOAEL (29,000 ng*hr/mL).

In the MAD study (Table 2) of CM4620-IE (CM4620-102), subjects in the first group were randomized to receive a single dose of active treatment, 0.50 mg/kg, versus placebo for seven consecutive days. Eight healthy subjects were enrolled in the first group, with five receiving active treatment and three receiving placebo. One of the subjects received placebo at the maximum dose volume of emulsion, 1.3 mL/kg, for 7 days, whereas all others were dosed on a weight-based adjustment of dose volume. There were no SAEs and no AEs classified as moderate or severe in intensity. There were 15 clinical AEs that were all classified as mild. In each case, no action was taken with respect to study treatment because of the AEs. No laboratory abnormalities were observed that were considered clinically significant.

Table 2 MAD (CM4620-102)

Group	Active Treatment Daily for 7 days	Number of Active Treatment Subjects	Number of Placebo Treatment Subjects	IV Dose Volume (mL/kg)
1	0.5 mg/kg	5	3	0.3125a
2	1.0 mg/kg	6	2	0.625

[a] one placebo patient received maximum dose volume of 1.3 mL/kg

Subjects in the second group of CM4620-102 were randomized to receive a single dose of active treatment, 1.0 mg/kg, versus placebo for seven consecutive days. Eight healthy subjects were enrolled in the second group, with six receiving active treatment and two receiving placebo for seven consecutive days. There were no SAEs and no AEs classified as moderate or severe in intensity. There were three AEs that were all classified as mild in intensity. In each case, no action was taken with respect to study treatment because of the AEs. No laboratory abnormalities were observed that were considered clinically significant.

There were vehicle-related increases in serum triglyceride noted in some subjects in both groups with levels returning to baseline within 24 hours. Cholesterol levels accumulated in some subjects in both groups with daily dosing but the increases were not considered clinically significant and were related to the vehicle. Thus, the largest rise in cholesterol levels was in the subject who received placebo at the maximum dose volume of emulsion. The rise in cholesterol is believed to be due to the release of tissue cholesterol induced by the lecithin in the emulsion (Byers 1962), was noted in the pre-clinical studies in monkeys, and was reversible with cessation of dosing. There was no evidence of any sustained treatment-related increase in systolic or diastolic blood pressure. In addition, cardiac function, monitored by continuous electrocardiographic recording and serial biomarker testing, showed no evidence of any sustained treatment-related effect on heart rate, QTcF or B-type natriuretic peptide levels.

Non-compartmental PK analysis of Group 1 in CM4620-102 (0.5 mg/kg) indicates that CM4620 accumulated in plasma, with a 2.6-fold increase in systemic exposure (AUC_{24h}) on Day 7 compared to Day 1 of dosing, consistent with modeling simulations. C_{max} accumulated 1.6-fold (geometric mean of 363 ng/mL on Day 7). The geometric mean of the AUC_{24h} on Day 7 was 3190 ng*hr/mL, which is 9.1-fold below the NOAEL AUC_{24h} in monkey (29,000 ng*hr/mL). PK analysis of Group 2 in CM4620-102 (1.0 mg/kg) indicates that CM4620 accumulated in plasma, with a 2.6-fold increase in AUC_{24h} on Day 7 compared to Day 1 of dosing, consistent with modeling simulations. C_{max} accumulated 1.4-fold (geometric mean 637 ng/mL on Day 7). The geometric mean of the AUC_{24h} on Day 7 was 6830 ng*hr/mL, which is 4.2-fold below the NOAEL AUC_{24h} in monkey (29,000 ng*hr/mL). After the end of 7 days of infusion, there remained a prolonged period of relatively low residual drug levels in both MAD groups, in which plasma levels on Days 11-270 remained significantly lower (69-90% lower) than the C_{max} on Day 7.

Subjects in Groups 4 and 5 of the SAD study and Groups 1 and 2 of the MAD study who received CM4620 were followed for 365 days in a long-term extension study to assess for adverse events and serious adverse events. In addition, PK levels were drawn in all 4 groups on Day 270 to

further characterize the terminal phase and the prolonged period of residual drug level as well as recalculate the terminal half-life. There were no SAEs or AEs reported as moderate or severe in severity in subjects followed for 365 days.

A population PK model was built using the data from the SAD and MAD studies. The model suggested three compartments for distribution as well as gender and body weight-dependent differences in exposures. The model showed that females have a higher volume of distribution compared to males and that body-weight also had a significant influence on volume of distribution. These features may be related to lower plasma AUC_{24h} values in females versus males, and patients with higher body weights may have a lower AUC. The model was then used to identity the dosing regimens for the first and second phases of study CM4620-201, an open-label dose-response study of CM4620 injectable emulsion in patients with acute pancreatitis and accompanying systemic inflammatory response syndrome that is currently enrolling patients.

1.6 Rationale for the Study and Selected Doses

As mentioned above, an open-label study in patients with acute pancreatitis is currently being performed to further characterize the safety, efficacy and pharmacokinetic profile of a higher exposure of CM4620-IE than that obtained on Day 7 in the 5th group of the SAD and the 2nd group of the MAD. There will be three dose groups in the open-label study: patients who receive no drug, patients who receive dosing of drug that would result in a mean plasma AUC_{24h} after dosing on Day 4 similar to the mean AUC_{24h} on Day 7 in the 5th group of the SAD study and the 2nd group of the MAD study, and patients who receive dosing of drug that would result in a mean plasma AUC_{24h} on Day 4 that is 30% higher than that in Phase 1 of the open-label study.

The first dose level selected for the current pharmacodynamic and pharmacokinetic study (CM4620-202) comes from doses to be administered on Day 1 of study CM4620-201 (1.0 or 2.08 mg/kg), the open label safety, efficacy and pharmacokinetic study that is currently active and screening patients. Doses of ≥1.0 mg/kg are projected to achieve blood levels of CM4620 at T_{max} that will be inhibitory to CRAC channels and in an *ex vivo* whole blood assay of stimulated IL-2 release from T lymphocytes that depends on CRAC channel activity, thereby demonstrating pharmacological activity of CM4620 in blood. It is hypothesized that with the proper dose regimen, pharmacological activity of CM4620 in blood will indicate potential for achieving efficacy in treating acute pancreatitis and accompanying SIRS.

2 OBJECTIVES

2.1 Primary Objective

- To assess the change in IL-2 production by stimulated T-lymphocytes ex vivo after a single dose of CM4620-IE in patients with acute pancreatitis.

2.2 Secondary Objectives

- To assess the safety and tolerability of a single dose of CM4620-IE in patients with acute pancreatitis.
- To determine the pharmacokinetic profile of CM4620-IE after a single dose in patients with acute pancreatitis.
- To assess changes in circulating levels of IL-6.

3 INVESTIGATIONAL PLAN

3.1 Study Design

This open-label, dose-response, study will evaluate the pharmacodynamic and pharmacokinetic profile of CM4620-IE in patients with acute pancreatitis. The first 5 patients will receive ≤2.08 mg/kg of CM4620-IE by continuous IV infusion on Day 1. If necessary, up to an additional 4 patients may be treated at a different dose of CM4620-IE determined by the obtained PK and PD data. The infusion of CM4620-IE will start within 12 hours from the time the patient or LAR provides informed consent.

The decision to enroll additional patients will be made after CalciMedica reviews the available pharmacodynamic, pharmacokinetic, safety and tolerability data from the first 5 patients enrolled and discusses the data with the Principal Investigator.

