A Phase 2 Randomised, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Efficacy and Safety of CAM-3001 in Subjects with Rheumatoid Arthritis

Sponsor Protocol Number: MI-CP219

Application Number: EudraCT Number: 2009-014735-20
US IND Number: 103, 411

Investigational Product: CAM-3001

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Sponsor Agreement:

[redacted] Medical Monitor, whose signature is on file at MedImmune, is authorised to sign the protocol on behalf of the sponsor.

Signature [redacted] Date [redacted]

Investigator Agreement: MI-CP219

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), the ethical principles set forth in the Declaration of Helsinki, and other applicable local regulatory requirements.

The protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authorities and Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and must be approved by the IRB/IEC prior to their implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor/designee immediately upon receipt.

Signature_____ Date _____

Investigator Name and Title_____
(please print)

Investigator Affiliation, City, State/Province_____

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(please print)

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List of Abbreviations

Abbreviation	Definition
ACR	American College of Rheumatology
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
ATP	according to protocol
AUC	Area under the concentration-time curve
BAL	bronchoalveolar lavage
BCG	Bacillus Calmette-Guérin
CCP	Cyclic citrullinated peptide
C_{max}	maximum observed concentration
CMV	Cytomegalovirus
CRP	c-reactive protein
CRPS	clinical research pharmacy services
DAS	disease activity score
DLCO	diffusing capacity for carbon monoxide
DMARD	disease modifying anti-rheumatic drugs
DNA	deoxyribonucleic acid
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
eCRF	electronic case report form
ECL	Electrochemiluminescence
EU	European Union
ESI	Events Of Special Interest
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FACIT-Fatigue	functional assessment of chronic illness therapy-fatigue
FEV_1	forced expiration volume in first second
FVC	Forced Vital Capacity
FTIH	first time in human
GCP	Good Clinical Practice

Abbreviation	Definition
GH	general health
GLP	Good Laboratory Practice
GM-CSF	granulocyte macrophage-colony stimulating factor
GM-CSFRα	granulocyte macrophage-colony stimulating factor Receptor (alpha)
HAQ-DI	Health Assessments Questionnaire-Disability Index
HAV	hepatitis A virus
Hb	Haemoglobin
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IA	intra-articular
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent-to-treat
IV	Intravenous
IVRS	interactive voice response system
IWRS	interactive web response system
LOCF	last-observation-carried-forward
MCHC	mean corpuscular haemoglobin concentration
MCV	mean corpuscular haemoglobin volume
mRNA	messenger ribonucleic acid
miRNA	micro RNA
MOS	Medical Outcomes Study
NOAEL	no observed adverse effect level
NSAID	non-steroidal anti-inflammatory drug
PAP	pulmonary alveolar proteinosis
PCR	polymerase chain reaction

Abbreviation	Definition
PD	pharmacodynamic/pharmacodynamics
PK	pharmacokinetic/pharmacokinetics
PPD	purified protein derivative
QRT	quantitative reverse transcriptase
RA	rheumatoid arthritis
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SF-36	Short form-36
SJC	swollen joint count
SMC	Safety Monitoring Committee
TB	Tuberculosis
TJC	Tender joint count
TK	Toxicokinetics
T_{max}	time to maximum concentration
TNFα	tumour necrosis factor alpha
ULN	Upper limit of normal
VAS	Visual Analogue Scale

Study Abstract

TITLE A Phase 2 Randomised, Double-Blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the Efficacy and Safety of CAM-3001 in Subjects with Rheumatoid Arthritis

OBJECTIVES

Primary Objective

The primary objectives of this study are to evaluate the safety, tolerability and efficacy of multiple doses of CAM-3001 administered subcutaneously (SC) in subjects with at least moderately active rheumatoid arthritis (RA).

Secondary Objectives

The secondary objectives of this study are:

1) To evaluate clinical outcomes in RA.

2) To explore CAM-3001 dose and the relationship with safety and efficacy.

3) To evaluate the pharmacokinetics (PK) and immunogenicity of CAM-3001.

Exploratory Objectives

The exploratory objectives of this study may include the following:

1) To investigate the effects of CAM-3001 on:
   - Expression of proteins such as GM-CSF, biomarkers of disease activity, autoantibodies and other inflammatory proteins in serum.
   - The potential relationship between inhibition of GM-CSF-inducible gene signature, clinical activity, GM-CSF receptor occupancy and drug concentration (PK) and the miRNA and/mRNA expression pattern in the periphery of subjects enrolled.
   - Patient reported outcomes

2) To assess whether DNA polymorphisms are associated with the safety or clinical response to CAM-3001 (optional for subjects)

STUDY DESIGN This is a multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of multiple ascending SC doses of CAM-3001 in combination with stable methotrexate in subjects aged 18-80 years of age with active RA.

Approximately 72 sites worldwide may be involved in the study. A total of 216 subjects will be recruited into 4 cohorts of 54 subjects to receive either 10, 30, 50 or 100 mg SC doses of CAM-3001 or placebo every other week for 12 weeks. All cohorts will be randomised in a 2:1 ratio (active:placebo). For Cohorts 1 to 3, decisions relating to dose escalation will be made by the sponsor (including the medical monitor, the safety physician, the project medical director and additionally final approval by the MedImmune Safety Monitoring Committee, which includes internal and external experts). These reviews of all cumulative safety data will occur after at least 18 subjects have completed dosing on Day 29. In Cohort 4, an initial 18 subjects will be recruited. Once at least 6 of these subjects have been exposed to investigational product for the entire treatment period (Day 85) and no safety concerns have been detected, randomisation will resume to enrol the remaining number of subjects planned for this cohort.

Additional subjects will be recruited at sites in Japan. A total of 48 subjects from Japan will be randomised into 4 cohorts in a 2:1 ratio (active:placebo) with a total of 12 subjects per cohort. Details are included in a local protocol amendment for Japan.

The assigned dose of CAM-3001 or placebo (1 mL) will be administered as SC injections in the upper arm, thigh, or abdomen. The intention of the protocol is that subjects will be maintained on the same stable dose of

concomitant RA treatment from Screening until Day 85. Adverse events and serious adverse events will be collected from the time of consent until the end of the safety follow-up period. Disease activity will be assessed throughout the treatment period and during safety follow-up.

Cumulative safety data will be reviewed continuously throughout the study. Formal safety reviews will include all subjects in the study at the data cut-off irrespective of the number of doses that subjects have received at that point.

Screening evaluations will be carried out within 28 days prior to randomisation. The treatment period for each cohort will be to Day 85 ± 2 days. This will be followed by a safety follow-up period of 12 weeks ± 1 week.

SUBJECT POPULATION The subjects in this study will be male or female adults with RA as defined by the 1987 American College of Rheumatology classification criteria, and at least moderately active disease, as defined by Disease Activity Score (DAS) 28 criteria (DAS ≥ 3.2), despite treatment with methotrexate for at least 12 weeks prior to Screening, which has been kept at a stable dose for at least 4 weeks (7.5-25 mg/week).

TREATMENT A total of 264 subjects are required to be randomised into this study, (216 subjects outside of Japan and 48 subjects in Japan). The treatment regimen for the study is below. Cohorts are randomised 2:1 CAM-3001:Placebo.

Dose Cohort	N	Treatment
1 1 (Japan)	54 12	CAM-3001 10 mg (N = 36) or placebo (N = 18) SC every other week (total 7 doses) CAM-3001 10 mg (N = 8) or placebo (N = 4)
2 2 (Japan)	54 12	CAM-3001 30 mg:(N = 36) or placebo (N = 18) SC every other week (total 7 doses) CAM-3001 30 mg placebo (N = 4)
3 3 (Japan)	54 12	CAM-3001 50 mg (N = 36) or placebo (N = 18) SC every other week (total 7 doses) CAM-3001 50 mg placebo (N = 4)
4 4 (Japan)	54 12	CAM-3001 100 mg (N = 36) or placebo (N = 18) SC every other week (total 7 doses) CAM-3001 100 mg placebo (N = 4)

ASSESSMENT OF ENDPOINTS The primary efficacy objective will assess DAS28 response rates of CAM-3001 treated subjects compared with subjects who received placebo on the day of last dose of investigational product (Day 85). The safety and tolerability of CAM-3001 will be assessed primarily by summarising the incidence of AEs and SAEs.

The secondary endpoints of this study include disease activity (summarised descriptively by treatment group and time and include ACR20, ACR50 and ACR70 and DAS28 responses), the onset of response, duration of response after withdrawal of treatment, the need for additional medications during the study as well as an analysis of the PK and immunogenicity of multiple SC doses of CAM-3001. CAM-3001 serum concentrations will be summarised using descriptive statistics at each time point by treatment group. Noncompartmental PK data analysis will be performed for CAM-3001 treated subjects following first dose, and descriptive statistics of these noncompartmental PK parameters (eg, C_{max}, T_{max}, AUC and $T_{1/2}$) will be provided.

INTERIM ANALYSIS:

The primary efficacy analysis will be performed when all randomised subjects, excluding randomised subjects in Japan, have completed the Day 85 assessments or have discontinued from the study.

MedImmune will be unblinded at the primary analysis (Day 85) excluding subjects enrolled at Japanese sites.. The purpose of this analysis is for internal decision making on the progression of the clinical programme, so this analysis will not impact the conduct of the current study. This is the final analysis of the primary efficacy

endpoint, so no alpha adjustment for analysis will be made.

A further analysis may be performed when all randomised subjects, excluding randomised subjects in Japan, have completed all study assessments.

The final analysis will be performed when all randomised subjects, including Japanese subjects, have completed the all study assessments. This analysis will rerun the primary efficacy endpoint of DAS28 as well as all other study endpoints.

SAMPLE SIZE The primary objective of the study is to evaluate safety, tolerability and efficacy of multiple doses of CAM-3001. No formal sample size calculation was performed for the primary objective of safety.

With respect to the primary efficacy analysis (Day 85). A further 48 subjects will be randomised in Japan to give an overall sample size of 264 subjects in 4 equal sized cohorts of 66 subjects

The sample size computation for the primary efficacy endpoint of the study is based on the objective of evaluating the effect of CAM-3001 on the response rate in terms of improvement in DAS28 score at Day 85. A responder will be defined as a subject experiencing a decrease from baseline in DAS28 score at Day 85 of more than 1.2. Assuming a placebo response rate of 10%, a combined CAM-3001 response rate of 30%, a two sided Type 1 error of 0.05, 86% power, and a 2:1 (active: placebo) randomisation ratio, an evaluable sample size of 180 subjects (120 active: 60 placebo) will be required to detect a 20% difference in response rates for an analysis based on a two-sided Fisher's exact test.

This sample size of 216 evaluable subjects (144 CAM-3001 subjects and 72 placebo subjects) including Japanese subjects will have a 92% power at alpha level 0.05 using two-sided Fisher's exact test on the primary efficacy endpoint of comparing response rates between the combined CAM-3001 and combined placebo groups.

MedImmune will be unblinded at the primary analysis (Day 85), excluding subjects enrolled in Japanese sites.

The data from the primary analysis will not be communicated to personnel at the Contract Research Organisation or investigational sites or to enrolled subjects. The purpose of this analysis is for internal decision making on the progression of the clinical programme, so this analysis will not impact the conduct of the current study. This is the final analysis of the primary efficacy endpoint, so no alpha adjustment for analysis will be made.

A further analysis may be performed when all randomised subjects, excluding randomised subjects in Japan, have completed all study assessments.

The final analysis will be performed when all randomised subjects, including Japanese subjects, have completed the all study assessments. This analysis will rerun the primary efficacy endpoint of DAS28 as well as all other study endpoints.

1 Introduction

AstraZeneca AB, a company incorporated in Sweden with offices at SE-151 85 Södertälje, Sweden ("AstraZeneca"), is the global sponsor of this study. MedImmune Limited, with offices at Milstein Building, Granta Park, Cambridge, CB21 6GH, UK ("MedImmune") is an affiliate of AstraZeneca.

A brief summary of the background and experience with CAM-3001 is provided below.

1.1 Disease Background

Rheumatoid arthritis (RA) is characterised by chronic inflammatory synovitis that causes pain, loss of function and disability, and can significantly reduce health-related quality of life. The clinical efficacy of biologics that inhibit tumour necrosis factor-α (TNF-α) has demonstrated a key role of TNF-α in disease pathogenesis, however, despite this treatment about one in three subjects fail to respond to anti-TNF therapy (do not achieve an American College of Rheumatology definition of improvement by 20% [ACR20]) and only about one in five achieve ACR70 (Kristensen et al, 2008). Thus there is a need for new effective treatments to reduce disease activity in patients with RA.

In animal models of RA, selective depletion of joint macrophages improves bovine serum albumin and interleukin (IL)-1 induced arthritis in mice (Bishof et al, 2002; Lawlor et al, 2005), whilst in patients clinical improvement in RA disease activity is associated with reduced sublining synovial macrophages, with oral corticosteroids being the most potent inhibitors (Wijbrandts et al, 2007). Granulocyte macrophage-colony stimulating factor (GM-CSF) is a small glycoprotein produced by a number of inflammatory cells that promotes neutrophil and macrophage colonies from precursor cells and mediates the functional activation of mature neutrophils, eosinophils and macrophages. Low levels are normally present in human serum with most production occurring locally at the site of inflammation; this GM-CSF production in turn exacerbates the inflammatory reaction via a colony stimulating factor network. Inhibition of GM-CSF signalling should therefore have an anti-inflammatory effect by decreasing the number of mature or activated inflammatory cells at the site of inflammation.

Recent research data suggest a potential role of GM-CSF in disease pathogenesis of RA, with an increase in both ligand and receptor in patients. Plasma levels of GM-CSF are elevated

about 2-fold in patients with RA (Fiehn et al, 1992), with GM-CSF levels also increased in synovial fluid (Ottonello et al, 2002; Bell et al, 1995) and GM-CSF protein has been identified in synovial membranes (Farahat et al, 1993). Supporting these findings is the observation that GM-CSF production is increased from cultured synovial cells or tissue (Xu et al, 1989; Bucala et al, 1991; Ritchlin et al, 1994). Expression of granulocyte macrophage-colony stimulating factor receptor alpha (GM-CSFRα) is increased in patients with RA, GM-CSFRα protein expression is increased on circulating mononuclear cells from patients with RA (Field and Clinton, 1993) and GM-CSFR messenger ribonucleic acid (mRNA) levels are increased in synovial tissue (Berenbaum et al, 1994). Additionally, treatment with GM-CSF has exacerbated RA symptoms in patients with RA (de Vries et al, 1991; Pereira et al, 1994) and treatment with GM-CSF has been shown to exacerbate the disease in mouse models of RA. The induction of collagen-induced arthritis is suppressed in GM-CSF deficient mice.

MedImmune in collaboration with CSL Limited (formerly Zenyth Therapeutics), has engineered a human monoclonal immunoglobulin G4 (IgG4) antibody (CAM-3001) that neutralises GM-CSF by binding specifically to the alpha subunit of the GM-CSF receptor and therefore has potential utility in the treatment of RA.

1.2 Description of CAM-3001

CAM-3001 is a human monoclonal IgG4 antibody that neutralises GM-CSF by binding specifically to the alpha subunit of the GM-CSF receptor. CAM-3001 was isolated and optimised using phage display and formatted as an IgG4 molecule. The manufacture of the CAM-3001 cell line was established using proven technology involving a clonal mammalian glutamine synthetase-chinese hamster ovary cell line. Fermentation and purification processes for the final product are performed by Lonza Biologics plc for cell banking and manufacture according to Good Manufacturing Practice.