A study physician or appropriately trained delegate will perform in all patients enrolled in the study who remain hospitalized, selected safety assessments daily through Day 10 and every 48 hours from Day 12 until Day 30, or until discharge if occurring earlier. Patients discharged prior to Day 30 will be asked to return on Day 30 to provide a blood draw for PK and PD determinations and to record any SAEs and readmissions to the hospital. For patients that cannot return to the hospital on Day 30, they will be contacted on Day 30 (± 2 days) to capture SAEs and any readmissions to the hospital. Patients will also be contacted on Day 90 (± 7 days) to assess mortality.

CalciMedica may submit modifications to the protocol to change the planned doses, the dosing schedule, the infusion time, the number of sites in the study and the total number of patients enrolled in the study for safety and/or tolerability considerations.

3.2 End of Study

The End of Study is considered the date on which the last patient completes the visit on Day 90, unless CalciMedica or the Regulatory Authority overseeing this program terminates the study early.

3.3 Sponsor or Regulatory Agency Termination of the Study

Although CalciMedica intends to complete the study as outlined, CalciMedica reserves the right to terminate the study at any time for any clinical or administrative reason, or if required by a regulatory agency.

4 SELECTION OF PATIENTS

4.1 Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in a cohort:

1. Diagnosis of acute pancreatitis established by the presence of abdominal pain consistent with acute pancreatitis and 1 of the following 2 criteria:
   a. Serum lipase and/or serum amylase > 3 times the upper limit of normal (ULN);
   b. Characteristic findings of acute pancreatitis on abdominal imaging;
2. Adults ≥ 18 years of age;
3. A female patient of child-bearing potential who is sexually active with a male partner must be willing to practice acceptable methods of birth control for 365 days after the last dose of CM4620-IE;
4. A male patient who is sexually active with a female partner of childbearing potential must be willing to practice acceptable methods of birth control for 365 days after the last dose of CM4620-IE and must not donate sperm for 365 days;
5. Willing and able to, or have a LAR who is willing and able to, provide informed consent to participate and cooperate with all aspects of the protocol.

4.2 Exclusion Criteria

Patients with any of the following conditions or characteristics must be excluded from enrolling in a cohort:

1. Any concurrent clinical condition that a study physician believes could potentially pose an unacceptable health risk to the patient while involved in the study or may limit expected survival to < 6 months;
2. Suspected presence of cholangitis, in the judgment of the treating investigator;
3. Any malignancy being treated with chemotherapy or immunotherapy;
4. Any autoimmune disease being treated with immunosuppressive medication or immunotherapy (Section 5.3 for list of prohibited medications);
5. History of:
    a. Chronic pancreatitis, pancreatic necrosectomy, or pancreatic enzyme replacement therapy;
    b. Biopsy proven cirrhosis, portal hypertension, hepatic failure/hepatic encephalopathy;
    c. Known hepatitis B or C, or HIV;
    d. History of organ or hematologic transplant;
    e. Myocardial infarction, revascularization, cardiovascular accident (CVA) in the 30 days prior to Day 1;
6. Current renal replacement therapy;
7. Current known abuse of cocaine or methamphetamine;
8. Known to be pregnant or are nursing;
9. Participated in another study of an investigational drug or therapeutic medical device in the 30 days prior to Day 1;
10. History of allergy to eggs or known hypersensitivity to any components of CM4620-IE.
11. Prior treatment with CM4620-IE.

5 TREATMENT OF PATIENTS

5.1 Overview

All patients in the study should receive supportive care consistent with the 2013 IAP/APA evidence-based guidelines for the management of acute pancreatitis, and local SOC for the management of other medical conditions. Fluid resuscitation should be provided to all patients as recommended in the guidelines; lactated Ringer's solution may be the preferred replacement fluid for patients with acute pancreatitis.

A summary of recommendations from the 2013 IAP/APA evidence based guidelines for the management of acute pancreatitis is listed in Appendix 1.

5.2 Discharge Criteria

All patients should be discharged from the hospital using criteria consistent with local standard of care (SOC). The suggested criteria for discharging patients with acute pancreatitis from the hospital are:

- Abdominal pain has resolved
- Normal oral diet is tolerated
- There is no clinical or laboratory evidence of an infection or continued inflammation

5.3 Prohibited Medications

Any medication, with the exception of those listed below, may be given at the discretion of the PI. Immunosuppressive medications/immunotherapy that should not be administered during the study include:

- Chemotherapy
- Cyclosporine, Tacrolimus
- Sirolimus, Everolimus
- Azathioprine
- Cyclosphosphamide
- Methotrexate
- Mycophenolate
- Biologics/Monoclonals: abatacept, adalimumab, alemtuzumab, anakinra, basilizimab, belimumab, bevacizumab, brodalumab, canakinumab, certolizumab, cetuximab, daclizumab, eculizumab, etanercept, golimumab, infliximab, interferon, ixekizumab,

muromonab, natalizumab, omalizumab, rituximab, secukinumab, tocilizumab, trastuzumab, ustekinumab, vedolizumab

5.4 Compliance

Only the PI or his/her appropriately trained study staff will administer CM4620-IE to patients entered into the trial in accordance with the protocol. CM4620-IE must not be used for any reasons other than that described in the protocol.

6 PROCEDURES

6.1 Enrollment Procedures

Patients will be sequentially enrolled to receive CM4620-IE in addition to supportive care consistent with the 2013 IAP/APA evidence-based guidelines for the management of acute pancreatitis.

6.2 Discontinuation and Withdrawal

Discontinuation refers to the patient or PI discontinuing the administration of CM4620-IE before the 4-hour infusion has been completed. Patients have the right to discontinue the administration of CM4620-IE at any time for any reason, without prejudice to their medical care. The PI may discontinue the administration of CM4620-IE because of an adverse event or change in medical status that raises a safety concern about the patient receiving the administration of CM4620-IE. The PI **must** discontinue the administration of CM4620-IE if the patient is discovered to have a new or recurrent malignancy, or if the patient was concomitantly administered a prohibited medication. If possible, the PI should contact the Medical Monitor to review the reasons for a patient's discontinuation from study drug. The PI should also record the reason for the discontinuation in the eCRF and appropriate source documents at the site. Even if the patient discontinues receiving CM4620-IE, diligence should occur to ensure that all study visits and assessments are completed.

Withdrawal refers only to the complete withdrawal of the patient from the study because of the withdrawal of consent. The PI should inform the Medical Monitor of the withdrawal of consent and record the withdrawal of consent in the eCRF and appropriate source documents at the site.

7 CM4620-IE MATERIALS AND MANAGEMENT

7.1 CM4620-IE Product Description

CM4620-IE is to be administered as an IV infusion and is supplied as a translucent, white-to-yellowish colored, sterile, non-pyrogenic emulsion containing 1.6 mg/mL of the active pharmaceutical ingredient CM4620. CM4620-IE is supplied as an 80 mL fill in a 100 mL, single-use glass vial. The drug product is formulated as an emulsion due to the low solubility of CM4620 in aqueous solution. CM4620-IE contains egg phospholipids, medium chain triglycerides, glycerin, edetate disodium salt dehydrate (EDTA), sodium hydroxide (as needed to adjust pH), and sterile water for injection (Table 3).

Table 3 CM4620-IE Product Information

Product Name:	CM4620 Injectable Emulsion
Dosage Form:	Injectable Emulsion (Liquid)
Concentration	1.6 mg/mL
Route of Administration	IV
Physical Description	Translucent, non-separated, white to yellowish emulsion
Inactive Ingredients	Sterile Water for Injection USP, Egg Phospholipid NF (80% Phosphatidylcholine), Medium Chain Triglycerides NF, Glycerin USP, and Edetate Disodium Salt Dihydrate (EDTA) USP. Sodium Hydroxide and Hydrochloric Acid may be added to adjust the pH.
Manufacturer	Bioserv Corporation San Diego, CA 92121

7.2 CM4620-IE Storage

CM4620-IE must be maintained in a secure location with refrigerated temperature conditions of 2 to 8°C (36 to 46°F). Precaution should be taken to ensure that the CM4620-IE does not freeze. Temperature logs should be maintained and available at each monitoring visit. When a temperature is noted outside the temporary excursion range of 2°C to 8°C for 24 hours or more, or if the temperature exceeds 20°C (68°F) or is below 0°C (32°F), CalciMedica or its designee must be notified. The stability of CM4620-IE has been demonstrated to 18 months and is being evaluated for longer periods in ongoing studies. Sites will be notified if any meaningful decrement in stability is discovered.

7.3 CM4620-IE Preparation

The study pharmacist and/or designee will be responsible for the preparation and dispensation of CM4620-IE. Prior to administration, CM4620-IE must be transferred to a sterile container using sterile technique. Specific details on how to calculate and prepare CM4620-IE, as well as the specific components that will be used to administer CM4620-IE, will be provided in a

Pharmacy Manual. The Pharmacy Manual will also contain tables detailing the Volume to Be Infused (VTBI) of CM4620-IE that is based upon the body weight of the patient, the selected dose level, and the concentration of CM4620-IE (1.6 mg/mL).

7.4 CM4620-IE Administration

CM4620-IE will be administered IV over 4 hours at a constant rate of infusion. The dose of CM4620-IE that will be administered will be calculated using the patient weight obtained at Screening. A line into a peripheral or central vein may be used for the infusion. The peripheral IV should be 20 gauge in size or larger. The peripheral IV or central line port should be dedicated, i.e., only for the administration of CM4620-IE and 0.9% normal saline. CM4620-IE is compatible with 0.9% normal saline. The IV tubing used to administer CM4620-IE must contain a 1.2 micron filter. The Pharmacy Manual will contain a recommended procedure to prime the IV tubing and flush the tubing, but this may be adapted to local nursing standards. 0.9% normal saline may be used to flush the line to ensure that the VTBI is completely administered. If the administration of CM4620-IE is stopped because of a technical reason, such as failure of the IV site, or IV pump malfunction, the administration of CM4620-IE should be resumed when the technical reason is resolved and continued at the same rate until the infusion is completed. The total amount of time from the start of infusion to end of infusion of CM4620-IE should be recorded.

CalciMedica may modify at any time the administered doses of CM4620-IE, the timing of the infusion and the rate of infusion based on its review of the safety and tolerability data. CalciMedica will discuss with the PI before implementation. If the administration of CM4620-IE is stopped because of a serious adverse event that is considered to be probably or definitely related to CM4620-IE, the Medical Monitor must be immediately contacted.

7.5 Packaging and Labeling

Preparation, packaging and labeling of CM4620-IE will be in accordance with current Good Manufacturing Practice of Medicinal Products (cGMP) guidelines. Medication labels will comply with legal requirements for labeling of investigational products in the United States.

7.6 Accountability, Handling and Disposal

The PI or designee will ensure that deliveries of CM4620-IE from CalciMedica or its designee are received by a responsible person, and such deliveries are recorded; that CM4620-IE is handled and stored safely and properly; that CM4620-IE is only dispensed to study patients in accordance with the protocol; and that unused CM4620-IE is returned to CalciMedica or its designee or disposed of using standard procedures approved of in advance by CalciMedica or its designee. Appropriately trained study staff will administer all doses of CM4620-IE. The pharmacy will maintain a record of CM4620-IE accountability.

8 VISITS AND ASSESSMENTS

8.1 Screening

The PI or designee must provide informed consent to the patient, or LAR, allowing the patient or LAR adequate time to consider, ask questions and receive answers, prior to agreeing to participate.

- Record the time the patient or LAR provides informed consent

After informed consent is obtained, the following procedures are to be performed:

- Record the time of the onset of abdominal pain
- Record demographics and medical history, including medication history
- Record vital signs, height and weight
- Perform a limited physical examination
- Draw serum pregnancy test if the patient is a woman of child bearing potential – analyze at local lab
  - If already performed as part of standard of care, record results
- Draw a blood sample for serum amylase and/or lipase – analyze at local lab;
  - If already performed at local lab as part of standard of care for the evaluation of abdominal pain, record results

If the patient satisfies all of the inclusion criteria and none of the exclusion criteria, enroll the patient in the study and immediately proceed to Day 1.

8.2 Day 1 (-1 hour to <24 hours)

Perform the following procedures immediately prior to infusion of CM4620-IE:

- Record vital signs
- Record specified concomitant medications
- Record patient's pain using the PNRS (Pain Numeric Rating Scale)
- Assess pain using the CPOT (Critical-care Pain Observation Tool)
- Draw a blood sample for CBC, platelets and differential and chemistry profile - analyze at local lab
- Draw a blood sample for IL-6 assay – send to testing lab
- Draw blood sample for PD assay 1 hour (± 30 minutes) prior to administration of CM4620-IE-send to testing lab
- Start the administration of CM4620-IE within 12 hours from the time the patient or LAR provided informed consent

- Draw a blood sample(s) for PD and PK assays 30 minutes (± 15 minutes) after completing the administration of CM4620-IE - send to testing labs
- Draw a blood sample for serum biomarker assay (IL-6) 30 minutes (± 15 minutes) after completing the administration of CM4620-IE - send sample for IL-6 analysis to testing lab
- Perform AE/SAE assessment after completing the administration of CM4620-IE

8.3 Day 2 (24 hours to <48 hours)

At 24 hours (±1 hour) from the start of administration of CM4620-IE:

- Record vital signs
- Record specified concomitant medications
- Draw a blood sample for CBC, differential and platelets, chemistry profile - analyze at local lab
- Record patient's pain using the PNRS
- Assess pain using the CPOT
- Perform AE/SAE assessment
- Draw a blood sample(s) for PD and PK assays 24 hours (±1 hour) from the start of the administration of CM4620-IE - send to testing labs
- Draw a blood sample for serum biomarker assay (IL-6) 24 hours (±1 hour) from the start of the administration of CM4620-IE - send sample for IL-6 analysis to testing lab

8.4 Days 3-4 (48 hours to 72 hours)

For all patients who remain hospitalized, at 48 hours (±1 hour) and 72 hours (±1 hour) from the start of administration of CM4620-IE:

- Record vital signs
- Record specified concomitant medications
- Record patient's pain using the PNRS
- Assess pain using the CPOT
- Perform AE/SAE assessment

8.5 Day 5 (96 hours)

For all patients who remain hospitalized, at 96 hours (±1 hour) from the start of administration of CM4620-IE:

- Record vital signs
- Record specified concomitant medications
- Record patient's pain using the PNRS
- Assess pain using the CPOT
- Perform AE/SAE assessment
- Draw a blood sample for CBC, differential and platelets, chemistry profile - analyze at local lab
- Draw a blood sample(s) for PD and PK assays 96 hours (±1 hour) from the start of the administration of CM4620-IE - send to testing labs
- Draw a blood sample for serum biomarker assay (IL-6) 96 hours (±1 hour) from the start of the administration of CM4620-IE - send sample for IL-6 analysis to testing lab.