1.3 Nonclinical Experience with CAM-3001

CAM-3001 inhibits the activity of GM-CSF in a panel of human in vitro cell-based assays, such as GM-CSF-induced TNF-α release from human monocytes and GM-CSF-induced human granulocyte survival. It is a highly specific and selective antibody only binding human and cynomolgus monkey GM-CSFRα, with no binding to rodent GM-CSFRα.

CAM-3001 binds to primate GM-CSFRα with an affinity similar to the human antigen. From repeat-dose studies, the pharmacokinetics (PK) of CAM-3001 was linear with dose in cynomolgus monkeys in the dose range investigated (10-100 mg/kg intravenous [IV] and 50-400 mg subcutaneous [SC]). No gender difference in PK was observed. The elimination half-life of CAM-3001 was 1-2 weeks, typical for a human IgG in cynomolgus monkeys. CAM-3001 was immunogenic in some cynomolgus monkeys, which was associated with an increased clearance of CAM-3001 in these animals. The surrogate murine antibody, CAM-3003, passed through the placenta following repeated IV administrations to female mice. The serum level of CAM-3003 in the foetus was similar to that in dams.

The nonclinical safety of CAM-3001 was evaluated in several studies with cynomolgus monkeys as the pharmacologically relevant species and in a local tolerance study in rabbits. Two human tissue panel cross-reactivity studies and a cynomolgus monkey tissue panel cross-reactivity study showed the distribution of CAM-3001-specific staining was similar and supported the use of cynomolgus monkey as a relevant toxicology species. CAM-3001-specific staining on both human and cynomolgus monkey tissues was present in the membrane of inflammatory cells (or mononuclear cells) in lymphoid tissues and bone marrow, and in the cytoplasm of cells of the placenta in both human and cynomolgus monkey tissues. CAM-3001 was well tolerated following SC injection in rabbits with no signs of erythema or oedema and no histopathological findings at the injection site. Results from an embryo-foetal development study in mice using mouse surrogate CAM-3003 showed no findings. CAM-3001 was generally well-tolerated in several IV and SC repeat-dose studies in cynomolgus monkeys with no changes in any of the evaluated parameters and no microscopic findings in any tissues other than lung.

The development of foamy macrophages in lung tissues was observed in several studies following long-term dosing (at least 11 weeks) and is predictable based on the pharmacology of inhibiting normal GM-CSF function (Yoshida et al, 2001; Trapnell and Whitsett, 2002; Uchida et al, 2009). Where this occurred in the absence of any other changes in the pulmonary anatomic pathology or any other toxicology parameters, a no-observed-adverse-effect-level (NOAEL) was identified. In a Good Laboratory Practice (GLP) 26-week repeat IV dose study, the presence of lung foreign material, cholesterol clefts, and granulomatous inflammation was observed at higher doses and was considered adverse. In this study, the NOAEL was considered to be 15 mg/kg/week. This exaggerated response to lung foreign material and cholesterol clefts is consistent with CAM-3001 inhibitory effects on lung macrophage function.

The safety margin was calculated based on the comparison of observed toxicokinetics (TK) exposure in the GLP repeat-dose cynomolgus monkey study at the NOAEL and model-predicted steady-state PK exposure in patients with RA upon biweekly SC administrations of CAM-3001. At a NOAEL of 15 mg/kg CAM-3001 in cynomolgus monkeys, the mean maximum concentration (C_{max}) and area under the concentration-time curve $(AUC)_{(0\text{-}7d)}$ were 1260 µg/mL and 6450 µg·d/mL, respectively. The model-projected steady-state C_{max} and $AUC_{(0\text{-}14d)}$ in patients with RA upon multiple 100 mg SC dosing are 15.1 µg/mL and 162 µg·d/mL, respectively. By comparing the steady-state CAM-3001 exposure, the safety margin for the highest dose (100 mg) was calculated as approximately 83- and 80-fold based on C_{max} and AUC, respectively (cynomolgus AUC was doubled to account for the dosing frequency difference).

1.4 Clinical Experience with CAM-3001

CAM-3001 has been assessed in a first time in human (FTIH) study (Study CAM-3001-0702 A double-blind, placebo-controlled, single ascending dose study of the safety, tolerability, PK and pharmacodynamics [PD] of CAM-3001 in patients with RA). Thirty-two subjects were dosed, of whom 27 received IV CAM-3001 at doses ranging from 0.01 to 10 mg/kg, and 5 received placebo.

The most common treatment-emergent adverse events (AEs) were infections. Nasopharyngitis was the most common individual AE and was observed at a similar incidence for the placebo and CAM-3001 groups. Diarrhoea and back pain were also reported at similar incidences for both groups. The majority of AEs were mild or moderate with 2 severe events reported, one was hernia repair and the other pre-treatment emergent breast cancer, these were both reported as serious adverse events (SAEs) and neither was considered treatment-related. No subjects died during the study and no subject withdrew from the study due to an AE. There was one AE of Grade 2 urticaria of neck and face during infusion in the 10 mg/kg cohort, which required the infusion to be stopped. The subject responded rapidly to appropriate antihistamine therapy, and the event was judged as moderate in severity.

Further information on this study is available in the current version of the CAM-3001 Investigator's Brochure and in published literature (Burmester et al, 2009; Wang et al, 2009).

Serum concentrations of CAM-3001 were determined using a validated electrochemiluminescence (ECL) method. Consistent with previously reported anti-receptor

monoclonal antibodies, CAM-3001 PK was nonlinear at low dose levels. From the noncompartmental analysis, the systemic clearance of CAM-3001 approaches the intrinsic clearance of endogenous IgG by the reticuloendothelial system when the dose was above 1 mg/kg, suggesting saturation of the antigen sink (full GM-CSFRα occupancy) at higher dose levels. CAM-3001 PK half-life was more prolonged in higher dose cohorts. At the highest dose level investigated (10 mg/kg), the elimination half-life was approximately 15 days.

Serum samples were analysed for the presence of anti-CAM-3001 antibodies using a validated ECL immunoassay. All immunogenicity samples collected from this study tested negative for the presence of anti-drug antibodies.

In summary, human experience to date has shown that CAM-3001 is well tolerated in subjects with active RA when administered IV in single ascending doses from 0.01 to 10.0 mg/kg, and has a safety profile that supports further clinical development.

1.5 Rationale for Study

Granulocyte macrophage-colony stimulating factor is considered to play a major role in disease pathogenesis in RA. CAM-3001 blocks cellular activation by GM-CSF through its binding to the GM-CSF receptor, and hence, may provide clinical benefit to patients with moderate-to-severely active RA who need disease control. Further clinical development of CAM-3001 is supported by the safety profile observed in a Phase 1 study (CAM-3001-0702).

MI-CP219 will be the first study to test the efficacy and safety of SC administered CAM-3001. The study is intended to provide efficacy and safety data over a range of doses to enable progression of the clinical development program. The effects of CAM-3001 on validated RA clinical outcomes, dose identification and the PK, PD and immunogenicity of CAM-3001 in this subject population will be assessed. In addition the study includes scheduled data reviews of available safety data across the range of doses, and exploratory analyses of relationships between CAM-3001 exposure, GM-CSFα receptor occupancy, inhibition of GM-CSF gene signature and micro RNA (miRNA) expression, which will assist in dose selection for future studies.

1.5.1 Dose Justification

In this Phase 2 study, CAM-3001 will be administered SC at fixed doses of 10 mg, 30 mg, 50 mg or 100 mg every other week, based on the PK/PD simulations and nonclinical/clinical safety considerations.

From in vitro studies and literature, 10% of available GM-CSFRα is adequate to elicit maximum biological activity. Therefore, it is assumed that inhibition of macrophage activity with CAM-3001 would require at least 90% receptor blockade. Furthermore, preclinical investigations of CAM-3001 in non-human primates, has shown a dose and time dependant effect on alveolar macrophages, which in absence of GM-CSF stimulation, become unable to process surfactant and assume the characteristic "foamy" appearance due to its accumulation in these cells. This is predictable based on the pharmacology of inhibiting normal GM-CSF function (Yoshida et al., 2001). In these preclinical investigations, there were no changes in clinical observations, body weights, clinical pathology parameters, urinalysis, immunophenotyping, organ weights, macroscopic observations, or microscopic findings in any other tissues.

A population PK model was constructed using data from the FTIH study in subjects with RA (CAM-3001-0702) to describe the PK of a typical human IgG4, binding of CAM-3001 to GM-CSFRα, and the internalisation of GM-CSFRα and CAM-3001/ GM-CSFRα complex. The population PK model was then used to predict the PK profiles of CAM-3001 for this study, assuming a 65% SC bioavailability (typical for IgG) and 80 kg average body weight.

Based on this model, the predicted GM-CSFRα receptor occupancy profiles upon multiple SC administrations of CAM-3001 show that doses above 30 mg SC every other week achieve ≥ 90% receptor occupancy systemically. An initial dose of 10 mg is predicted to induce transient and < 90% GM-CSFRα occupancy in RA patients and offers a cautious approach to subject safety. Doses of 10, 30, 50 and 100 mg of CAM-3001 SC every other week provide an adequate dose range to demonstrate a PD effect systemically (including synovial tissue) but limit lung concentrations because of limited partitioning of CAM-3001 to the alveolar space. The lung:serum partitioning for other IgG monoclonal antibodies developed by MedImmune have been approximately 1:50 for lung tissue, 1:200 for sputum, and 1:1000 for bronchoalveolar lavage (BAL) fluid. Partitioning to synovial fluid is expected to be approximately 1:4.

The safety margin was calculated based on the comparison of observed TK exposure in a multiple-dose GLP study in cynomolgus monkeys at the NOAEL (15 mg/kg/week) and model predicted steady-state PK exposure in subjects with RA upon biweekly SC administrations of CAM-3001. The estimated safety margins for MI-CP219 are listed in Table 1.5.1-1.

Table 1.5.1-1 Predicted Human Exposure and Calculated Safety Margin

	Predicted steady-state human exposure (EOW SC)				15 mg/kg NOAEL in Cynomolgus monkeys	Safety Margin for MI-CP219			
	10mg	30mg	50mg	100mg		10mg	30mg	50mg	100mg
AUCτ (µg d/mL)	2.39	20.8	58.9	162	12900*	5400	620	219	79.6
Cmax (µg/mL)	0.514	2.55	5.97	15.1	1260	2450	494	211	83.4

AUC_τ = area under the concentration-time curve at steady-state in the 14-d dosing interval; C_{max} = maximal observed concentration EOW - every other week; NOAEL = no observed adverse effect level; SC = subcutaneous.

* Steady-state AUC in a 2-week interval

The 12-week treatment period was chosen in order to maximize the opportunity of demonstrating a benefit of study medication and is considered to be the minimum duration for an assessment of efficacy in subjects with RA. In this study, CAM-3001 will be dosed based on a cohort dose-escalation design providing a cautious approach to subject exposure. Continuous safety monitoring and safety review by the sponsor will be performed before proceeding to the next cohort (Section 4.5.5). The dosing schedule in this study will provide sufficient exposure and number of dose administrations to allow the assessment of safety of the SC formulation prior to progression of the clinical development program.

A 12-week safety follow-up period is considered adequate for this study as the unoccupied GM-CSFRα are expected to return to close to baseline level approximately 2-8 weeks after the last dose of CAM-3001, thus allowing for one additional month of safety follow-up. It is therefore considered that the proposed dosing schedule for the SC study is fully justified.

2 Study Objectives

2.1 Primary Objective

The primary objectives of this study are to evaluate the safety, tolerability and efficacy of multiple doses of CAM-3001 administered SC in subjects with at least moderately active RA.

2.2 Secondary Objectives

The secondary objectives of this study are:

1) To evaluate clinical outcomes in RA
2) To explore CAM-3001 dose and the relationship with safety and efficacy
3) To evaluate the PK and immunogenicity of CAM-3001

2.3 Exploratory Objectives

The exploratory objectives of this study may include the following:

1) To investigate the effects of CAM-3001 on:
   - Expression of proteins such as GM-CSF, biomarkers of disease activity, autoantibodies and other inflammatory proteins in serum
   - The potential relationships between inhibition of GM-CSF-inducible gene signature, clinical activity, GM-CSF receptor occupancy and drug concentration (PK) and the miRNA and/or mRNA expression pattern in the periphery of subjects enrolled.
   - Patient reported outcomes
2) To assess whether deoxyribonucleic acid (DNA) polymorphisms are associated with the safety or clinical response to CAM-3001 (optional for subjects)

3 Study Design

3.1 Overview of Study Design

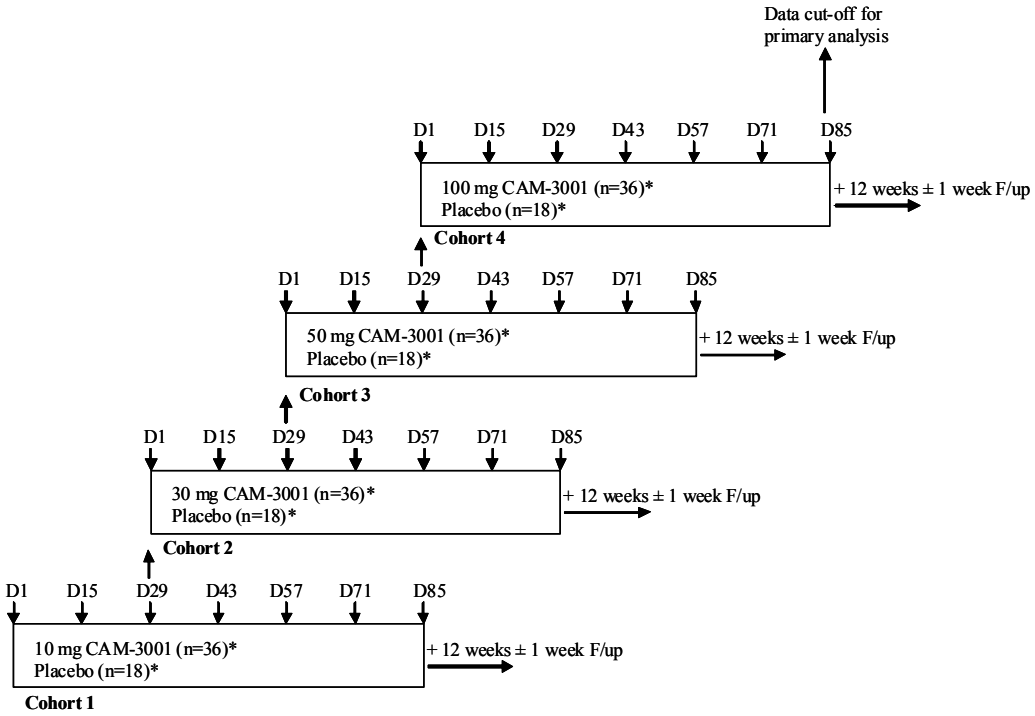
This is a multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of multiple ascending SC doses of CAM-3001 in combination with stable methotrexate in subjects aged 18 to 80 years of age with active RA.

Approximately 72 sites worldwide may be involved in the study. A total of 216 subjects will be recruited into 4 cohorts of 54 subjects to receive either 10 mg, 30 mg, 50 mg or 100 mg SC doses of CAM-3001 or placebo every other week for 12 weeks. All cohorts will be randomised in a 2:1 ratio (active:placebo). For Cohorts 1 to 3, decisions relating to dose escalation will be made by the sponsor (including the medical monitor, the safety physician, the project medical director and additionally final approval by the MedImmune Safety Monitoring Committee (SMC) which includes internal and external experts). These reviews of all cumulative safety data will occur after at least 18 subjects have completed dosing on Day 29. In Cohort 4, an initial 18 subjects will be recruited; once at least 6 of these subjects have been exposed to investigational product for the entire treatment period (Day 85) and no safety concerns have been detected, randomisation will resume to enrol the remaining number of subjects planned for this cohort.