8.6 Days 6 – 9

For all patients who remain hospitalized, at 120 hours (±1 hour), 144 hours (±1 hour), 168 hours (±1 hour), 192 hours (±1 hour) from the start of administration of CM4620-IE:

- Record vital signs
- Record specified concomitant medications
- Record patient's pain using the PNRS
- Assess pain using the CPOT
- Perform AE/SAE assessment

8.7 Day 10

For all patients who remain hospitalized, at 216 hours (±1 hour) from the start of administration of CM4620-IE:

- Record vital signs
- Record specified concomitant medications
- Perform limited physical examination
- Draw a blood sample for CBC, differential and platelets, chemistry profile - analyze at local lab
- Draw a blood sample(s) for PD and PK assays 216 hours (±1 hour) from the start of the administration of CM4620-IE - send to testing labs
- Draw a blood sample for serum biomarker assay (IL-6) 216 hours (±1 hour) from the start of the administration of CM4620-IE - send sample for IL-6 analysis to testing lab

- Record patient's pain using the PNRS
- Assess pain using the CPOT
- Perform AE/SAE assessment

If the patient is discharged before Day 10, Day 10 procedures should be performed prior to discharge.

8.8 Days 12 – 30

For all patients who remain hospitalized:

- Perform AE/SAE assessment if the patient is in the hospital every 48 hours starting on Day 12 until discharge, or until Day 30
- If the patient has been discharged from the hospital and returns for a follow-up visit on Day 30 (± 7 days), on Day 30 (± 7 days) draw a blood sample(s) for PD and PK assays - send to testing labs. Also, perform an SAE assessment and determine if patient has been readmitted to the hospital. If the patient has been discharged from the hospital and does not plan to return for a follow-up visit, contact the patient on Day 30 (± 7 days) for SAE assessment and to determine if patient has been readmitted to the hospital (may be conducted by phone call to patient, LAR, primary MD, or chart review)

8.9 Day 90

For all patients:

- On Day 90 (± 7 days), conduct a mortality assessment (may be completed by phone call to patient, LAR, primary MD, or chart review)

8.10 Study Assessments

8.10.1 Medical History

To the extent possible given the patient's medical condition, a complete medical history will be collected at Screening. Demographic data will be collected as the initial part of the medical history. Patients must be specifically questioned for whether they have had previous episodes of acute pancreatitis and whether they have been given a diagnosis of chronic pancreatitis. A family history of either acute or chronic pancreatitis will be obtained. Smoking and alcohol history will be noted as part of the social history. Medications that were being taken prior to enrollment in the study will be collected as part of the medical history as will, if available, baseline laboratories.

8.10.2 Concomitant Medications

Concomitant medications will be recorded from Day 1 through Day 10, or until discharge if occurring earlier. The name, dose and frequency of all analgesics, antipyretics and antimicrobials that the patients are taking will be recorded as well as vasopressor(s) and highest dose of vasopressors. If a prohibited medication has been administered, it will be recorded. The time of administration of the individual doses, and the route of administration will also be recorded. Generic names should be used when possible.

8.10.3 Physical Examination

A limited physical examination will be performed and recorded at Screening and Day 10, or at discharge if occurring earlier. The physical examination will evaluate the following systems: cardiovascular, respiratory, gastrointestinal, musculoskeletal, and skin. The examination must specifically assess if the patient has abdominal guarding or rebound tenderness.

8.10.4 Vital Signs

The recorded vital signs must include the patient's current temperature, heart rate (beats per minute), systolic and diastolic blood pressures, and the respiratory rate (breaths per minute).

8.10.5 Pregnancy Testing

A serum pregnancy test must be performed for all women of childbearing potential from a blood sample collected at Screening. The result of the test must be negative for the patient to be enrolled and receive CM4620-IE.

8.10.6 Laboratory Analyses

On Days 1, 2, 5 and on Day 10, or until discharge if occurring earlier, a CBC, differential, platelet count, and chemistry profile will be drawn once. The chemistry profile sent to the local lab will consist of sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, total protein, globulin, albumin, alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, lactate dehydrogenase (LDH), total cholesterol and triglycerides.

The PI or treating physician will order all additional laboratory testing necessary for the management of the patient and analysis will be performed at the local laboratory.

8.10.7 PD, PK and Biomarker analysis

On Day 1, blood samples for PD analysis will be obtained 1 hour (± 30 minutes) prior to administration of CM4620-IE. Blood samples for IL-6 will also be drawn 1 hour prior to administration of CM4620-IE. Blood samples for PD and PK analysis, plus IL-6, will be obtained 30 minutes (± 15 minutes) after completing the administration of CM4620-IE and at 24

hours (± 1 hour) from the start of the administration of CM4620-IE. In patients who remain hospitalized at Day 5 and Day 10, blood samples for PD and PK analysis, plus IL-6, will be obtained 96 (± 1 hour) and 216 hours (± 1 hour), respectively, from the start of the administration of CM4620-IE. The date and time of the blood samples (both the absolute time and the time before or after administration of CM4620-IE) should be recorded. A blood sample for PD and PK analysis will also be drawn at the Day 30 visit. All blood samples will be sent to the appropriate testing labs. Results will not be provided to the PI or treating physician.

8.10.8 Pain Numeric Rating Scale (PNRS)

In patients who are able to self-report their pain, the Pain Numeric Rating Scale (PNRS, Appendix 2) will be used to grade the severity of the abdominal pain from Day 1 – 10, or until discharge if occurring earlier. The timing of the last dose of an analgesic prior to assessing the patient's pain should also be recorded.

8.10.9 Critical-Care Pain Observation Tool (CPOT)

The Critical-Care Pain Observation Tool (CPOT) will be employed by the PI or study designee to assess the patient's pain from Day 1 – 10, or until discharge if occurring earlier. The patient must be observed for one minute at rest. The timing of the last dose of an analgesic prior to assessing the patient's pain should be recorded. The sum of the scores for facial expression, body movements, compliance with ventilator, or vocalization if extubated, and muscle tension will be determined using the CPOT (Appendix 3).

9 ADVERSE EVENTS

9.1 Definition of Adverse Event

An adverse event (AE) is defined as any untoward medical event in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant medical test abnormality), symptom, or disease temporally associated with the use of CM4620-IE, whether or not it is considered related to CM4620-IE administration. Included in this definition is any newly occurring event or previous condition that has increased in severity or frequency since the administration of CM4620-IE.

A medical test abnormality (e.g., laboratory test value, vital sign recording, ECG finding, physical examination finding) will be considered clinically significant and consequently recorded as an AE only if it meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires interruption or discontinuation of study medication

9.2 Definition of Serious Adverse Event

A serious adverse event (SAE) is any AE occurring at any dose and regardless of causality that:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life function
- Is a congenital anomaly or birth defect in an offspring of a patient receiving CM4620-IE
- Is an important medical event

The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during CM4620-IE administration or the thirty days thereafter. Certain pregnancy outcomes will require submission as an SAE.

9.3 Eliciting Adverse Event Information

At every AE/SAE assessment, the patient must be asked a standard, non-directed question, such as, "how have you been feeling since you were last contacted?" to elicit any medically related changes in their well-being. In addition, the hospital chart and other documents relevant to patient safety must be reviewed when the patient is in the hospital.

9.4 Recording Adverse Events

Recording of AEs must begin upon initiation of study drug dosing on Day 1. All conditions present before initiation of study treatment on Day 1, including untoward medical events during Screening, should be documented as medical history. Documentation shall continue until the patient dies, the patient withdraws consent, or the patient's participation in the study ends. Information to be collected includes:

- Type of event
- Date of onset
- Date of resolution
- Investigator-specified relationship to CM4620-IE and assessment of severity
- Seriousness
- Any action taken

While an AE is ongoing, changes in the severity (e.g., worsening and improving) should be noted in the source documents, but when documenting the AE, only the total duration and the greatest severity should be recorded in the case report form. AEs characterized as intermittent require documentation of onset and duration.

All AEs reported or observed during the study must be followed to resolution. Or, if not fully resolved, until the condition has stabilized, the patient dies, withdraws consent, or CalciMedica ends the trial whichever is first.

Adverse events resulting from concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in condition (e.g., "worsening of…").

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s).

Elective procedures (surgeries or therapies) performed to manage/treat conditions that existed prior to the patient enrolling in the trial should not be recorded as AEs but should be documented in the patient's source documents. If a planned procedure is performed early (e.g., as an

emergency) because the pre-existing condition worsens, the worsening condition should be captured as an AE.

9.5 Assessment of Relationship to CM4620-IE

The Investigator must use the following classification and criteria to characterize the relationship or association of CM4620-IE in causing or contributing to the AE:

- **Unrelated**: This relationship suggests that there is no association between CM4620-IE and the reported event
- **Unlikely**: This relationship suggests that there is an unlikely association between CM4620-IE and the reported event
- **Possible**: This relationship suggests that treatment with CM4620-IE caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of CM4620-IE administration, and/or follows a known response pattern to CM4620-IE, but could have been produced by other factors
- **Probable**: This relationship suggests that a reasonable temporal sequence of the event with CM4620-IE administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with CM4620-IE administration seems likely
- **Definite**: This relationship suggests a definite causal relationship exists between CM4620-IE administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event

9.6 Assessment of Severity

The Investigator must use the following criteria to rate the intensity of the AE:

- **Mild**: Symptoms causing no or minimal interference with usual social and functional activities
- **Moderate**: Symptoms causing greater than minimal interference with usual social and functional activities
- **Severe**: Symptoms causing inability to perform usual social and functional activities

9.7 Reporting of Serious Adverse Events

The PI is responsible for reporting to CalciMedica or designee within 24 hours from the time when site personnel learn about the event all SAEs that are observed or reported by the patient during the study (from initiation of study drug treatment on Day 1 until the patient dies, the patient withdraws consent, or the patient's participation in the study ends) regardless of the relationship to CM4620-IE or clinical significance. Any additional information that becomes available later should be submitted within 1 working day of receipt. All SAEs reported or observed during the study must be followed to resolution or until the PI deems the event to be chronic or the patient to be stable. CalciMedica or its designee may contact the PI to obtain additional information on any SAE that has not resolved at the time the patient completes the study. SAEs ongoing at database lock will be noted as such.

CalciMedica or its designee will notify the regulatory authority of any fatal or life threatening unexpected events associated with the use of CM4620-IE as soon as possible but no later than seven calendar days after the initial receipt of the information. Initial notification will be followed by a written report within fifteen calendar days. For SAEs that do not meet the fatal or life threatening unexpected criteria, CalciMedica or its designee will notify the appropriate regulatory agencies in writing within fifteen calendar days.

CalciMedica or its designee will provide copies of any reports to regulatory agencies regarding unexpected SAEs to the PI for review and submission to the institutional review board (IRB), Ethics Committee (EC) or Research Ethics Board (REB). The PIs are responsible for informing their IRB, EC, or REB of any SAEs at their site. SAE correspondence with regulatory authorities, IRBs, ECs or REBS must be submitted to CalciMedica or its designee for filing.

In addition, the following adverse events that are commonly observed in this patient population will not be reported to the regulatory authority as individual expedited reports except in unusual circumstances:

- Hypoxemia and acute respiratory distress syndrome
- Oliguria and acute kidney injury
- Hypotension and shock
- Bacteremia
- Pneumonia
- Obtundation
- Splanchnic venous thrombosis
- Abdominal compartment syndrome
- Gastroparesis and ileus
- Local complications of the pancreas and peripancreatic tissue
- Endoscopic retrograde cholangiopancreatography
- Abdominal surgery including but not limited to cholecystectomy, pancreatic necrosectomy, and placement of pancreatic drains

9.8 Suspected Pregnancy in a Woman of Childbearing Potential

A female patient of childbearing potential is a female who is not surgically sterile (no history of a bilateral salpingo-oophorectomy) and is not postmenopausal for at least 1 year.

A female patient of childbearing potential who receives CM4620-IE and is sexually active with a male partner, and a male patient who receives CM4620-IE and is sexually active with a female of childbearing potential, must be willing to use two highly effective methods of contraception (e.g., barrier methods, spermicidals, intrauterine devices, and/or hormonal contraception) for 365 days after last dose of CM4620-IE. No contraception is required if a female patient or partner has undergone a bilateral salpingo-oophorectomy.

Two of the following methods of birth control must be practiced unless a sexually active female patient or partner of childbearing potential has undergone a bilateral salpingo-oophorectomy:

- Male partner has a vasectomy for at least six months duration
- Use of an intrauterine device
- Use of hormonal contraceptives (oral, parenteral, vaginal or transdermal)
- Double barrier contraception with the male partner using a condom and the female using a contraceptive sponge, spermicidal jelly or cream or diaphragm plus spermicidal jelly or cream

The PI should be immediately informed if a female patient or partner of childbearing potential suspects she is pregnant up to 365 days after last dose of CM4620-IE. If the female patient is receiving CM4620-IE when discovered to be pregnant, the CM4620-IE should be immediately discontinued. If a pregnancy is confirmed, the PI must immediately report a pregnancy and record the event using a Pregnancy Report Form. Pregnancy is not considered an AE but the Investigator must follow a pregnant patient or partner. The PI must report follow-up information regarding the course of the pregnancy, including perinatal or neonatal outcome. Infants resulting from such pregnancies should be assessed for normality at birth. CalciMedica or its designee may contact the PI to request additional information throughout the course of the pregnancy.

The following pregnancy outcomes must be considered SAEs and will require additional reporting in the eCRF and on an SAE form:

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

10 STATISTICAL ANALYSIS

10.1 Sample Size

This open-label study will enroll 5 patients, with the possibility of enrolling 4 more patients. The sample size was selected based on practical considerations to initially evaluate the pharmacodynamic and pharmacokinetic profile of CM4620-IE in patients with acute pancreatitis. This study is not powered for analysis of study data with inferential statistics.

10.2 Study Assessments

- Safety assessments will include physical examinations, vital sign measurements, clinical laboratory measurements, specified concomitant medications and incidence, intensity and relationship of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

- Pharmacodynamic assessment will include IL-2 production by stimulated T-lymphocytes

- Pharmacokinetic assessment will include CM4620 concentration-time data and selected pharmacokinetic parameters including maximum plasma concentration

10.3 Analysis Sets

- The full analysis set includes all patients with acute pancreatitis who receive one complete administration of CM4620-IE

- The safety population includes all patients who receive any amount of study drug treatment

10.4 Statistical Analyses Plan

A Statistical Analysis Plan (SAP) detailing the analyses for the study will be developed prior to the database lock. The SAP will serve as the final arbiter of all statistical analyses. Data will be summarized using descriptive statistics only. Continuous data will be summarized with number of patients (n), mean, median, minimum, maximum, standard of deviation, coefficient of variation and or geometric mean. Categorical data will be summarized with number and proportion of patients. The number of patients enrolled in the study and the number of patients completing assessments for each Day will be summarized by cohort, sex and treatment arm. The number of patients and reasons for discontinuation of CM4620-IE or withdrawal from the study will be summarized.

11 ADMINISTRATIVE CONSIDERATIONS

11.1 Electronic Case Report Forms

The study will use a data capture system that is 21 CFR Part 11 compliant to electronically capture data for all screened and enrolled patients.

11.2 Monitoring of the Study

The site monitor, as a representative of CalciMedica, will closely follow the conduct of the study. The site monitor will visit the study site periodically and maintain necessary telephone and letter contact with the PI and his/her study staff. The site monitor will maintain current knowledge of the site's study activity by observing the conduct of the study at the site, reviewing study records and source documentation, and discussing the conduct of the study with the PI and his/her study staff.