Additional subjects will be recruited at sites in Japan. A total of 48 subjects from Japan will be randomised into 4 cohorts in a 2:1 ratio (active:placebo) with a total of 12 subjects per cohort. Details are included in a local protocol amendment for Japan.

The assigned dose of CAM-3001 or placebo (1 mL) will be administered as SC injections in the upper arm, thigh, or abdomen. The intention of the protocol is that subjects will be maintained on the same stable dose of concomitant RA treatment from Screening until Day 85. Adverse events and SAEs will be collected from the time of consent until the end of the safety follow-up period. Disease activity will be assessed throughout the treatment period and during safety follow-up. The schedules of subject evaluations are presented in Table 5.2-1.

Cumulative safety data will be reviewed by the sponsor continuously throughout the study. Formal safety reviews will include all subjects in the study at the data cut-off irrespective of the number of doses that subjects have received at that point.



For cohorts 1 to 3, dose escalation to the next cohort will occur after at least 18 subjects have completed dosing on Day 29.

In cohort 4, an initial 18 subjects will be recruited (12 CAM-3001 and 6 placebo). Once at least 6 of these subjects have been exposed to study treatment for the entire treatment period (Day 85) and no safety signals have been detected, recruitment will resume and complete.

* In each cohort, 12 Japanese subjects will be recruited (8 CAM-3001 and 4 placebo)
In Japan, the dose escalation decision (all cohorts) will be made based on a review of all cumulative safety data available after 6 Japanese subjects have completed dosing on Day 29.

Figure 3.1-1 Study Flow Diagram

D = days; F/up = Follow-up

The endpoints to be measured in this study are described in Section 7.3.

3.2 Estimated Study Duration

Screening evaluations will be carried out within 28 days prior to randomisation. The treatment period for each cohort will be to Day 85 ± 2 days. This will be followed by a safety follow-up period of 12 weeks ± 1 week.

4 Study Procedures

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification number will be assigned by a central system (eg, an interactive voice/web response system, IVRS/IWRS), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The subject identification number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who were consented but did not meet study eligibility criteria and/or were not randomised), including the reason(s) for screening failure (see Section 9.1 for details).

4.2 Subject Selection

The subjects in this study will be male or female adults with RA as defined by the 1987 American College of Rheumatology (ACR) classification criteria, and at least moderately active disease, as defined by Disease Activity Score (DAS) 28 criteria (DAS $\geq$ 3.2), despite treatment with methotrexate for at least 12 weeks prior to Screening, which has been kept at a stable dose for at least 4 weeks (7.5 to 25 mg/week).

The investigator (physician) or qualified designee will discuss the study with a subject who is considered a potential candidate for the study and provide the subject with the study-specific informed consent form approved by the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). The investigator or designee will address any questions and/or concerns that the subject may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and any locally required authorisation (eg, Health Insurance Portability and Accountability Act [HIPAA] authorisation in the USA, European Union [EU] Data Privacy Directive authorization in the EU), will be obtained prior to conducting any protocol-related procedures, including screening evaluations. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1) Male or female

2) Age 18 through 80 years at the time of Screening

3) Signed and dated informed consent, prior to receipt of any study medication or any study related procedures.

4) A diagnosis of adult onset RA of at least 3 months duration as defined by the 1987 ACR classification criteria (Arnett et al, 1988).

5) Treatment with methotrexate (7.5-25 mg/week) for at least 12 weeks and at stable and tolerated doses for at least 4 weeks prior to Screening.

6) Positive anti-cyclic citrullinated peptide (CCP) IgG antibodies (> 5 IU/mL) and/ or rheumatoid factor (> 14 IU/mL) at Screening.

7) Subjects must receive ≥ 5 mg/week folic acid as a single or divided dose during the study.

8) At least moderately active disease as defined by DAS28 ≥ 3.2 at Screening and Baseline (see Section 5.3.4.1; Smolen et al, 2003).

9) a) Females of childbearing potential; unless surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy), has a sterile male partner, is premenarchal or at least 2 years postmenopausal, or practices abstinence; must use 2 effective methods of avoiding pregnancy (including oral, transdermal, or implanted hormonal contraceptives, intrauterine device, female condom with spermicide, diaphragm with spermicide, cervical cap with spermicide, or use of a condom with spermicide by the sexual partner) for 21 days prior to randomisation and at Day 1, and must agree to continue using such precautions until the end of the 12 weeks safety follow-up; cessation of birth control after this point should be discussed with a responsible physician. A negative pregnancy test is required both at Screening and prior to dosing.

   b) Males, unless surgically sterile, must use 2 effective methods of birth control with a female partner and must agree to continue using such contraceptive precautions from Screening through the end of the 12 weeks safety follow-up.

10) No evidence of medically significant respiratory disease. A local pulmonologist will review subjects' respiratory system including, chest x-ray, pulmonary function, and diffusing capacity for carbon monoxide (DLCO), which are performed at Screening. Subjects must have:

- DLCO ≥ 80% predicted value
- Forced expiration volume in first second (FEV_1) by spirometry ≥ 80% predicted value

- No pneumonitis and clinically significant obstructive or restrictive lung disease

11) Willing and able to comply with the protocol and complete the study period.

4.2.2 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

Relating to Rheumatoid Arthritis

1) A rheumatic autoimmune disease other than RA, or significant systemic extra-articular involvement secondary to RA (including but not limited to; vasculitis, pulmonary fibrosis, or Felty's syndrome). Subjects with secondary Sjögren's syndrome or secondary limited cutaneous vasculitis with RA are eligible.

2) A history of, or current, inflammatory joint disease other than RA (eg, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy, Lyme disease) or other systemic autoimmune disorder (eg, systemic lupus erthymatosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease or other overlap syndrome).

3) Functional class IV defined by the 1992 ACR Classification of Functional Status in RA (Hochberg et al, 1992).

Relating to Concomitant Medications, Previous Biologic and Non-biologic Treatments

4) Treatment with any investigational drug therapy within 28 days or 5 half-lives of the drug, whichever is longer, prior to Screening.

5) Previous treatment with > 1 biologic therapy for RA that was discontinued for lack of efficacy.

6) Any cell depleting therapies (eg, anti-CD20) within 12 months prior to Screening; or previous treatment with non-depleting biologic therapies (such as anti-TNFα, recombinant interleukin-1 receptor anatagonist, anti-interleukin-6, or abatacept) within 30 days or 5 half-lives (8 weeks for infliximab) of the biologic agent, whichever is longer, prior to Screening.

7) Previous administration of CAM-3001.

8) History of known allergy or reaction to any monoclonal antibody or any component of the CAM-3001/investigational product formulation.

9) Treatment with disease modifying anti-rheumatic drugs (DMARDs), other than background methotrexate, including sulfasalazine, azathioprine, cyclosporine, thalidomide, D-penicillamine, or tacrolimus within 28 days of Screening, and leflunomide within 12 weeks (or 28 days if after 11 days of standard cholestyramine washout) before Screening.

10) Treatment with alkylating agents 12 weeks prior to Screening.

11) If receiving current treatment with non steroidal anti-inflammatory drugs (NSAIDS), these must be on a stable dose for ≥ 28 days prior to Screening and remain stable for the duration of the treatment phase of the study.

12) Intramuscular (IM), IV or intra-articular (IA) corticosteroids within 28 days before Screening.

13) Treatment with > 10 mg/day dose prednisone (or equivalent) within 28 days of Screening. Concomitant treatment with oral corticosteroids ≤ 10 mg/day prednisone or equivalent is permitted providing that the dose is stable for ≥ 28 days prior to Screening and remains stable for the duration of the treatment phase of the study.

Relating to Medical History

14) Female subjects who are pregnant, intend to become pregnant, or are breastfeeding.

15) Subjects who in the opinion of the investigator or qualified designee have evidence of active tuberculosis (TB), either treated or untreated, or latent TB without completion of an appropriate course of treatment or appropriate ongoing prophylactic treatment. Evaluation will be according to the local standard of care and will consist of history and physical examinations, chest x-ray, and TB test (eg, purified protein derivative [PPD][1]) testing, etc with the standard of care as determined by local guidelines.

16) Active infection including symptoms, signs suggestive of clinically significant infection, any significant recurrent or chronic infection (including positive HCV antibody and chronic active HBV infection), or any episode of infection requiring hospitalisation or treatment with IV antibiotics within 12 weeks before Screening. Subjects with any opportunistic infection within 6 months before Screening will be excluded from the study.

17) Subjects at a high risk of infection eg, a history of an infected joint prosthesis at any time with that prosthesis still in situ, leg ulcers, indwelling urinary catheter, persistent or recurrent chest infections.

18) History of hereditary or acquired immune deficiency disorder including a history of known HIV infection.

19) Receipt of live (attenuated) vaccine within the 28 days before Screening or during the study.

20) Any history of cancer except basal and squamous cell carcinoma of the skin or in situ carcinoma of the cervix treated and considered cured.

21) Any surgical procedure (except for minor surgeries requiring local or no anaesthesia and without any complications or sequelae), including bone or joint

[1] The TB test procedure will be agreed and documented by country and approved by MedImmune prior to recruitment.

surgery/synovectomy (including joint fusion or replacement) within 12 weeks prior to Screening or any planned surgery within 3 months after randomisation.

22) Any neurological (congenital or acquired), psychiatric, vascular, or systemic disorder that could also affect the evaluation of efficacy assessments; in particular, joint pain and swelling (eg, Parkinson's disease, cerebral palsy, diabetic neuropathy, chronic fatigue syndrome, or chronic remitting anaemia of unknown origin or requiring transfusion).

23) Significant respiratory or pulmonary disease including symptomatic lung fibrosis, pneumonitis, uncontrolled asthma, dyspnoea, malignancy and history of chronic respiratory tract infections.

24) Congestive heart failure New York Heart Association classification III or IV.

25) History of methotrexate or any drug induced lung fibrosis or pneumonitis.

26) History of deep space/tissue infection (eg, fasciitis, abscess, osteomyelitis, septic arthritis) within 12 months prior to Screening.

27) Evidence of any disease or history of any disease, any finding upon physical examination, or any clinically significant laboratory or radiographic abnormality that, in the opinion of the investigator, designated healthcare provider, or medical monitor, may compromise the safety of the subject in the study or confound the analysis of the data.

28) At Screening blood tests; any of the following:

- Aspartate transaminase (AST) > 2.5 × upper limit of the normal range (ULN)
- Alanine transaminase (ALT) > 2.5 × ULN
- Haemoglobin (Hb) < 8.0 g/dL
- Neutrophils < 1,500/mm^3

4.3 Treatment Assignment

An interactive web response system (IWRS) will be used for randomisation to a treatment arm and assignment of blinded investigational product kit numbers. A subject is considered randomised into the study when the investigator/designee notifies the IWRS that the subject meets eligibility criteria and the IWRS allocates the assignment of a blinded investigational product number to the subject. An interactive voice response system (IVRS) will also be available as a back-up.

Subjects will be randomised at a 2:1 ratio to receive either CAM-3001 or placebo.

The procedure for using IWRS/IVRS is as follows:

- The investigator or designee confirms that written informed consent has been obtained and that the subject meets all eligibility criteria.
- The unblinded investigational product manager will log onto the IWRS/IVRS to obtain the treatment allocation on the day indicated by the investigator/designee.
- The IWRS/IVRS assigns a treatment arm (CAM-3001 or placebo) and investigational product number(s) to the subject and then sends a confirmatory fax or e-mail with the subject identification number and investigational product number(s) is sent to the unblinded investigational product manager.

Investigational product (CAM-3001 or placebo) must be administered as soon as possible after receipt of the investigational product number. If there is a delay in the administration of investigational product such that it will not be administered on the day of receipt of the investigational product number, the MedImmune study monitor and/or its designee must be notified immediately.

4.4 Blinding

This is a double-blind study. Since CAM-3001 and placebo are not identical in appearance/viscosity, investigational product will be handled by an unblinded investigational pharmacist at the site and will be administered by an unblinded study team member who will not be involved in the management of study subjects. An independent investigational product monitor will also be unblinded to perform investigational product accountability. Neither the subject nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects will be aware of the treatment received (International Conference on Harmonisation [ICH] E9).

The vendor for packaging and labelling of the clinical supplies, designated IWRS/IVRS personnel and designated MedImmune Clinical Research Pharmacy Service (CRPS) personnel will have access to information that may identify a subject's treatment allocation. At site, an independent monitor, who will only review the pharmacy records, and the investigational product manager are the only individuals who will have access to information that identifies a subject's treatment allocation. These individuals must not reveal randomisation or treatment information to anyone or participate in or be associated with the evaluation of study subjects. In the event that the treatment allocation for a subject becomes known to the investigator or other study staff or needs to be known to treat an individual subject for an AE, the sponsor must be notified *immediately* by the investigator.

To prevent potential unblinding at site because of observed efficacy or laboratory changes, a "dual assessor" approach will be used to evaluate efficacy and safety. A Joint Count Assessor is a skilled arthritis assessor and will be responsible for completing the joint counts only. The Safety Assessor should be a rheumatologist and will have access to both safety and efficacy data. The Safety Assessor will have access to source documents, laboratory results, and electronic case report forms (eCRFs) and be responsible for making treatment decisions based on a patient's clinical response and laboratory parameters. The Safety Assessor will not complete the joint count assessments.

In the case of a medical emergency, where the treatment received by the subject needs to be identified to appropriately treat the subject or manage their condition, the sponsor should be notified immediately and prior to unblinding whenever possible. The investigator will have the ability to unblind the subject treatment in case of such an emergency. Any unblinding due to an emergent safety issue will be performed according to the IWRS/IVRS manual. The investigator will also document and report the action to the sponsor without revealing the treatment given to the subject.

The primary statistical analysis of the primary efficacy endpoint and other endpoints at Day 85 will be performed when the last subject recruited outside of Japan has completed all assessments at Day 85. MedImmune will be unblinded at the primary analysis excluding subjects enrolled in Japanese sites. The purpose of this analysis is for internal decision making on the progression of the clinical programme, so this analysis will not impact the conduct of the current study. This is the final analysis of the primary efficacy endpoint, so no alpha adjustment for analysis will be made. The analysis methodology and the review of the resulting data by the sponsor will be described in the Statistical Analysis Plan (SAP). The treatment assignment of the Japanese subjects will remain blinded at the primary analysis.

Investigational product will be supplied to the site as individually numbered CAM-3001 or placebo vials. The vials will be packaged into cartons and each carton will be labelled with a unique number range that corresponds to the labelled number series of the vials within the carton. Detailed instructions are in the Investigational Product Manual supplied by MedImmune.

4.5 Study Treatment

4.5.1 Investigational Product (CAM-3001 and Placebo)

Investigational product will be distributed to clinical sites using designated distribution centres. The sponsor will provide the investigator(s)/designee with adequate quantities of investigational product. Vials are to be stored at 2-8°C at which temperature the product is viable until its listed expiry date on the IWRS/IVRS. Detailed instructions on the preparation of the investigational product, investigational product supply, dose preparation, and accountability will be provided in the Investigational Product Manual supplied by MedImmune/delegate.

Information in this manual will be specific for the unblinded product manager who will manage the preparation of the syringes for the study.

CAM-3001: CAM-3001 is to be provided as a 1.15 mL fill in 2 mL vials. This fill volume was selected to allow volumes of 1 mL (100 mg) to be extracted. The active ingredient is formulated at a concentration of 100 mg/mL in a liquid formulation [redacted]

Placebo: Placebo will be supplied as 10.3 mL in 10 mL vials. This fill volume was selected to allow volumes of 10 mL to be extracted. Subjects randomised to the placebo group will receive 1 mL placebo per dosing. The placebo formulation is identical to the drug product with the exception of the active ingredient: [redacted]

Vials are to be labelled in accordance with local regulatory requirements.

Specific details regarding investigational product supplies, dose preparation, and accountability will be provided in the Investigational Product Manual supplied to the sites.

The investigator's or site's designated investigational pharmacist is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to the sponsor or designee. All unused investigational product will be returned to a MedImmune-authorised depot or disposed of upon authorisation by MedImmune or authorised representative (refer to the

Investigational Product Manual or other written instructions provided by MedImmune or its designee for contact information and specific shipping instructions).

4.5.2 Treatment Regimens

A total of 264 subjects are required to be randomised into this study (216 subjects outside of Japan and 48 subjects in Japan); in order that at least 216 evaluable subjects (180 plus 36 evaluable subjects from Japan) complete the study to Day 85. Table 4.5.2-1 includes the treatment regimens for the study.

Table 4.5.2-1 Treatment Regimens

Dose Cohort	N	Treatment
1 1(Japan)	54 12	CAM-3001 10 mg (N = 36) or placebo (N = 18) SC every other week (total 7 doses)* CAM-3001 10 mg (N = 8) or placebo (N = 4)
2 2(Japan)	54 12	CAM-3001 30 mg (N = 38) or placebo (N = 18) SC every other week (total 7 doses)* CAM-3001 30 mg (N = 8) or placebo (N = 4)
3 3(Japan)	54 12	CAM-3001 50 mg (N = 36) or placebo (N = 18) SC every other week (total 7 doses)* CAM-3001 50 mg (N = 8) or placebo (N = 4)
4 4(Japan)	54 12	CAM-3001 100 mg (N = 36) or placebo (N = 18) SC every other week (total 7 doses)* CAM-3001 100 mg (N = 8) or placebo (N = 4)

SC=subcutaneous
*2:1 randomisation CAM-3001:Placebo

4.5.3 Investigational Product Preparation and Administration

The dose of investigational product for administration must be prepared by the investigator's or site's designated investigational product manager. Detailed instructions regarding investigational product preparation can be found in the Investigational Product Manual that will be provided to the investigator's or site's designated investigational pharmacist.

The day of receipt of the first dose of investigational product is considered Day 1. CAM-3001 or placebo should be dispensed by qualified personnel and will be administered as SC injections in the upper arm, thigh, or abdomen.

Severe hypersensitivity reactions have been reported with the administration of IV gammaglobulins and nearly all approved monoclonal antibodies. Similar reactions are reported to be much less common with SC injection of monoclonal antibodies. Before the investigational product administration, medications and supplies for the emergency management of investigational product hypersensitivity reactions should be available. See Section 6.4.3 and Appendix 1 for additional information.

4.5.4 Concomitant Medications and RA Treatment

A concomitant medication is any drug taken during the study including over the counter drugs, herbal supplements, vitamins and vaccines, given to the subject during the study. All concomitant medications, including any changes during the study, will be recorded on the eCRF.

Concomitant therapies taken for the long term treatment of pre-existing conditions may be continued during the study provided they are in accordance with the exclusion criteria. It is preferred that these medications be stabilised prior to entry and continued wherever practical without variation of dose or regimen during the study.

In addition to the investigational product, all subjects will receive methotrexate at a weekly dose of 7.5 to 25 mg/week (oral or parenteral). Eligible subjects will have received methotrexate by the same route for at least 12 weeks and at stable and tolerated doses for at least 4 weeks prior to Screening. In addition, subjects will be allowed to receive stable doses of NSAIDS and stable dose of oral corticosteroids (≤ 10 mg/day prednisolone or equivalent (see study reference manual) if the dose has been stable for at least 4 weeks prior to Screening.

As stated in the inclusion criteria, all subjects must receive ≥ 5 mg/week folic acid during the study as a single or divided dose to minimise methotrexate toxicity.

4.5.4.1 Modification of Treatments for RA

All changes to the RA treatment and the reasons for change must be clearly documented in the eCRF.

Methotrexate and Corticosteroids

Changes in ongoing RA treatment or introduction of new therapies are not allowed during the study period (Screening until Day 85). This includes the dose of methotrexate, corticosteroids and NSAIDS. After the Day 85 study visit, where possible the doses of background medication should be kept as constant as possible up to completion of the safety follow-up period (Day 169). Modifications to background RA medication will be permitted for safety reasons such as adverse reactions due to these medications (eg, gastrointestinal adverse events), and infectious diseases.

Subjects who require a change to their RA therapies for reasons other than safety, such as for poor disease control or worsening of their RA between Day 1 and Day 85 may be discontinued from dosing upon review by the medical monitor, but will remain in the study and be followed-up for safety. All study assessments should be completed, unless consent is withdrawn.

The risk/benefit to the subject should be carefully assessed and consideration given to the timing of any necessary dose modification or introductions of new medications during the study period and should be discussed with the medical monitor where possible.

Injection of IA corticosteroids is discouraged, but a maximum of 2 IA injections of corticosteroids (dose up to 40 mg of triamcinolone or equivalent) are allowed as needed to control joint flares during the treatment period of the study. Treated joints will not be counted for tenderness and swelling for 12 weeks post injection.

Analgesics

Analgesics and NSAIDS should be maintained at a stable dose for the duration of the study. Subjects should refrain from taking the usual morning dose of analgesics on visit days until after all clinical assessments have been completed (see Table 5.2-1 for Frequency of Assessments).

Disallowed Medications

The following medications are prohibited during the treatment period of the study:

- Any investigational agent other than CAM-3001
- Alkylating agents, including cyclophosphamide

- Biologic agents or non-biologic DMARDS other than methotrexate
- Immunoabsorption columns, plasmapheresis and IV immunoglobulin therapy
- Live or live-attenuated vaccines

Immunisation with any live or live attenuated vaccine (ie, measles, mumps, rubella and polio vaccine, Bacillus Calmette-Guérin (BCG), typhoid, yellow fever, cold adapted live influenza strain vaccine or any other vaccines not yet licensed but belonging to this category) is specifically excluded during the treatment period (Centers for Disease Control and Prevention, ACIP Recommendations, 1993).

Subjects who are eligible for yearly influenza vaccine or who require booster vaccinations for other diseases can receive vaccination with killed/toxoid vaccines consistent with normal clinical practice. The effect of CAM-3001 on vaccine response is not known.

4.5.5 Dose Escalation and Cohort Progression

For Cohorts 1 to 3, decisions relating to dose escalation will be made by the sponsor (including the medical monitor, the safety physician, the project medical director and additionally final approval by the MedImmune SMC which includes internal and external experts). These reviews based on a review of all cumulative safety data, will occur after at least 18 subjects have completed dosing on Day 29. Once recruitment to Cohort 4 is initiated, an initial 18 of the planned total of 54 subjects for this cohort, will be recruited (12 CAM-3001 and 6 placebo); once at least 6 of these subjects have been exposed to study treatment for the entire treatment period (Day 85) and no safety concerns have been detected, recruitment will resume to enrol the remaining number of subjects planned for this cohort.

Note that where data is available from subjects in Japan, these data will be included in the safety reviews.

The safety evaluations for dose escalation (Cohorts 1 to 3) and completion of recruitment (Cohort 4) will include cumulative, blinded safety information; including AEs, SAEs, events of special interest (ESIs) including pulmonary function testing and DLCO, laboratory data and any associated information.

Events of special interest are events that might be anticipated considering the mechanism of action of CAM-3001, or might be associated with monoclonal antibodies in general. For this protocol the ESIs are defined as: reproductive toxicity, haematopoietic effects, susceptibility to infection, pulmonary alveolar proteinosis (PAP), anaphylactoid-like and anaphylactic

reactions (see Investigator's Brochure for detailed information). Specifically, the following ESIs are defined below and will be closely monitored by the investigator/designee and will be reviewed by the medical monitor throughout the study:

- Neutropenia; neutrophils < 1.0×10^9/L unless the cause for neutropenia can be clearly attributed to causes other than investigational product.
- Serious or life threatening infections, or opportunistic infection requiring hospitalisation, or septic shock unless a relationship to investigational product can be clearly excluded.
- Acute hypersensitivity reaction - severe or life-threatening hypersensitivity reaction (as defined in Appendix 1) unless a relationship to investigational product can clearly be excluded.
- Death or life threatening AE, which is considered to be possibly attributable to investigational product.
- Clinically significant respiratory diseases and deterioration of pulmonary function and DLCO, confirmed by the study pulmonologist, considered to be possibly attributable to investigational product.

The sponsor may recommend that dose escalation continues as defined below:

1) If none of the events described above occur, and there are no other observations suggesting that there may be a change to the risk/benefit profile of the product; or
2) If, one or more ESIs (including laboratory abnormalities) are observed but these do not represent a material change to the risk/benefit profile of the product as described by the Investigator Brochure and as agreed by the sponsor.

Conversely, even if no ESIs are observed but there are any other reasons for the sponsor to believe that there has been a material change to the risk-benefit of the product which requires a change in the conduct of the study, then the study will be stopped immediately until an update can be provided to the IRB/IEC along with a recommendation for further action.

4.5.6 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor compliance.

4.6 Subject Status

Subject Completion

The primary analysis will be performed when all subjects have completed the treatment period through Day 85. An individual subject will be considered to have completed the safety follow-up of the study if the subject was followed up through Day 169, regardless of the number of doses of investigational product that was received.

It should be specified on the source document whether or not the subject completed the study safety follow-up procedures through Day 169.

Subjects will be considered not to have completed the study if one of the following conditions applies:

- Withdrawal of consent: If consent for follow-up is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may need to undergo additional tests or tapering of treatment to withdraw safely. Subjects who withdraw consent will be asked to give a reason; however the subjects may decline to provide this information.
- Lost to follow-up: Subjects will be considered lost-to-follow-up only if no contact has been established by the time the study is completed such that there is insufficient information to determine the subject's status on Day 169.

Note: Subjects refusing to return to the site or to continue participation in the study should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost-to-follow-up and any evaluations should resume according to the protocol.

4.7 Study Completion

Study completion is defined as the date of the last protocol-specified visit/assessment for the last subject in the study. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion, as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed.

5 Assessment of Efficacy and Clinical Pharmacology

5.1 Efficacy and Clinical Pharmacology Parameters

5.1.1 Efficacy Parameters

5.1.1.1 Primary Efficacy Endpoint

The effect of CAM-3001 on the response rate in terms of improvement in DAS28 c-reactive protein (CRP) score on the day of last dose of investigational product (Day 85) will be evaluated. According to the European League Against Rheumatism (EULAR) response criteria an improvement from baseline (Day 1) in DAS28(CRP) of more than 1.2 would be considered a good response in subjects experiencing low disease activity (baseline DAS28 < 3.2) and a moderate response in subjects experiencing medium to high disease activity (baseline DAS28(CRP) ≥ 3.2). A responder will be defined as a subject experiencing a decrease of more than 1.2 from their baseline DAS28(CRP) score, on the day of last dose of investigational product (Day 85 per protocol).

5.1.1.2 Other Efficacy Endpoints

Other efficacy endpoints include assessment of the effects of CAM-3001 on clinical outcomes in RA as measured by ACR20, ACR50 and ACR70, with further assessments of DAS28 response.

The CAM-3001 dose relationship with efficacy will also be explored by looking at endpoints including the onset of response, the duration of response after withdrawal of treatment and the need for additional medications.

5.1.2 Clinical Pharmacology Parameters

Noncompartmental analysis will be performed for CAM-3001 treated subjects. The PK parameters to be reported include the C_{max} and AUC following the first dose, and trough concentrations following subsequent administrations. Descriptive statistics by dose cohort will be provided. If the data allow, population PK analysis will be performed.

5.2 Schedule of Study Procedures

All subjects who are assigned a subject identification number and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviation. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IRB/IEC.

Subjects will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

A schedule of study procedures is presented in Table 5.2-1, followed by a description of each visit. A description of the study procedures is included in Section 5.3.

Table 5.2-1 Schedule of Subject Evaluations

Evaluations	Screen Up to -28	Treatment Period (Study Days)									Follow-up (Study Days)			
		1	4	8	15	29	43	57	71	85	88 ±2	99 ±3	113 ±7	169/ Disc ±7
VISIT	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Written informed consent	X													
Verify eligibility criteria	X	X												
Demographics	X													
Medical history	X													
Physical examination	X	X										X		X
ECG	X													X
TB test	X													
Chest x-ray	X													
Hepatitis A, B, C; CMV, EBV	X													
Serum βHCG	X													

Table 5.2-1 Schedule of Subject Evaluations

Evaluations	Screen Up to -28	Treatment Period (Study Days)									Follow-up (Study Days)			
		1	4	8	15	29	43	57	71	85	88 ±2	99 ±3	113 ±7	169/ Disc ±7
VISIT	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Urine βHCG		X			X	X	X	X	X	X				X
INVESTIGATIONAL PRODUCT ADMINISTRATION		**X**			**X**	**X**	**X**	**X**	**X**	**X**				
SAFETY ASSESSMENT														
Height	X													
Weight	X													X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE/SAE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical chemistry, haematology with differential, platelets	X	X			X	X	X	X	X	X		X	X	X
Urinalysis	X	X			X	X	X	X	X	X		X	X	X
Modified Borg scale (subjects completed) and O_2 saturation (pulse oximetry)	X	X			X	X	X	X	X	X		X	X	X
Pulmonary Function Tests	X	X				X				X				X
PK/Immunogenicity														
CAM-3001 serum concentration		X	X	X	X	X		X		X	X	X	X	X
Anti-CAM-3001 antibodies		X				X		X		X		X	X	X
DISEASE ACTIVITY														
Swollen joint count (66 joints)	X	X		X	X	X	X	X	X	X		X	X	X
Tender joint count (68 joints)	X	X		X	X	X	X	X	X	X		X	X	X
Patient assessment of pain	X	X		X	X	X	X	X	X	X		X	X	X
Patient's global assessment of disease activity	X	X		X	X	X	X	X	X	X		X	X	X

Table 5.2-1 Schedule of Subject Evaluations

Evaluations	Screen Up to -28	Treatment Period (Study Days)									Follow-up (Study Days)			
		1	4	8	15	29	43	57	71	85	88 ±2	99 ±3	113 ±7	169/ Disc ±7
VISIT	**Screen**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Physician's global assessment of disease activity	X	X		X	X	X	X	X	X	X		X	X	X
HAQ-DI	X	X		X	X	X	X	X	X	X		X	X	X
Rheumatoid factor, anti-CCP antibodies	X	X		X	X	X	X	X	X	X		X		X
PATIENT REPORTED OUTCOMES														
SF-36		X				X				X				
FACIT-Fatigue		X			X	X		X		X			X	X
MOS-sleep scale		X				X				X				
CORRELATIVE STUDIES														
Receptor occupancy		X	X	X	X	X		X		X	X	X	X	X
Whole blood for mRNA and miRNA analysis		X	X	X	X	X		X		X	X	X	X	X
Serum for exploratory biomarker analysis		X		X	X	X		X		X	X	X	X	X
DNA Sample (optional)		X												

AE = adverse event; βHCG = β human chorionic gonadotrophin; CCP = cyclic citrullinated peptide; CMV = cytomegalovirus; DNA = deoxyribonucleic acid; EBV = Epstein-Barr virus; ECG = electrocardiogram; FACIT = functional assessment of chronic illness therapy; HAQ-DI = Health Assessments Quesionairre-Disability Index; miRNA = micro ribonucleic acid; mRNA = messenger ribonucleic acid; MOS = Medical Outcomes Study; O_2 = oxygen; PK = pharmacokinetics; TB = tuberculosis; SAE = serious adverse event; SF-36 = Short Form 36

It is essential that assessments completed by the subject and the Joint Count Assessor are made before those by the Safety Assessor. Consequently, assessments should be made in the order presented below for each visit as far as possible, where not possible (eg, pulmonary function tests and DLCO) these may be performed at a separate visit as long as the test is within the visit window. Assessments listed before "Administer investigational product" should be completed predose:

5.2.1 Screening

All screening procedures must be performed within 28 days before randomisation. Written informed consent and any locally required authorisation (eg, HIPAA in the USA, EU Data Privacy Directive authorisation in the EU) must be obtained prior to performing any study-related procedure, including screening evaluations.