11.3 Inspection of Records

The PI, his/her study staff and the study site will provide direct access to all study records to assist study-related monitoring and audits, Institutional Review Board/Ethics Committee/Research Ethics Board (IRB/EC/REB) reviews, and regulatory inspections. In the event of an audit, the PI agrees to allow CalciMedica or its representatives and relevant regulatory authorities access to all study records.

If any regulatory agency schedules an audit, the PI should promptly notify CalciMedica or its representatives and promptly forward to CalciMedica copies of any audit reports he/she receives.

11.4 Study Record Retention

The PI or his/her study staff must retain essential documents for at least 2 years after the last approval of a marketing application in an ICH region. They should retain these documents longer if required because of regulatory requirements or because of an agreement with CalciMedica.

11.5 Study Conduct: Good Clinical Practice and Declaration of Helsinki

CalciMedica will design the clinical study, shall implement it, and report it in accordance with the ICH Harmonized Guideline for Good Clinical Practice, with applicable local regulations (e.g., European Directive 2001/83/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The PI agrees to conduct the study in accordance with the ICH Guideline for Good Clinical Practice, with applicable local regulations (e.g., European Directive 2001/83/EC and US Code of Federal Regulations Title 21) and with the principles of the Declaration of Helsinki. The PI must

conduct all aspects of this study in accordance with all national, state and local laws or regulations.

11.6 Responsibilities of the Investigator and the IRB/EC/REB

A properly constituted IRB/EC/REB must review and approve the protocol and the proposed informed consent form before the start of the study at the site. The PI or his/her study staff must provide CalciMedica or its designee a signed and dated statement that the IRB/EC/REB has approved the protocol and the informed consent form before consenting patients for the study. Prior to starting the study, the PI will sign a protocol signature page confirming that he/she will conduct the study in accordance with this protocol and he/she will give CalciMedica or its designee and regulatory authorities access to all relevant data and records.

The IRB/EC/REB chairperson or designee must sign all IRB/EC/REB approvals and must identify the IRB/EC/REB by name and address, the clinical protocol, and the date of approval.

The PI is responsible for obtaining reviews of the clinical research at intervals specified by the IRB/EC/REB. The specified intervals should not exceed 1 year. The PI must supply CalciMedica or its designee written documentation of the reviews of the clinical research.

11.7 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's LAR) except as necessary for monitoring and auditing by CalciMedica or its designee, inspections by relevant regulatory authorities, or reviews by the IRB/EC/REB.

The PI, all study staff and all co-workers involved in the study may not disclose or use for any purpose other than the conduct of the study any data, record or other unpublished confidential information disclosed to them for the purpose of the study. They must obtain prior written agreements from CalciMedica or its designee for the disclosure of any said confidential information to other parties.

11.8 Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. Amendments (substantial/non-substantial) require regulatory approval and IRB/EC/REB approval or notification. Only after approval by CalciMedica, the PI, the IRB/EC/REB, and if applicable the regulatory authorities, will the protocol amendments become effective. In cases when the protocol is amended to enhance patient safety, the amendment may be implemented but must be immediately submitted to the IRB/EC/REB and regulatory authorities.

The revision number and date of the amendment will be recorded on the title page of the protocol.

The PI is responsible for informing the IRB/EC/REB of all problems involving risks to patients. In case of urgent safety measures, CalciMedica or its designee will immediately notify the PI and relevant regulatory authorities.

11.9 Informed Consent

Because the study will be conducted under a United States Investigational New Drug Application, informed consent that is in compliance with Title 21 of the United States Code of Federal Regulations (CFR) Part 50 will be obtained from each patient or LAR before the patient enters the study or before any unusual or non-routine procedure is performed.

CalciMedica or it designee may provide to the PI or his/her study staff an informed consent form template. The informed consent form must be reviewed by CalciMedica or its designee before the PI or his/her study staff submits it to the IRB/EC/REB. After CalciMedica or its designee review the informed consent form, the PI or his/her study staff will submit it to the IRB/EC/REB for review and approval. If the informed consent form is revised during the course of the study, CalciMedica or its designee must agree with revisions before the PI or his/her study staff submits it to the IRB/EC/REB. The study staff must provide CalciMedica or its designee a copy of the revised informed consent form after IRB/EC/REB approves it. All patients or LARs affected by the revision must sign the revised informed consent form after the IRB/EC/REB approves it.

Before enrolling in the study, each prospective patient or LAR will receive a full explanation of the study and review the approved informed consent form. Once the PI or designee is assured that the patient or LAR understands the implications of participating in the study, he/she will ask the patient or LAR to give consent for the patient to participate in the study by signing the informed consent form.

A patient may participate in the study only after providing consent using an IRB/EC/REB approved informed consent form. A LAR of the patient may provide informed consent on behalf of the patient under conditions authorized by local laws and regulations. The patient or LAR must provide informed consent before the patient undergoes any study-specific procedures described in the protocol. The PI or designee will provide a copy of the informed consent form to the patient and/or LAR. The process of obtaining informed consent must also be documented in the patient source documents.

11.10 Protocol Violations and Deviations

The PI or designee must document any protocol deviation or violation. Reporting of protocol deviations and violations to the appropriate IRB/EC/REB is the responsibility of the PI and must follow the applicable IRB/EC/REB guidelines.

If there is an immediate hazard to the patient, the PI may deviate from the protocol without prior approval from CalciMedica or its designee and the IRB/EC/REB but must notify CalciMedica or its designee and IRB/EC/REB of the deviation as soon as he/she is able to do so.

11.11 Financial Disclosure

The PI and sub-investigators are required to provide financial disclosure information prior to starting the study. In addition, the PI and sub-investigators must provide CalciMedica or its designee with updated information if any relevant changes occur during the course of the study and for one year following the completion of the study.

Any PI, sub-Investigators or study staff with a vested financial interest in the success of the study may not participate in the study.

11.12 Sponsor Obligations

CalciMedica or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during Screening. In addition, CalciMedica is not financially responsible for the treatment of the patient's underlying disease.

11.13 Investigator Documentation

Before beginning the study, the PI will be asked to comply with ICH E6 (R2) 8.2 and title 21 CFR by providing to CalciMedica or designee the following documents:

- An original signed investigator agreement page of the protocol
- The IRB/EC/REB approval of the protocol
- The IRB/EC/REB approved informed consent form
- Any written information regarding the study that will be provided to the patient or LAR
- A Form FDA 1572, fully executed, and all updates on new fully executed Form FDA 1572 (Unless granted an exemption by the FDA and in compliance with local regulations)
- Curricula Vitae for the PI and each sub-Investigator listed on Form FDA 1572. Evidence of licensure must be noted on the Curricula Vitae or a copy of the license must be provided. The Curricula Vitae must have been signed and dated by the PI and sub-Investigators within 2 years before study start-up to indicate that the documents are accurate and current
- Completed financial disclosure forms to allow CalciMedica or designee to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the PI and sub-Investigators must provide to CalciMedica or designee a commitment to update this information promptly if any relevant changes occur during the course of the study and for 1 year following completion of the study
- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of the study

11.14 Clinical Study Insurance

CalciMedica has subscribed to an insurance policy, covering in its terms and provisions its legal liability for injuries caused to participating persons and arising out of this research that is performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

11.15 Use of Information

All information supplied by CalciMedica to the PI and his/her study staff is privileged and confidential. The PI and his/her study staff agree to use this information to accomplish the study and not to use it for other purposes without consent from CalciMedica. Furthermore, the PI and his/her study staff is obligated to provide CalciMedica with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of CM4620-IE, and may be disclosed to regulatory authorities, other Investigators, corporate partners or consultants as required.

11.16 Publications

CalciMedica Inc. reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but rather to allow CalciMedica to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study investigators. CalciMedica Inc. supports communication and publication of study results whatever the findings of the study. CalciMedica Inc. also encourages disclosure of any conflict of interest from all authors or investigators when manuscripts are submitted for publication.

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Appendix 1 IAP/APA Summary of Recommendations

A. Diagnosis of Acute Pancreatitis and Etiology

1. The definition of acute pancreatitis is based on the fulfillment of 2 out of 3 of the following criteria: clinical (upper abdominal pain), laboratory (serum amylase or lipase >3x upper limit of normal) and/or imaging (CT, MRI, ultrasonography) criteria. (GRADE 1B, strong agreement)

2. On admission, the etiology of acute pancreatitis should be determined using detailed personal (i.e. previous acute pancreatitis, known gallstone disease, alcohol intake, medication and drug intake, known hyperlipidemia, trauma, recent invasive procedures such as ERCP) and family history of pancreatic disease, physical examination, laboratory serum tests (i.e. liver enzymes, calcium, triglycerides), and imaging (i.e. right upper quadrant ultrasonography). (GRADE 1B, strong agreement)

3. In patients considered to have idiopathic acute pancreatitis, after negative routine work-up for biliary etiology, endoscopic ultrasonography (EUS) is recommended as the first step to assess for occult microlithiasis, neoplasms and chronic pancreatitis. If EUS is negative, (secretin-stimulated) MRCP is advised as a second step to identify rare morphologic abnormalities. CT of the abdomen should be performed. If etiology remains unidentified, especially after a second attack of idiopathic pancreatitis, genetic counseling (not necessarily genetic testing) should be considered. (GRADE 2C, weak agreement)

B. Prognostication/Prediction of Severity

4. Systemic inflammatory response syndrome (SIRS) is advised to predict severe acute pancreatitis at admission and persistent SIRS at 48 hours. (GRADE 2B, weak agreement)

5. During admission, a 3-dimension approach is advised to predict outcome of acute pancreatitis combining host risk factors (e.g. age, co-morbidity, body mass index), clinical risk stratification (e.g. persistent SIRS) and monitoring response to initial therapy (e.g. persistent SIRS, blood urea nitrogen, creatinine). (GRADE 2B, strong agreement)

C. Imaging

6. The indication for initial CT assessment in acute pancreatitis can be: 1) diagnostic uncertainty, 2) confirmation of severity based on clinical predictors of severe acute pancreatitis, or 3) failure to respond to conservative treatment or in the setting of clinical deterioration. Optimal timing for initial CT assessment is at least 72-96 hours after onset of symptoms. (GRADE 1C, strong agreement)

7. Follow up CT or MR in acute pancreatitis is indicated when there is a lack of clinical improvement, clinical deterioration, or especially when invasive intervention is considered. (GRADE 1C, strong agreement)

8. It is recommended to perform multi-detector CT with thin collimation and slice thickness (i.e. 5mm or less), 100-150 ml of non-ionic intra-venous contrast material at a rate of 3mL/s, during the pancreatic and/or portal venous phase (i.e. 50-70 seconds delay). During follow up only a portal venous phase (monophasic) is generally sufficient. For MR, the recommendation is to perform axial FS-T2 and FS-T1 scanning before and after intravenous gadolinium contrast

administration. (GRADE 1C, strong agreement)

D. Fluid Therapy

9. Ringer's lactate is recommended for initial fluid resuscitation in acute pancreatitis. (GRADE 1B, strong agreement)

10a. Goal directed intravenous fluid therapy with 5-10 ml/kg/h should be used initially until resuscitation goals (see Q10b) are reached. (GRADE 1B, weak agreement)

10b. The preferred approach to assessing the response to fluid resuscitation should be based on one or more of the following: 1) non-invasive clinical targets of heart rate <120/min, mean arterial pressure between 65-85 mmHg (8.7-11.3 kPa), and urinary output > 0.5 ml/kg/h, 2) invasive clinical targets of stroke volume variation, and intra-thoracic blood volume determination, and 3) biochemical targets of hematocrit 35-44%. (GRADE 2B, weak agreement)

E. Intensive Care Management

11. Patients diagnosed with acute pancreatitis and one or more of the parameters identified at admission as defined by the guidelines of the Society of Critical Care Medicine (SCCM). Furthermore, patients with severe acute pancreatitis as defined by the revised Atlanta Classification (i.e. persistent organ failure) should be treated in an intensive care setting. (GRADE 1C, strong agreement)

12. Management in, or referral to, a specialist center is necessary for patients with severe acute pancreatitis and for those who may need interventional radiologic, endoscopic, or surgical intervention. (GRADE 1C, strong agreement)

13. A specialist center in the management of acute pancreatitis is defined as a high- volume center with up-to-date intensive care facilities including options for organ replacement therapy, and with daily (i.e. 7 days per week) access to interventional radiology, interventional endoscopy with EUS and ERCP assistance as well as surgical expertise in managing necrotizing pancreatitis. Patients should be enrolled in prospective audits for quality control issues and into clinical trials whenever possible. (GRADE 2C, weak agreement)

14. Early fluid resuscitation within the first 24 hours of admission for acute pancreatitis is associated with decreased rates of persistent SIRS and organ failure. (GRADE 1C, strong agreement)

15. Abdominal compartment syndrome (ACS) is defined as a sustained intra-abdominal pressure > 20 mmHg that is associated with new onset organ failure. (GRADE 2B, strong agreement)

16. Medical treatment of ACS should target 1) hollow-viscera volume, 2) intra/extra vascular fluid and 3) abdominal wall expansion. Invasive treatment should only be used after multidisciplinary discussion in patients with a sustained intra-abdominal pressure >25mmHg with new onset organ failure refractory to medical therapy and nasogastric/ rectal decompression. Invasive treatment options include percutaneous catheter drainage of ascites, midline laparostomy, bilateral subcostal laparostomy, or subcutaneous linea alba fasciotomy. In case of surgical decompression, the retroperitoneal cavity and the omental bursa should be left

intact to reduce the risk of infecting peripancreatic and pancreatic necrosis. (GRADE 2C, strong agreement)

F. Preventing Infectious Complications

17. Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis. (GRADE 1B, strong agreement)

18. Selective gut decontamination has shown some benefits in preventing infectious complications in acute pancreatitis, but further studies are needed. (GRADE 2B, weak agreement)

19. Probiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis. (GRADE 1B, strong agreement)

G. Nutritional Support

20. Oral feeding in predicted mild pancreatitis can be restarted once abdominal pain is decreasing and inflammatory markers are improving. (GRADE 2B, strong agreement)

21. Enteral tube feeding should be the primary therapy in patients with predicted severe acute pancreatitis who require nutritional support. (GRADE 1B, strong agreement)

22. Either elemental or polymeric enteral nutrition formulations can be used in acute pancreatitis. (GRADE 2B, strong agreement)

23. Enteral nutrition in acute pancreatitis can be administered via either the nasojejunal or nasogastric route. (GRADE 2A, strong agreement)

24. Parenteral nutrition can be administered in acute pancreatitis as second-line therapy if nasojejunal tube feeding is not tolerated and nutritional support is required. (GRADE 2C, strong agreement)

H. Biliary Tract Management

25. ERCP is not indicated in predicted mild biliary pancreatitis without cholangitis. (GRADE 1A, strong agreement) ERCP is probably not indicated in predicted severe biliary pancreatitis without cholangitis. (GRADE 1B, strong agreement) ERCP is probably indicated in biliary pancreatitis with common bile duct obstruction. (GRADE 1C, strong agreement) ERCP is indicated in patients with biliary pancreatitis and cholangitis. (GRADE 1B, strong agreement)