1) Obtain subject identification from the IWRS/IVRS
2) Verify eligibility criteria

Patient reported assessments:

3) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, Health Assessments Questionnaire-Disability Index (HAQ-DI) to subjects

Joint counts assessor (skilled arthritis assessor):

4) Perform tender and swollen joint count

Safety assessor (physician):

5) Perform medical history
6) Perform physical examination
7) Perform electrocardiogram (ECG)
8) Perform TB test
9) Perform chest x-ray (may be performed at a separate screening visit)
10) Review pulmonary function tests (may be performed at a separate screening visit)
11) Collect blood for screening samples:
    - Serum chemistry
    - Haematology with differential, platelets
    - Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies
    - Serum for hepatitis A antibody (HAV), HBV surface antigen, HCV, cytomegalovirus (CMV) and Epstein-Barr Virus (EBV)
    - Serum pregnancy test for females (βhuman chorionic gonadotropin [βHCG])
12) Collect urine for screening sample
13) Complete physician global assessment of disease activity
14) Assess modified Borg scale score and pulse oximetry

15) Take vital signs

16) Collect demographic data (age, gender, ethnicity and race)

17) Measure height and weight

18) Assess for AEs and SAEs

19) Record concomitant medications and previous RA medications

5.2.2 Treatment Period

During the treatment period, a visit window of ± 2 day will be permitted if required.

Day 1: First Injection

Visit 1

1) Confirm eligibility

Patient reported assessments:

2) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, HAQ-DI, short form-36 (SF-36), functional assessment of chronic illness therapy-fatigue (FACIT-Fatigue) and Complete Medical Outcomes Study (MOS)-Sleep scale to subjects

Joint counts assessor (skilled arthritis assessor):

3) Perform tender and swollen joint count

Safety assessor (physician):

4) Review pulmonary function tests

Note: If pulmonary function tests are performed within 7 days of Day 1, then these tests do not need to be repeated at Day 1 if there is no clinically significant change in dyspnoea (Borg scale) or any clinically significant respiratory problem.

5) Perform physical examination (if applicable, record new findings as AEs or SAEs)

6) Update concomitant medications

7) Complete physician global assessment of disease activity

8) Assess modified Borg scale score and pulse oximetry

9) Collect urine for urinalysis

10) Collect predose blood for baseline samples:

- Serum chemistry

- Haematology with differential platelets
- Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies
- CAM-3001 serum concentration
- Serum for anti-CAM-3001 antibodies
- Whole blood for mRNA and miRNA analysis
- Serum for exploratory biomarker studies
- Whole blood for receptor occupancy analysis
- DNA sample (optional)

11) Assess for AEs and SAEs
12) Collect urine for pregnancy test; ensure result is negative
13) Randomise and assign investigational product number
14) Administer investigational product
15) Take vital signs (pre and postdose)

Day 4: Follow-up after First Injection

Visits 2

Safety assessor (physician):

1) Take vital signs
2) Assess for AEs and SAEs
3) Update concomitant medications
4) Collect blood and serum for assessment of:
   - CAM-3001 serum concentrations
   - Whole blood for mRNA and miRNA analysis
   - Whole blood for receptor occupancy analysis

Day 8: Follow-up after First Injection

Visits 3

Patient reported assessments:

1) Administer patient assessment of pain, patient global assessment of disease activity and HAQ-DI to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Assess for AEs and SAEs
4) Take vital signs
5) Complete physician global assessment of disease activity
6) Update concomitant medications
7) Collect blood and serum for assessment of:
   - CAM-3001 serum concentrations
   - Whole blood for mRNA and miRNA analysis
   - Serum for exploratory biomarker studies
   - Whole blood for receptor occupancy analysis
   - Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies

Day 15: Second Injection

Visit 4

Patient reported assessments:

1) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, HAQ-DI, and FACIT-Fatigue to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Assess for AEs and SAEs
4) Update concomitant medications
5) Complete physician global assessment of disease activity
6) Collect predose blood and serum for assessment of:
   - Serum chemistry
   - Haematology with differential platelets
   - Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies

- CAM-3001 serum concentrations
- Whole blood for mRNA and miRNA analysis
- Serum for exploratory biomarker studies
- Whole blood for receptor occupancy analysis

7) Collect urine for urinalysis

8) Assess modified Borg scale score and pulse oximetry

9) Collect urine for pregnancy test; ensure result is negative

10) Administer investigational product

11) Take vital signs (pre and postdose)

Day 29: Third Injection

Visit 5

Patient reported assessments:

1) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, HAQ-DI, SF36, FACIT-Fatigue and MOS-Sleep scale to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Assess for AEs and SAEs

4) Update concomitant medications

5) Complete physician global assessment of disease activity

6) Collect predose blood and serum for assessment of:

- Serum chemistry
- Haematology with differential platelets
- Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies
- CAM-3001 serum concentrations
- Anti-CAM-3001 antibodies
- Whole blood for mRNA and miRNA analysis
- Serum for exploratory biomarker studies

- Whole blood for receptor occupancy analysis

7) Collect urine for urinalysis

8) Review pulmonary function tests (may be performed one day prior to dosing)

9) Assess modified Borg scale score and pulse oximetry

10) Collect urine for pregnancy test; ensure result is negative

11) Administer investigational product

12) Take vital signs (pre and postdose)

Day 43: Fourth Injection

Visit 6

Patient reported assessments:

1) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, and HAQ-DI to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Assess for AEs and SAEs

4) Update concomitant medications

5) Complete physician global assessment of disease activity

6) Collect predose blood and serum for assessment of:

- Serum chemistry
- Haematology with differential platelets
- Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies

7) Collect urine for urinalysis

8) Assess modified Borg scale score and pulse oximetry

9) Collect urine for pregnancy test; ensure result is negative

10) Administer investigational product

11) Take vital signs (pre and postdose)

Day 57: Fifth Injection

Visit 7

Patient reported assessments:

1) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, HAQ-DI and FACIT-Fatigue to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Assess for AEs and SAEs
4) Update concomitant medications
5) Complete physician global assessment of disease activity
6) Collect predose blood and serum for assessment of:
   - Serum chemistry
   - Haematology with differential platelets
   - Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies
   - CAM-3001 serum concentrations
   - Anti-CAM-3001 antibodies
   - Whole blood for mRNA and miRNA analysis
   - Serum for exploratory biomarker studies
   - Whole blood for receptor occupancy analysis
7) Collect urine for urinalysis
8) Assess modified Borg scale score and pulse oximetry
9) Collect urine for pregnancy test; ensure result is negative
10) Administer investigational product
11) Take vital signs (pre and postdose)

Day 71: Sixth Injection

Visit 8

Same as Day 43 (Visit 6).

Day 85: Seventh Injection

Visit 9

Same as Day 29 (Visit 5).

5.2.3 Safety Follow-up Period

Day 88

Visit 10

Safety assessor (physician):

1) Take vital signs
2) Assess for AEs and SAEs
3) Update concomitant medications
4) Collect blood and serum for assessment of:
   - CAM-3001 serum concentrations
   - Whole blood for mRNA and miRNA analysis
   - Serum for exploratory biomarker studies
   - Whole blood for receptor occupancy analysis

Day 99

Visit 11

Patient reported assessments:

1) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, and HAQ-DI to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Perform physical examination
4) Take vital signs
5) Assess for AEs and SAEs

6) Update concomitant medications

7) Perform physician's global assessment of disease activity

8) Collect blood and serum for assessment of:

- Serum chemistry
- Haematology with differential platelets
- Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies
- CAM-3001 serum concentrations
- Anti-CAM-3001 antibodies
- Whole blood for mRNA and miRNA analysis
- Serum for exploratory biomarker studies
- Whole blood for receptor occupancy analysis

9) Collect urine for urinalysis

10) Assess modified Borg scale score and pulse oximetry

Day 113

Visit 12

Patient reported assessments:

1) Patient assessment of pain, patient's global assessment of disease activity, HAQ-DI and FACIT-Fatigue to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Take vital signs

4) Assess for AEs and SAEs

5) Update concomitant medications

6) Perform physician's global assessment of disease activity

7) Collect blood and serum for assessment of:

- Serum chemistry
- Haematology with differential platelets
- CAM-3001 serum concentrations

- Anti-CAM-3001 antibodies
- Whole blood for mRNA and miRNA analysis
- Serum for exploratory biomarker studies
- Whole blood for receptor occupancy analysis

8) Collect urine for urinalysis

9) Assess modified Borg scale score and pulse oximetry

5.2.4 End of Study Visit (Day 169/Visit 13) /Early Discontinuation Visit

These evaluations will be performed in subjects who discontinue the study prematurely, unless the evaluation was performed within 2 weeks of the discontinuation visit

Patient reported assessments:

1) Administer patient assessment of pain, patient global assessment of disease activity, modified Borg scale, HAQ-DI and FACIT-Fatigue to subjects

Joint counts assessor (skilled arthritis assessor):

2) Perform tender and swollen joint count

Safety assessor (physician):

3) Perform physical examination

4) Perform ECG

5) Take vital signs

6) Measure weight

7) Assess for AEs and SAEs

8) Update concomitant medications

9) Perform physician's global assessment of disease activity

10) Collect blood and serum for assessment of:

- Serum chemistry
- Haematology with differential platelets
- Rheumatoid factor (including isotypes IgM, A and G) and anti-CCP antibodies
- CAM-3001 serum concentration
- Anti-CAM-3001 antibodies
- Whole blood for mRNA and miRNA analysis

- Serum for exploratory biomarker studies
- Whole blood for receptor occupancy analysis

11) Collect urine for pregnancy test

12) Collect urine for urinalysis

13) Assess modified Borg scale score and pulse oximetry

14) Review pulmonary function tests

5.3 Description of Study Procedures

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information.

5.3.1 Medical History, Physical Examination, ECG, Weight, Vital Signs and Respiratory Function

Physical Examination

Physical examinations are to be performed at the time points specified in Table 5.2-1. At Screening, a physical examination is performed to assist in determining the subject's eligibility for the study. Physical examinations will include the following assessment: head, eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal, musculoskeletal; neurological; dermatological; lymphatic; endocrine system; body weight; and body height.

Scheduled surgeries during the study are not permitted according to the exclusion criteria (Section 4.2.2); however, if a subject has already been entered into the study and is required to have surgery or another procedure during the study and the event does not fulfil the definition of an AE/SAE, then following consultation with the medical monitor, these events are allowed and should be recorded in the eCRF.

Vital Signs

Vital signs include blood pressure, pulse rate, temperature, and respiration rate, unless otherwise indicated above. Blood pressure and pulse rate are to be recorded at the Screening visit and at time points during the study and safety follow-up as specified in the Schedule of Subject Evaluations (Table 5.2-1). Supine blood pressure and pulse rates are to be recorded with the subject in a rested supine position for at least 10 minutes.

On Study Day 1, vital signs (temperature, blood pressure, pulse rate, respiratory rate) will be obtained before and after administration of the investigational product. Subjects will be observed at the study site after dosing to monitor for immediate drug reactions for a minimum of ~2 hours, with vital signs measured at least approximately every 30 minutes. For subsequent dosing, measurements of vital signs should be taken prior to investigational product administration, and ~30 minutes after investigational product administration or until stable, whichever is later. Any medically significant change from the screening vital signs will be recorded as an AE.

Electrocardiogram

A 12-lead ECG will be done during the study according to investigative site procedures. 12-lead ECGs are to be recorded with the subject in a rested supine position for at least 10 minutes. Food and drink should not be consumed by the subject within the 30 minutes before the 12-lead ECG is to be recorded. 12-lead ECGs are to be recorded at the Screening visit, at the end of study, and at the discontinuation visit for subjects withdrawing from the study prematurely. The principal investigator or qualified designee will review and indicate if the ECG is normal or abnormal. Any medically significant change from the screening ECG will be recorded as an AE. The QT interval will also be recorded in the eCRF.

Chest X-Ray

A chest x-ray will be performed during the Screening period and assessed by an expert pulmonologist for evidence of any medically significant respiratory disease. Additionally if any abnormalities are detected in the results of the lung function tests or any signs and symptoms suggestive of lung abnormalities are found, additional chest x-rays and/or other procedures may be performed.

If a recent chest x- ray has been performed within 4 weeks prior to Screening, then the chest x-ray does not need to be repeated during the Screening period.

Tuberculosis Test

A TB test will be performed and read at Screening in order to evaluate an eventual infection with TB.

Based on the study site's normal practice and acceptable clinical practice in each country (which will be agreed and documented in advance of the study with the sponsor) QuantiFeron

test may replace PPD skin test at Screening, in subjects with BCG vaccination. A positive QuantiFeron test at Screening will exclude the subjects from participation in the study as per local guidelines.

Because the PPD test (induration) will take 48-72 hours to develop, the subject must return to the investigators' site within that time for a proper evaluation of the test site. This will determine whether the subjects have had a significant reaction to the PPD test. A reaction is measured in millimetres of induration (hard swelling) at the site. The interpretation of the PPD skin test will be according to local regulations.

Pulmonary Function Testing

Pulmonary function testing at study sites will be performed to assess forced vital capacity (FVC), FEV_1 and DLCO. Both absolute values and the percentage of predicted normal value (Hankinson et al, 1999) will be recorded on the eCRF.

Pulmonary function tests including both spirometry and DLCO will be performed at Screening, Baseline (Day 1), on Days 29 and 85, and at the end of study (Day 169) and at the discontinuation visit for subjects withdrawing from the study prematurely.

Pulmonary function testing may be performed one day prior to dosing on Days 1, 29 and 85. In addition, if the screening pulmonary function tests are performed within 7 days of Day 1, then these tests do not need to be repeated at Day 1 if there is no clinically significant change in dyspnoea (Borg scale) or any clinically significant respiratory problem.

Any medically significant change from the screening pulmonary function tests, as interpreted by a pulmonologist, or in the event of a deterioration of more than 20% from baseline values, the event will be recorded as an AE. The subject will not receive any further treatment with CAM 3001 until the test has been repeated (within approximately 5 days) and the sponsor has confirmed that dosing can resume.

Modified Borg Scale (Dyspnoea) and Oxygen Saturation

In addition, at each visit the investigator or qualified designee will assess the subject's dyspnoea as measured by the modified Borg scale score and measure oxygen saturation by pulse oximetry. The modified Borg scale (Borg, 1982) is a validated patient reported outcome that will be completed by subjects in the study. The safety assessor will evaluate completed questionnaires for subjects' perceived difficulty in breathing (dyspnoea). The scale ranges

from 0 (nothing at all) to 10 (maximal) with 10 being the maximal possible score. Higher scores indicate greater difficulty in breathing.

Oxygen saturation will be assessed by pulse oximetry at Screening, Baseline (Day 1) and at the time points specified in the Schedule of Subject Evaluations (Table 5.2-1) as part of respiratory system assessment.

In the case that a subject develops any new significant respiratory symptoms/signs such as shortness of breath, difficulty in breathing, cough, experience an exacerbation of any current respiratory symptoms, or a significant deterioration in dyspnoea score as judged clinically significant by the investigator, the subject should not receive any further treatment with CAM-3001 and will be referred promptly to a specialist pulmonologist for further assessment. Upon resolution of symptoms/signs and exclusion of the diagnosis of any clinical significant respiratory event the treatment schedule could be resumed.

5.3.2 Clinical Laboratory Tests

Clinical laboratory safety tests will be performed in a licensed, central clinical laboratory. Urine pregnancy and urinalysis tests may be performed at the site using a licensed test (dipstick). Any laboratory test result that fall outside of the normal ranges may be repeated at the discretion of the Investigator, A urine sample may be sent to the central laboratory for evaluation of urine chemistry if clinically indicated (as judged by the investigator/designee). New medically significant abnormal laboratory results, which in the opinion of the investigator are related to safety, should be repeated as soon as possible (preferably within 24 to 48 hours). Any medically significant change in laboratory evaluations will be recorded as an AE (for the definition of AE see Section 6.1.1).

The following clinical laboratory tests will be performed (see Table 5.2-1 for the schedule of tests):

Serum Chemistry

- Calcium
- Potassium
- Sodium
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Alkaline phosphatase (ALP)
- Gamma glutamyl transferase (GGT)
- Total bilirubin
- CRP
- Erythrocyte sedimentation rate (ESR) locally tested
- Urea
- Creatinine
- Albumin
- Total cholesterol
- Triglycerides
- Rheumatoid factor
- Anti-CCP antibodies
- Glucose

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted and assessed concurrently.

Haematology

- Haemoglobin
- Leukocyte count
- Leukocyte count – differential
- Reticulocytes
- Platelet count
- Mean corpuscular volume (MCV)
- Mean corpuscular haemoglobin concentration (MCHC)

Urinalysis

- Blood
- Protein/Albumin
- Protein
- Glucose
- Nitrite

If clinically indicated, urine chemistry:

- Creatinine, microalbumin and microalbumin/creatinine ratio

Pregnancy Test (females of childbearing potential only)

- Serum beta- human chorionic gonadotropin (hCG) (at Screening only)
- Urine hCG

Other Safety Tests

Additional laboratory tests will be performed at Screening and are listed below. A laboratory manual will be provided specifying specific procedures for collection, processing, storage, and shipping of samples.

- Hepatitis A antibody, hepatitis B surface antigen, hepatitis C antibody
- Virology; CMV and EBV

5.3.3 Pharmacokinetic and Immunogenicity Evaluation and Methods

For PK analyses, it is important that the exact time of the SC injection and of each PK sample taken is recorded for each subject. Serum samples will be collected predose at designated visit days starting with Study Day 1 for CAM-3001 level and anti-CAM-3001 antibody determination. Specific procedures for sample collection, processing, storage, and shipment can be found in a separate laboratory manual provided to sites. CAM-3001 serum concentrations and anti-CAM-3001 antibody detection will be measured using Enzyme-linked immunosorbent assay and ECL assays, respectively.

5.3.4 Disease Evaluation and Methods

A clinical evaluation of disease activity should be done as described in the Study Reference Manual. This evaluation will encompass DAS28 and ACR responses.

5.3.4.1 DAS28

The DAS28(CRP) has been validated against radiographic progression and physical function (HAQ-DI) and the validation profile is similar to the DAS28 Erythrocyte Sedimentation Rate (ESR) (Wells et al, 2009). In this study both CRP and ESR will be collected. Subjects are required to have at least moderately active disease as defined by DAS28 $\geq$ 3.2 at Screening and Day 1 in order to be included in this study. The investigator will calculate DAS28(CRP) for Screening and DAS28(ESR) for Day 1 to assess this criterion.

The DAS28 considers 28 of the 68 tender joint count (TJC) and 28 of the 66 swollen joint count (SJC), general health (GH) using patient assessment of disease activity using the numerical rating scale with 0 = best, 100 = worst, plus levels of CRP (mg/L) or ESR (mm/hour).

DAS28(CRP) values will be calculated as follows (Wells et al, 2009):

DAS28(CRP) = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.014*GH + 0.36 ln(CRP+1) + 0.96

DAS28(ESR) values will be calculated as follows:

DAS28(ESR) = 0.56 * sqrt(TJC28) + 0.28 * sqrt(SJC28) + 0.70*ln(ESR) + 0.014*GH

DAS28 will be categorised using the EULAR response criteria:

Table 5.3.4.1-1 DAS28 Improvement

Baseline DAS Score	Level of Improvement from Baseline (Day 1)		
	> 1.2	**≥ 0.6 to ≤ 1.2**	**< 0.6**
< 3.2	Good response	Moderate response	No response
≥ 3.2 to ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

DAS = Disease Activity Score

DAS28 defined remission is DAS28 of < 2.6. Low disease activity is < 3.2 and high disease activity is > 5.1.

5.3.4.2 ACR20, ACR50, and ACR70 Responses

The core components of the ACR response criteria are:

- Swollen joint count (66 joints; see below for details)
- Tender joint count (68 joints)
- Physician global assessment of disease activity (0-10 visual analogue scale [VAS]; see below for details)
- Patient global assessment of disease activity (0-100 VAS; see below for details)
- Patient pain assessment (0-100 VAS; see below for details)
- Patient reported functional disability (HAQ-DI; see below for details)
- Acute phase reactant (CRP and ESR)

A subject has an ACR response if all of the following occur:

- An improvement in the swollen joint count (66 joints)
- An improvement in the tender joint count (68 joints)
- An improvement in at least 3 of the following 5 assessments:
  - Physician global assessment of disease activity
  - Patient global assessment of disease activity
  - Patient pain assessment
  - Patient reported functional disability using the HAQ-DI
  - CRP or ESR

Subjects will be considered to have had an ACR20, ACR50 or ACR70 response if at least a 20%, 50% or 70% improvement from Day 1 (respectively) was observed in the criteria specified above.

68 Joint Assessments

The 68 joints to be assessed for tenderness are: temporomandibular (n = 2), sternoclavicular (n = 2), acromioclavicular (n = 2), the 8 proximal interphalangeal joints of the fingers, the interphalangeal joints of the thumbs (n = 2), the 8 distal interphalangeal joints, the 10 metatarsophalangeal, the 10 metacarpophalangeal joints plus the wrists (n = 2), elbows (n = 2), shoulders (n = 2), hips (n = 2), ankle mortise and tarsus (n = 4), knees (n = 2), and toes (n = 10) (Felson et al, 1993).

The 66 joints assessed for swelling are the same as those assessed for tenderness, except the hip joints are not included.

In order to calculate the ACR and DAS28 responses, each of the 68 joints will be evaluated for tenderness and swelling. Standardised metrology training will be provided if necessary.

Physician Global Assessment of Disease Activity

The physician global scale is a 10 cm VAS that asks the safety assessor to rate their subject's level of disease activity due to RA **'TODAY'.** Higher scores on this scale indicate increased (worse) disease activity.

Patient Global Assessment of Disease Activity

Subjects in the study will be asked to complete the patient global assessment of disease activity. The patient global assessment of disease activity is a measure of patient's general health as a result of their arthritis on a VAS of 0 (= very well) to 100 (= very poorly). Higher scores on this scale indicate worse health.

Patient's Pain Assessment

Subjects in the study will be asked to complete pain assessment. The Pain VAS scale measures patient's severity of pain 'TODAY' as a result of their arthritis on a VAS of 0 (= no pain) to 100 (= severe pain). Higher scores on this scale indicate worse pain.

Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI will be used to assess the functional status of each subject (Fries et al, 1980). This 20-question instrument assesses the degree of difficulty a person has in accomplishing tasks of daily living in 8 functional areas (domains; dressing, arising, eating, hygiene, walking, reaching, grip, and errands/chores) over the past week. Scores range from 0 (without any difficulty) to 3 (unable to do). The highest scoring item in each domain is chosen. If an aid or device is used, or if assistance is required from another individual, then minimum score for that section is 2. The final scores are equal to the mean of these 8 highest scores and range from 0 to 3, with higher scores indicating greater functional disability. Additionally, subjects are asked to assess the severity of pain in the past week on a 100 mm VAS with 0 being no pain and 100 being severe pain. (Fries et al, 1980).

The global disease activity and pain assessments, modified Borg scale, HAQ-DI, FACIT-Fatigue, SF-36 and MOS-Sleep Scale questionnaires are all self-administered and are to be completed by the subject without the assistance of the investigational site personnel.

All questionnaires should be completed before any other study procedures are conducted at the visit.

5.3.4.3 Other Patient Reported Outcomes

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)

The FACIT-Fatigue is a 13 item subject-completed questionnaire to assess the impact of fatigue over the past 7 days. Responses range from 0 “Not at all” to 4 “Very Much”. Final scores are the sum of the responses (0-52) where higher scores indicate greater fatigue (Yellin et al, 1997). Changes in scores > 3-4 points are considered to be clinically meaningful (Cella et al, 2002).

SF-36

The SF-36 is a validated instrument for measuring a person’s general health status (Ware et al, 1993) over the past 4 weeks. The SF-36 includes 8 domains: Physical Function, Role Limitations-Physical, Vitality, General Health Perceptions, Bodily Pain, Social Function, Role Limitations-Emotional, and Mental Health and can be summarised into 2 summary scores, the Physical Component Summary and the Mental Component Summary. Final scores for the each scale range from 0-100 with higher scores indicating better health. The general

population has a mean score of 50 with a standard deviation of 10. Changes of ≥ 3-5 points in any of the summary scales or the individual scales are considered meaningful clinically important differences (Ware et al, 2007).

MOS-Sleep Scale

Medical Outcomes Study sleep questionnaire is a 12-item measure of sleep quality and quantity. Items are scored on a 5- to 6–point scale and responses to the questions are used to calculate aggregate scores for sleep adequacy, sleep disturbance, snoring, waking with shortness of breath or with a headache, somnolence, sleep index I (6-items), and sleep index II (9-items). All scales are scored on a 0-100 scale. For sleep adequacy, higher scores meant better sleep adequacy. For all other scales, lower scores indicated better sleep outcomes (Spritzer et al, 2003)

5.3.5 Correlative Studies

5.3.5.1 Exploratory Research

Samples will be obtained and analysed for exploratory research, that may include measurement of serum biomarkers, GM-CSF levels, analyses of serum autoantibodies and miRNA and/or mRNA expression. Analysis of the serum proteome will be carried out through the use of a large multiplex quantitative platform for known analytes. The mRNAs and/or miRNAs will be selected by both their presence in the GM-CSF pathway as well as potential downstream effectors. These analytes will be identified using ex vivo stimulation experiments where healthy donor cells are treated with GM-CSF to identify transcripts and/or miRNAs that are induced. CAM-3001 will then be utilised to determine which of these induced analytes are subsequently neutralised.

For both mRNA and miRNA experiments, a minimum 2.5 mL of blood per subject per time point are required. Specimens are stored in PaxGene tubes prior to processing. Aliquots of serum may be frozen and stored for additional exploratory studies based on research findings.

5.3.5.2 Receptor Occupancy

Assays of GM-CSF receptor occupancy will be performed at a central laboratory using flow cytometric techniques. The study schedule outlines when these samples will be collected. Instructions for sample collection, processing, storage, and shipment can be found in a

separate laboratory manual provided to the sites. Receptor occupancy will be evaluated in only those countries that can collect viable samples.

5.3.5.3 DNA Sample (optional) and RNA Sample

To investigate characteristics associated with subjects' clinical response and safety, one blood sample (8.5 mL) may be collected at Screening and frozen at –20°C (or lower temperature) for DNA sample preparation. The sample will be frozen and stored until used in exploratory analyses. The collection of blood for DNA analysis is optional. The completion of a separate informed consent form (Informed Consent Form for DNA Analysis) is requested. Subjects who do not wish to have the DNA test done will still be eligible for the study. Subjects who elect to have the DNA test done may, at any time before the end of the study, request that the blood collected for DNA analysis be destroyed.

All specimen and subject identifiers must be removed from the DNA blood samples such that under no circumstances can the DNA blood samples be linked back to a specific subject.

For DNA, miRNA and mRNA analyses, all collected specimens are identified on the sample itself only by study number and sample-ID (which is accession number and aliquot designation). Collection kits are supplied for each subjects visit and sample type. Accession numbers are pre-assigned to those kits. When a subject's samples are collected at a time point (for DNA samples, this is Day 1; for miRNA and mRNA samples, this is Day 1 and postdose), all samples of a single type have a sample ID, which is an aliquot plus accession number. The aliquot designation varies within a single collection; however the accession number remains constant within that collection. There are no personal identifiers associated with the sample tube. Samples are stored in this manner.

All labelling and shipments of bio hazardous materials must comply with International Air Transportation Association regulations.

6 Assessment of Safety

6.1 Safety Parameters

6.1.1 Adverse Events

The ICH Guideline for Good Clinical Practice E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after the subject signs the informed consent form but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline (Day 1) is not considered an AE (serious or nonserious). Furthermore, flares of RA or signs and symptoms of RA should not be considered as AEs unless, in the opinion of the investigator, there is a significant worsening in intensity or frequency of the symptoms above the subject's baseline condition in which case it will be recorded as an AE in the eCRF.

6.1.2 Serious Adverse Events

A SAE is any AE that:

- Results in death
- Is immediately life-threatening

  This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.

- Requires inpatient hospitalisation or prolongation of existing hospitalization

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.

- Results in persistent or significant disability/incapacity

  The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

  Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.2 Assessment and Recording of Safety Parameters

6.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. The determination of severity should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as generally defined below.

Grade 1	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject. The event poses a

	significant risk of harm to the subject, and hospitalisation may be required.
Grade 4	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or is with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5	The termination of life as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

6.2.2 Assessment of Relationship

The investigator or qualified designee is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered "not related" to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Associated with the use of the drug" means that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

6.2.3 Recording of Adverse Events

Adverse events will be recorded in the eCRF using a recognised medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification of the sponsor. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form (Section 6.2.4).

6.2.4 Recording of Serious Adverse Events

Serious adverse events will be recorded on the SAE Report Form using a recognised medical term or diagnosis that accurately reflects the event. Serious adverse events will be assessed by the investigator for severity, relationship to the investigational product, and possible aetiologies. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 regarding guidelines for assessment of severity and relationship, respectively.

For all SAEs an assessment of protocol relatedness must be made by the investigator. A protocol-related SAE may occur as a result of a procedure or intervention required during study participation (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of nontreatment-emergent SAEs:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative aetiology present in the subject's medical record.

Not protocol related: The event is related to an aetiology other than the procedure/ intervention that was described in the protocol (the alternative aetiology must be documented in the study subject's medical record).

6.2.5 Recording of Events of Hepatic Function Abnormality

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3× ULN **and concurrent** increase in bilirubin to greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

Events of hepatic function abnormality should be recorded according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively):

- If an event of hepatic function abnormality is considered to be related to a pre-existing condition and does not represent a worsening of this condition and/or is considered to be within the range of normal physiological fluctuation for the subject, the event does not meet the definition of an AE and does not need to be recorded as such.
- If a definitive diagnosis for an underlying condition unrelated to the investigational product is established for an event of hepatic function abnormality, the diagnosis should be recorded as an AE/SAE per Section 6.2.3 and Section 6.2.4.
- If no definitive diagnosis is determined for an event of hepatic function abnormality, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.2.3 and Section 6.2.4.