26. Urgent ERCP (<24 hrs) is required in patients with acute cholangitis. Currently, there is no evidence regarding the optimal timing of ERCP in patients with biliary pancreatitis without cholangitis.(GRADE 2C, strong agreement)

27. MRCP and EUS may prevent a proportion of ERCPs that would otherwise be performed for suspected common bile duct stones in patients with biliary pancreatitis who do not have cholangitis, without influencing the clinical course. EUS is superior to MRCP in excluding the presence of small (<5mm) gallstones. MRCP is less invasive, less operator-dependent and probably more widely available than EUS. Therefore, in clinical practice there is no clear superiority for either MRCP or EUS. (GRADE 2C, strong agreement)

I. Indications for Intervention in Necrotizing Pancreatitis

28. Common indications for intervention (either radiological, endoscopical or surgical) in necrotizing pancreatitis are: 1) Clinical suspicion of, or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off, 2) In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled-off. (GRADE 1C, strong agreement)

29. Routine percutaneous fine needle aspiration of peripancreatic collections to detect bacteria is not indicated, because clinical signs (i.e. persistent fever, increasing inflammatory markers) and imaging signs (i.e. gas in peripancreatic collections) are accurate predictors of infected necrosis in the majority of patients. Although the diagnosis of infection can be confirmed by fine needle aspiration (FNA), there is a risk of false-negative results. (GRADE 1C, strong agreement)

30. Indications for intervention (either radiological, endoscopical or surgical) in sterile necrotizing pancreatitis are: 1) Ongoing gastric outlet, intestinal, or biliary obstruction due to mass effect of walled-off necrosis (i.e. arbitrarily >4-8 weeks after onset of acute pancreatitis), 2) Persistent symptoms (e.g. pain, 'persistent unwellness') in patients with walled-off necrosis without signs of infection (i.e. arbitrarily >8 weeks after onset of acute pancreatitis), 3) Disconnected duct syndrome (i.e. full transection of the pancreatic duct in the presence of pancreatic necrosis) with persisting symptomatic (e.g. pain, obstruction) collection(s) with necrosis without signs of infections (i.e. arbitrarily >8 weeks after onset of acute pancreatitis). (GRADE 2C, strong agreement)

J. Timing of Intervention in Necrotizing Pancreatitis

31. For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention (i.e. percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) should be delayed where possible until at least 4 weeks after initial presentation to allow the collection to become 'walled-off'. (GRADE 1C, strong agreement)

32. The best available evidence suggests that surgical necrosectomy should ideally be delayed until collections have become walled-off, typically 4 weeks after the onset of pancreatitis, in all patients with complications of necrosis. No subgroups have been identified that might benefit from earlier or delayed intervention. (GRADE 1C, strong agreement)

I. Intervention Strategies in Necrotizing Pancreatitis

33. The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy. (GRADE 1A, strong agreement)

34. Percutaneous catheter or endoscopic transmural drainage should be the first step in the treatment of patients with suspected or confirmed (walled-off) infected necrotizing pancreatitis. (GRADE 1A, strong agreement)

35. There are insufficient data to define subgroups of patients with suspected or confirmed infected necrotizing pancreatitis who would benefit from a different treatment strategy. (GRADE 2C, strong agreement)

J. Timing of Cholecystectomy (or Endoscopic Sphincterotomy)

36. Cholecystectomy during index admission for mild biliary pancreatitis appears safe and is recommended. Interval cholecystectomy after mild biliary pancreatitis is associated with a substantial risk of readmission for recurrent biliary events, especially recurrent biliary pancreatitis. (GRADE 1C, strong agreement)

37. Cholecystectomy should be delayed in patients with peripancreatic collections until the collections either resolve or if they persist beyond 6 weeks, at which time cholecystectomy can be performed safely. (GRADE 2C, strong agreement)

38. In patients with biliary pancreatitis who have undergone sphincterotomy and are fit for surgery, cholecystectomy is advised, because ERCP and sphincterotomy prevent recurrence of biliary pancreatitis but not gallstone related gallbladder disease, i.e. biliary colic and cholecystitis. (GRADE 2B, strong agreement)

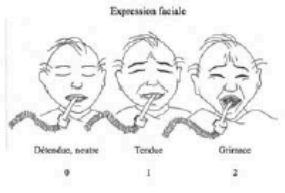
Appendix 2 Pain Numeric Rating Scale (PNRS)

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

Appendix 3 The Critical-Care Pain Observation Tool (CPOT)

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		

Adapted from Gélinas, 2006

Appendix 4 Schedule of Events

	Screen	Day 1	Day 2	Day 3	Day 4	Day 5	Days 6, 7	Days 8, 9	Day10 [g]	Days 12-28 [a]	Day 30 [b]	Day 90 [c]
Informed Consent	X											
Demographics & Medical History	X											
Prior & Concomitant Medications	X	X	X	X	X	X	X	X	X			
Physical Examination (limited)	X								X			
Vital Signs	X	X	X	X	X	X	X	X	X			
Height and Weight	X											
Serum Pregnancy Test for WOCBP	X											
Amylase or Lipase	X											
Blood Sample for Serum Chemistries		X	X			X			X			
Blood Sample for CBC, Diff & Platelets		X	X			X			X			
Blood Sample for PD Analysis [d]		X	X			X			X		X	
Blood Sample for PK Analysis [e]		X	X			X			X		X	
Blood Sample for IL-6 [f]		X	X			X			X			
Assess Pain		X	X	X	X	X	X	X	X			
AE/SAE Evaluation		X	X	X	X	X	X	X	X	X	X	X
CM4620-IE Administration		X										

[a] Safety and tolerability assessment after Day 10 will be done every 48 hours until Day 30 or until discharge, whichever occurs first

[b] Day 30 visit (± 7 days): for patients who have been discharged prior to Day 30, for a SAE evaluation and blood draw. If the patient does not return for the clinic visit, a telephone call to the patient will be made for an SAE evaluation.

[c] Day 90 (± 7 days) visit will consist of a telephone call to the patient, the LAR, or the primary MD, or chart a review for mortality.

[d] On Days 1 and 2, blood samples for PD analysis will be obtained 1 hour (± 30 minutes) prior to starting the administration of CM4620-IE, ± 30 minutes (± 15 minutes) after completing the administration of CM4620-IE, and 24 hours (± 1 hour) from the start of the administration of CM4620-IE. In patients hospitalized at Day 5 and 10, a PD blood sample will be drawn; if discharged earlier obtain a PD blood sample at the time of discharge.

[e] On Days 1 and 2, plasma samples for PK analysis will be obtained ± 30 minutes (± 15 minutes) after completing the administration of CM4620-IE and 24 hours (± 1 hour) from the start of the administration of CM4620-IE. In patients hospitalized at Day 5 and 10, a PK plasma sample will be obtained; if discharged earlier obtain a PK plasma sample at the time of discharge.

[f] On Day 1, serum or plasma samples for IL-6 will be obtained 1-hour prior to the administration of CM4620-IE, ± 30 minutes (± 15 minutes) after completing the administration of CM4620-IE, and 24 hours (± 1 hour) from the start of the administration of CM4620-IE. In patients hospitalized at Day 5 and 10, a serum or plasma sample for IL-6 will be drawn 96 (± 1 hour) and 216 hours (± 1 hour), respectively, from the start of the administration of CM4620-IE.

[g] Day 10 procedures will be performed if the patient is discharged prior to Day 10