6.3 Reporting Requirements for Safety Parameters

6.3.1 Study Reporting Period for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through Day 169. Any AE that starts within the reporting period will be followed up to the end of the clinical study (Day 169). New nonserious AEs that start after the reporting period will not be collected.

6.3.2 Study Reporting Period for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through Day 169 or completion of the study. After submitting

an initial SAE report for a subject (to MedImmune Patient Safety Department, the investigator is required to follow the subject proactively and provide further information on the subject's condition to MedImmune Patient Safety Department.

The investigator is responsible for following all SAEs until resolution, even if this extends beyond the study reporting period, or until the subject returns to baseline status or the condition has stabilised with the expectation that it will remain chronic.

At any time after completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational product, the event must be reported to MedImmune Patient Safety Department.

6.3.2.1 Notifying the Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax to MedImmune Patient Safety Department.

MedImmune contact information:

Patient Safety
MedImmune
[redacted]
Fax: [redacted]

Country specific toll-free numbers will be provided in the study documentation.

As sponsor of the study, MedImmune is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. MedImmune may be required to report certain SAEs (Suspected Unexpected Serious Adverse Reactions) to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by MedImmune as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety Department of an SAE. When

additional information becomes available, submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety Department within 24 hours of learning of the new information.

6.3.2.2 Notifying the Institutional Review Board or Independent Ethics Committee of Serious Adverse Events

The investigator must comply with the applicable regulatory requirements related to the reporting of SAEs to the IRB/IEC. Where required, the IRB/IEC must be informed in a timely manner by the investigator of SAEs occurring at their site during the study. The sponsor will submit information on serious unexpected and related events to any EU IECs. Investigators must also submit any additional safety information provided by MedImmune to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.3.3 Other Events Requiring Immediate Reporting

6.3.3.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported ***within 24 hours of knowledge*** of the event to MedImmune Patient Safety Department using the Fax Notification Form (see Section 6.3.2.1 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE CRF (see Section 6.3.1). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalisation, the event is serious and must be reported as an SAE (see Section 6.2.4 and Section 6.3.2).

6.3.3.2 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety Department using the Fax Notification Form (see Section 6.3.2.1 for contact information):

Subjects who become pregnant during the study period must not receive additional doses of investigational product and will be withdrawn from the study. If the subject requests to know

which treatment she received, this information will be provided to her. After obtaining the subjects consent, the pregnancy will be followed for outcome and any premature terminations reported. In addition, the health status of the mother and child, including date of delivery, and the child's gender and weight should be reported to MedImmune Patient Safety Department after delivery.

6.3.3.3 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.2.5) in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the SAE Report Form (see Section 6.3.2.1 for contact information), unless a definitive underlying diagnosis for the abnormality (eg, cholelithiasis and bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor. If the aetiology of the event remains unconfirmed and/or is considered related to the investigational product (see Section 6.2.2), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune SMC (see Section 6.4) to determine whether continued dosing of current study subjects and/or study randomisation should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the SMC is required for resumption of subject dosing or study randomisation in the event that the study is interrupted. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

6.3.3.4 Other Protocol-specific Events

The following events are considered immediately reportable events even if they do not meet the criteria for serious and must be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety Department using the Fax Notification Form (see Section 6.3.2.1 for contact information):

1) Any withdrawal of consent during the study after the first dose of investigational product
2) Any event resulting in discontinuation of investigational product
3) AEs that are considered to be allergic reactions related to investigational product
4) AEs that are considered to be anaphylactic or acute hypersensitivity reactions

   For purposes of this protocol, acute hypersensitivity reactions are defined as AEs related to the injection of the investigational product itself that usually occur within the first 24 hours after injection, especially within minutes to a few hours. Acute hypersensitivity reactions can be characterised by a complex of signs and symptoms that include flu-like illness, fever, chills/rigors, nausea, urticaria, headache, bronchospasm, angioedema, hypotension, hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation and cardiogenic shock. For purposes of this protocol, a classification of acute hypersensitivity reactions is given in Appendix 1, with suggested treatment options. Final treatment is at the discretion of the investigator and should reflect local standard of care.
5) A deterioration of pulmonary function test by spirometry or DLCO more that 20% of the baseline values
6) Any clinically significant deterioration in dyspnoea score, as assessed by the investigator.

6.4 Safety Management During the Study

The MedImmune medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes review of SAEs and timely review of AEs and “other events” reported during the study. MedImmune Patient Safety Department is responsible for the receipt, immediate medical/clinical review, investigation, and follow-up of SAEs reported from the clinical study sites.

The MedImmune SMC, chaired by the MedImmune Chief Medical Officer, provides safety surveillance, guidance, and oversight for all clinical development studies in which MedImmune has sponsor accountabilities. In addition to the Chief Medical Officer, SMC

members include the heads of Patient Safety, Clinical Development, and Regulatory Affairs, and external physician members with expertise in relevant therapeutic areas. The SMC reviews protocol-specific safety data at regularly scheduled meetings and ad hoc meetings, and provides oversight for individual study protocol safety committees, such as those specified for early-phase dose-escalation studies. Based on review of safety data, the SMC may suspend enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

6.4.1 Interruption or Permanent Discontinuation of Study Dosing in Individual Subjects

Interruption of dosing

The investigator may interrupt dosing if the subject experiences an event which, in the opinion of the investigator or the medical monitor, compromises subject safety such as active infection, deterioration of cardiopulmonary diseases meeting the exclusion criteria specified in Section 4.2.2or the development of other complications. A subject with a neutrophil count below 1.5 x 10^9/L will not receive any further investigational product until resolution of these symptoms. Similarly, a subject with a deterioration of pulmonary function (spirometry) or DLCO of more than 20% of the baseline values will not receive any further investigational product until the tests are repeated and an evaluation is performed by the pulmonologist that confirms the absence of any clinically significant lung problem. This opinion must then be communicated to the medical monitor. If the medical monitor gives approval to continue dosing, the scheduled dose should be administered at the latest within 5 days of the visit date. If dosing is not possible within 5 days, then the dose will be skipped at this visit. The next scheduled dose will be administered according to the protocol visit schedule.

Discontinuation of dosing

An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1) Withdrawal of consent.
2) Pregnancy.
3) Event which in the opinion of the investigator or the sponsor contraindicates further dosing such as illnesses or complications.
4) Any serious or life-threatening AE related to the investigational product.

5) A change in concomitant RA therapy or other restricted medication during the treatment period of the study as described in Section 4.5.4.

6) A neutrophil count below 1.0×10^9/L after administration of investigational product.

Subjects who are permanently discontinued from investigational product will be followed for the full study period (through Day 169). Where possible all study assessments should be completed, unless consent is withdrawn.

6.4.2 Study Stopping Criteria

Should any of the following listed events occur:

1) Death in any subject in which the cause of death is related to investigational product.

2) Any life-threatening clinical event related to the investigational product.

3) A deterioration of pulmonary function test by spirometry or DLCO of more the 20% of the baseline values for a given subject.

4) Any other safety finding assessed as related to investigational product that, in the opinion of the sponsor, contraindicates further dosing of study subjects

A cumulative review of safety data and the circumstances of the event(s) in question will be conducted by the sponsor to determine whether study entry/randomisation and dosing should be discontinued, whether the protocol will be modified, or whether the study will be discontinued permanently.

6.4.3 Monitoring of Dose Administration

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute hypersensitivity reactions must be immediately available, and study personnel must be trained to recognise and treat hypersensitivity reactions.

If an acute hypersensitivity reaction occurs, the subject will remain at the study site for a minimum of 2 hours for observation after resolution of symptoms and undergo the following procedures unless transfer to an emergency or hospital facility is warranted by the severity of the reaction:

- Clinical evaluation, treatment, and stabilisation of subject according to standard medical practice, with suggested approaches outlined above

- Close monitoring of vital signs, for example every 15 to 30 minutes for Grade 1 or Grade 2 acute hypersensitivity injection reactions and every 5 to 15 minutes for Grade 3 or Grade 4 acute hypersensitivity injection reactions until stable

7 Statistical Considerations

A detailed SAP will be compiled before the database lock. The SAP will detail all planned analysis in detail.

7.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarised by descriptive statistics including mean, standard deviation, median, minimum, and maximum. Day 1 will be defined as the day of first investigational product administration.

7.2 Analysis Populations

7.2.1 Safety

The safety population is defined as all subjects who receive any dose of study medication. The safety population will be used to summarise all safety endpoints.

7.2.2 Intent-to-Treat

The Intent-to-Treat (ITT) population includes all subjects who are randomised into the study regardless of whether subjects receive any investigational product. The ITT population will be used to summarise demographic and baseline characteristics.

7.2.3 According to Protocol

The According to Protocol (ATP) population includes all subjects who are randomised into the study and who complete the study without a major protocol violation of the entry criteria or postrandomization protocol procedures (eg, noncompliance with concomitant medications) that might affect the assessment of the primary endpoint and any other efficacy endpoints.

Definitions of these major violations will be documented prior to database lock as described in the SAP. The ATP population will be used to analyse disease activity endpoints. Treatment classification in ATP analyses will be on an 'as-treated' basis.

7.2.4 Evaluable Population

Subjects who receive scheduled investigational product and are followed according to the protocol until Day 85 will constitute the Evaluable Population; however, subjects who receive at least one dose but discontinue treatment prior to receiving complete treatment regimen due to safety reasons will also be included in the Evaluable Population. Treatment classification in evaluable population will be on 'as-treated' basis.

7.2.5 Pharmacokinetics

The PK population is defined as all subjects who receive CAM-3001 and for whom serum concentrations of CAM-3001 are evaluable for PK data analyses. The PK population will be used to summarise all PK/PD parameters.

7.2.6 Immunogenicity

The immunogenicity population is defined as all subjects who receive at least one dose of CAM-3001 and for whom at least one serum sample for immunogenicity testing is available.

The safety and PK/PD/Immunogenicity will be presented on an as-treated basis. The analyses of disease activity endpoints as well as summaries of baseline and demographic characteristics will be presented on an as-randomised basis; ie, treatment classification will be made according to the initial randomisation regardless of whether subjects received an investigational product different from that to which they were randomised.

Last-observation-carried-forward imputation may be used in certain disease activity endpoint analyses. All other missing data will be treated as missing without data imputation.

7.3 Endpoints

7.3.1 Primary Endpoint

7.3.1.1 Efficacy

The primary efficacy objective will assess DAS28 response rates of CAM-3001 treated subjects compared with subjects who received placebo on the day of last dose of investigational product (Day 85). According to the EULAR response criteria an improvement from baseline in DAS28 of more than 1.2 would be considered a good response in subjects experiencing low disease activity (baseline DAS28 < 3.2) and a moderate response in subjects experiencing medium-to-high disease activity (baseline DAS28 ≥ 3.2). A responder will be defined as a subject experiencing a decrease of more than 1.2 from their baseline DAS28 score, on the day of last dose of investigational product (Day 85).

Evaluable subjects will be cross-classified in a two-by-two contingency table according to their combined treatment group (CAM-3001 or Placebo) and by their responder status (Yes or No). The DAS28 response rate at Day 85 between combined CAM-3001 and combined placebo treatment groups will be compared using a two-sided Fisher's exact test.

Following the above comparison between the combined CAM-3001 and combined placebo treatment groups, each applicable dose cohort and the combined placebo group will be compared. These comparisons at the dose cohort level are not powered and as such their results will be considered in an exploratory setting. There will also be no adjustment for multiplicity. A 95% confidence interval of difference in DAS28 response rate between CAM-3001 and placebo treatment groups will be computed for each dose cohort to estimate the effect size of each CAM-3001 dose level.

The DAS28 response rate at Day 29 between CAM-3001 and placebo will also be compared using a Fisher's exact test.

To check the sensitivity of the comparisons, all the above analyses will be repeated over the respective cohort groupings but in the more restrictive ATP population. Due to the definition of the ATP population no imputation of the DAS28 score is needed for these analyses.

7.3.1.2 Safety

The safety and tolerability of CAM-3001 will be assessed primarily by summarising the incidence of AEs and SAEs. These will be recorded from the period immediately following signing of informed consent through the end of the study, and will be summarised by system organ class and preferred terms, by severity, and by relationship to investigational product. Adverse events and SAEs will be summarised for placebo, each of the CAM-3001 dose cohorts, and for all CAM-3001 dose cohorts combined. Additionally, results of pulmonary function testing (FVC, FEV_1, DLCO) and dyspnoea score will be summarised descriptively by treatment group and time.

Other variables used for the safety assessments include serum chemistry, and haematology with differential. These variables as well as their changes from baseline will be summarised descriptively by treatment group and time.

7.3.2 Secondary Endpoints

The secondary endpoints of this study include disease activity, the onset of response, duration of response after withdrawal of treatment, need for additional medications during the study and the PK and immunogenicity of multiple SC doses of CAM-3001.

The onset of response, duration of response after withdrawal of study treatment and need for additional medications during the study (Yes/No) will be summarised and tabulated together with descriptive statistics and listed by treatment arms. The time-to-events endpoints; the onset of response, duration of response after withdrawal of treatment will be analysed using non-parametric log-rank method and also Cox proportional hazard models (modelling baseline covariates as appropriate).

7.3.2.1 Disease Activity

The major clinical measures of RA disease activity will be summarised descriptively by treatment group and time and include ACR20, ACR50, and ACR70 responses and DAS28 responses, including moderate and good responses, and complete clinical responses.

The ACR20, ACR50, and ACR70 binary responses will be compared between the CAM-3001 and placebo treatment groups using the Fisher's exact test at each study time point.

The ACR response at Days 29, 43, 57, 71, 85, 99, 113, and 169 will also be analysed as a continuous variable. An appropriate continuity correction maybe applied if the data are interval bound or discrete. The ACR response will be compared between the CAM-3001 and placebo treatment groups using a repeated measures model.

The DAS28 responses at various study time points other than Day 29 and Day 85 will also be compared between the CAM-3001 and placebo treatment groups using the methodology described in the secondary endpoint analysis section, although no imputation will be used in these analyses.

The DAS28 responses will be compared between the CAM-3001 and placebo treatment groups according to the EULAR response criteria at certain study time points using a Cochran-Mantel-Haenszel test.

All the modelling and other comparative analysis described above will be conducted over the appropriate dose cohort groupings and time points as noted above. Each analysis will first compare between the combined CAM-3001 and combined placebo treatment groups. The analysis will then be conducted separately comparing combined placebo group and each of the applicable dose cohorts. Most of the above analysis will be conducted over both the evaluable and ATP populations. Details of all these analyses will be described in the SAP.

The predicted DAS28 and ACR values from the models above will be compared to the actual values observed at Day 85, and Day 169 for subjects in Cohort 3 as they become available. This will test the predictive capability of such models and will also help calibrate them as necessary.

Core components of the ACR and DAS28 responses will be summarised descriptively by treatment group and time and change from baseline. Levels of rheumatoid factor, anti-CCP antibodies, ESR, and subject's need for rescue corticosteroid therapy will be summarised descriptively by treatment group and time point and change from baseline.

7.3.2.2 PK and Immunogenicity

CAM-3001 serum concentrations will be summarised using descriptive statistics at each time point by treatment group. Noncompartmental PK data analysis will be performed for CAM-3001 treated subjects following the first dose, and descriptive statistics of these noncompartmental PK parameters such as C_{max}, time to maximum concentration (T_{max}), AUC and terminal half life ($T_{1/2}$), will be provided. Due to the limited sampling schedule, if

the data allow, population PK data analysis may be performed to better characterise the PK of CAM-3001 in this subject population.

Immunogenicity results will be summarised by counts and percentage of subjects who develop detectable anti-CAM-3001 antibodies by treatment group. The titre values, if available, will be summarised by cohort and time. The impact of immunogenicity on PK will be assessed if data allow.

7.3.3 Exploratory Endpoints

The potential effects of investigational product on patient-reported outcomes, and gene and protein expression will be evaluated. Associations of DNA single nucleotide polymorphisms with potential safety signals may be explored. The following exploratory analyses are among those that may be conducted.

GM-CSF-inducible gene expression and/or miRNA signature in the peripheral blood, and GM-CSFRα receptor occupancy will be used to measure the PD of CAM-3001.

The effects of CAM-3001 on levels of mRNA for GM-CSF-inducible genes will be analysed using microarray analyses and TaqMan® quantitative reverse transcriptase (QRT)-polymerase chain reaction (PCR) assay. The miRNA profiling in the blood will be assayed using TaqMan® QRT-PCR. Results will be described numerically and by percent change from baseline, by treatment group and time.

7.3.3.1 Patient Reported Outcomes

Patient pain assessment, patient global assessment of disease activity, and HAQ-DI are core components of the ACR or DAS28 responses and will be summarised descriptively, as outlined above. Additionally, these endpoints will be summarised individually, with change from baseline. SF-36v2 Heath Survey, HAQ-DI pain scale patient global assessment, FACIT-Fatigue rating scale, MOS-Sleep Scale and modified Borg scale results will be summarised descriptively for both domain and subscale scores by treatment group and time point, and change from baseline will be explored.

7.3.3.2 Biologic Activity and Mechanism of Action

Granulocyte macrophage-colony stimulating factor receptor occupancy may be explored in subjects from selected sites, and these results will be summarised descriptively by treatment group and time

Other descriptive analyses may include levels of expression of non-GM-CSF-inducible genes and miRNA expression in whole blood, serum GM-CSF levels, and changes in autoantibody levels or profiles, and gene polymorphisms associated with clinical or safety responses to CAM-3001.

7.4 Sample Size

The primary objective of the study is to evaluate safety, tolerability and efficacy of multiple doses of CAM-3001. No formal sample size calculation was performed for the primary objective of safety.

With respect to the primary efficacy analysis (Day 85), 216 subjects will be randomised to achieve at least 180 evaluable subjects, allowing for a 15% rate of drop outs. A further 48 subjects will be randomised in Japan to give an overall sample size of 264 subjects in 4 equal sized cohorts of 66 subjects.

The sample size computation for the primary efficacy endpoint of the study is based on the objective of evaluating the effect of CAM-3001 on the response rate in terms of improvement in DAS28 score at Day 85. A responder will be defined as a subject experiencing a decrease from baseline in DAS28 score at Day 85 of more than 1.2. Assuming a placebo response rate of 10%, a combined CAM-3001 response rate of 30%, a two sided Type 1 error of 0.05, 86% power, and a 2:1 (active: placebo) randomisation ratio, a total sample size of 180 subjects (120 active: 60 placebo) will be required to detect a 20% difference in response rates for an analysis based on two-sided Fisher's exact test.

The sample size of 216 evaluable subjects (144 CAM-3001 subjects and 72 placebo subjects) including Japanese subjects will have 92% power with Type 1 error of 0.05, using a two-sided Fisher's exact test on the primary efficacy endpoint of comparing DAS28 response rates between the combined CAM-3001 and combined placebo groups.

MedImmune will be unblinded at the primary analysis (Day 85), excluding subjects enrolled in Japanese sites. The data from the primary analysis will not be communicated to personnel

at the Contract Research Organisation or investigational sites or to enrolled subjects. The purpose of this analysis is for internal decision making on the progression of the clinical programme, so this analysis will not impact the conduct of the current study. This is the final analysis of the primary efficacy endpoint, so no alpha adjustment for analysis will be made.

A further analysis may be performed when all randomised subjects, excluding randomised subjects in Japan, have completed all study assessments.

The final analysis will be performed when all randomised subjects, including Japanese subjects, have completed the all study assessments. This analysis will rerun the primary efficacy endpoint of DAS28 as well as all other study endpoints.

7.4.1 Interim Analysis

The primary efficacy analysis will be performed when all randomised subjects, excluding randomised subjects in Japan, have completed the Day 85 assessments or have discontinued from the study.

MedImmune will be unblinded at the primary analysis (Day 85) excluding subjects enrolled at Japanese sites. The purpose of this analysis is for internal decision making on the progression of the clinical programme, so this analysis will not impact the conduct of the current study. This is the final analysis of the primary efficacy endpoint, so no alpha adjustment for analysis will be made.

A further analysis may be performed when all randomised subjects, excluding randomised subjects in Japan, have completed all study assessments.

The final analysis will be performed when all randomised subjects, including Japanese subjects, have completed the all study assessments. This analysis will rerun the primary efficacy endpoint of DAS28 as well as all other study endpoints.

8 Direct Access to Source Data and Documents

The study will be monitored by MedImmune or its designee on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, informed consent forms, treatment notes, laboratory reports, pharmacy records,

radiographs, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 Quality Control and Quality Assurance

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated informed consent forms, progress notes, hospital charts, nurse's notes, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, will be collected, as available, for all subjects who provide written informed consent. For subjects who provide informed consent and were not entered/randomized into the study, the reason the subject was not entered/randomised, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), will also be collected.

9.2 Study Monitoring

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be monitored/audited for the purposes of the study.

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter. The monitor will assess subject enrolment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; and the occurrence of AEs/SAEs. All aspects

of the study will be carefully monitored for compliance with the protocol, applicable government regulations, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that any problems noted in the course of the monitoring are resolved.

9.3 Audit and Inspection of the Study

During the conduct of the study, the sponsor or its representative may conduct audits of any data and facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralised filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, Quality Assurance monitors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

10 Ethics

10.1 Regulatory Considerations

The study will be conducted in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki. Good clinical practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the appropriate regulatory authority and the IRB or IEC of each participating country/centre prior to study initiation. The

investigator will keep the IRB/IEC informed as to the progress of the study. Protocol modifications or changes may not be initiated without prior written regulatory approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the appropriate regulatory authorities and written verification that the modification was submitted should be obtained.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB/IEC may need to fulfil its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The IRB/IEC's written unconditional approval of the study protocol, the informed consent form(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

The IRB/IEC must be informed of informed consent form changes or revisions of other documents originally submitted for review; serious and unexpected adverse events occurring during the study; new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed according to local reporting requirements and applicable national laws.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol in accordance with the ICH guidelines on GCP, the GCPs applicable to any region where the study is conducted, and the ethical principles set forth in the Declaration of Helsinki.

Information should be given in both oral and written form, and subjects must be given ample opportunity to inquire about details of the study. Subjects must be informed of the following:

- The study involves research.
- The aims, expected benefits, possible risks (including a statement that the particular treatment or procedure may involve risks to the subject or the foetus of the subject, if the subject should become pregnant) that are currently unforeseeable.
- The study procedures to be followed and alternative treatment available to them. Subjects must receive an explanation as to whether any compensation and any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.
- Who to contact for answers to any questions relating to the research project.
- Participation is voluntary and that they are free to withdraw from the study for any reason at any time, without penalty or loss of benefits to which they are otherwise entitled.
- The extent of the confidentiality of subject records must be defined, and subjects must be informed that applicable data protection legislation will be complied with.
- The monitor(s), auditor(s), IRB/IEC members, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject is authorizing such access.

The consent form generated by the investigator must be approved by the IRB/IEC and be acceptable to MedImmune. Consent forms must be written so as to be understood by the prospective subject. Informed consent will be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the subject, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by regulatory authorities and/or MedImmune professional and regulatory compliance persons. The subject should receive a copy of the signed and dated written informed consent form and any other written

information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

11 Data Handling and Record Keeping

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject identification number. All study records, source medical records, and code sheets or logs linking a subject's name to a subject identification number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the informed consent form (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured in accordance with MedImmune policies and applicable regulatory requirements for a period of 2 years following the last regulatory authority approval of a marketing application of CAM-3001 and until there are no pending or contemplated marketing applications, or for 2 years after centres have been notified that clinical development of CAM-3001 has been discontinued, or as otherwise required by local requirements, whichever is longer. There may be other circumstances for which MedImmune is required to maintain study records and, therefore, MedImmune should be contacted prior to removing study records for any reason.

12 Financing and Insurance

Financing and insurance are addressed in the individual site contracts.

13 Publication Policy

Publication by the site of any data from this study must be carried out in accordance with the clinical study agreement.

The investigator may prepare data derived from the study for publication. Such data will be submitted to the sponsor for review and comment prior to publication. In order to ensure that the sponsor will be able to make comments and suggestions, material for public dissemination will be submitted to the sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. The investigator agrees that all reasonable comments made by the sponsor in relation to a proposed publication will be incorporated into the publication. The sponsor will be entitled to delay the publication for a period of up to six (6) months from the date of first submission to the sponsor in order to enable the sponsor to take steps to protect its proprietary information and Intellectual Property Rights and Know How.

The sponsor may present at symposia, national or regional professional meetings, and publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the study and in particular, post a summary of study results in on-line clinical trials registers before or after publication by any other method. In the event the sponsor coordinates a multi-centre publication, the participation of the investigator shall be determined in accordance with the sponsor's policy and generally accepted standards for authorship. If the investigator is a named author of the multi-centre publication, the investigator will have access to the study data from all Clinical Trial sites as necessary to participate fully in the development of the multi-centred publication.

If the study is multi-centred, any publication based on data or other results of the study from the study site shall not be made before the first multi-centred publication or one year after completion of the study, whichever is the earlier.

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15 Summary Protocol Amendments and Administrative Changes to the Protocol

15.1 Protocol Amendment 1, [redacted]

The major changes to the original protocol are described below. A number of minor edits were also made for consistency and clarity within the document.

The medical monitor responsibilities have been taken over by [redacted], who has replaced [redacted] on the signature page on page 2.

1) The abstract was updated to reflect the changes made within the body of the document.

2) Section 1.3 Nonclinical Experience with CAM-3001: has been updated with the most recent information available from all nonclinical studies performed to date.

3) Section 1.4 and Section 1.5.1: The clinical PK has been revised based on the final population PK modelling information.

4) Section 3.1 Overview of the study design and Figure 3.1-1 Study Flow Diagram: The number of sites and subjects has been increased to reflect the addition of sites in Japan to this study. The dose escalation process for sites in Japan has also been added to provide a clear explanation of the process to be used for Japanese subjects (Section 4.5.5).

5) Section 4.2.1 Inclusion Criteria: The intention of the protocol is to allow subjects with DLCO and FEV_1 of 80% predicted value or higher to enter the study;. therefore inclusion criterion 10 has been clarified to change greater than (> 80%) to greater than or equal to (≥ 80%) for DLCO and FEV_1 as follows:

   No evidence of medically significant respiratory disease. A local pulmonologist will review subjects' respiratory system including, chest x-ray, pulmonary function, and diffusing capacity for carbon monoxide (DLCO), which are performed at Screening. Subjects must have:

- DLCO ≥ 80% predicted value
- Forced expiration volume in first second (FEV_1) by spirometry ≥ 80% predicted value

6) Section 4.4 Blinding: A description of the unblinding process for the possible analysis of the primary endpoint has been added to the protocol.

7) Section 4.5.4 Concomitant Medication: This section has been edited and reorganised to provide more clarity to sites around allowed/disallowed medications, and in what event treatment will be discontinued.

8) Section 5.2.1: The collection of demographic data has been specified on the Schedule of Subject Evaluations.

9) Section 5.2.2 Treatment Period: New text has been added to state that if screening pulmonary function tests are performed within 14 days of dosing on Day 1, then a repeat of the pulmonary function tests is not required. This has been added for study feasibility and for improved subject compliance.

10) Section 5.3.1 Pulmonary Function Test: Text has been added to allow for pulmonary function tests and DLCO to be tested the day before dosing. This has been added for study feasibility and for improved subject compliance.

11) Section 5.3.4.1 DAS28: DAS28 corrected to a 100 point scale. In addition the following has been clarified: subjects are required to have at least moderately active disease as defined by DAS28 ≥ 3.2 at Screening and Day 1 to be included in the study. The investigator will calculate DAS(CRP) for Screening and DAS(ESR) for Day 1 as CRP analysis will not be available on the same day.

12) Section 5.3.4.2 ACR: The ACR score components have been corrected to VAS rather than numerical rating scales as previously stated.

13) Section 5.3.4.3 Patient Reported Outcomes: The text was edited to provide clarity.

14) Section 5.3.5.1 Exploratory Research: More detail around the analysis of mRNA and miRNA has been added to the protocol. The volume of blood required for these analyses has also been added to provide more clarity around the potential exploratory analyses.

15) Section 5.3.5.3 DNA sample: More information around sample identification, storage and retention has been added to the protocol to provide more clarity around the potential exploratory analyses.

16) Section 6.1.1 Adverse Events: Text was added to clarify when abnormal laboratory test data should be reported as an AE.

17) Section 6.2.2: The assessment of relationship as related or not related is described and is in line with the current AE reporting process of the sponsor.

18) Section 6.3.3.1 Overdose and 6.3.3.2 Pregnancy: More detail has been added to the protocol regarding the reporting of overdose and pregnancy. This text is in accordance with the sponsor procedure.

19) Section 7.4 Sample Size: The sample size has been increased to account for the addition of sites and subjects in Japan. A description of a potential analysis of the primary endpoint was also added.

Clarifications were also made throughout the text:

20) The term "baseline" has been defined as either Screening or Day 1 as appropriate.

15.2 Protocol Amendment 2, [redacted]

There were no major changes to Amendment 1. A number of minor edits were made for consistency and clarity within the document. Amendment 1 was not submitted to any sites outside of Japan.

1) The Study Abstract was updated to clarify the analysis of the Japanese subject data relative to the primary analysis, in addition a section on Interim Analysis was added to clarify the analysis.

2) Section 3.1 Overview of Study Design was updated to be consistent with the Study Abstract.

3) Section 4.4 Blinding was updated to further re-enforce the robustness of the blind in the study analysis.

4) Section 4.5.5 Dose Escalation and Cohort Progression: The term "medical monitor" was changed to "sponsor" to correct this text.

5) The spelling of "oximetry" "absorption" and "plasmapheresis" were corrected throughout the protocol.

6) Section 4.3 Treatment Assignment: Text was corrected to remove the reference to a fax notification.

7) Section 5.2 Schedule of Study Procedures and Section 5.2.3 Safety Follow-up Period: The sections were updated to include 2 additional time points for the collection of FACIT- Fatigue; this assessment was omitted in error from the previous version of the protocol. In addition text was added to allow greater flexibility in the timing of the measurement of pulmonary function tests and DLCO. It was also clarified that the isotypes of rheumatoid factor are measured each time rheumatoid factor is measured. Section 5.3.1 Physical Examination: Text was included to allow recording of scheduled procedures and surgeries in the eCRF.

8) Section 5.3.1 Vital Signs: Text was corrected to indicate that vital signs need to be measured "approximately" every 30 minutes.

9) Section 5.3.1 Chest X-ray: The window for chest x-ray assessments was expanded to allow a recent chest x-ray to be used.

10) Section 5.3.2 Clinical Laboratory Tests: Urine dipsticks have been provided to the sites, the original text was corrected.

11) Section 6.4.1 Discontinuation of Dosing: Minor clarification in wording to clarify when dosing can be skipped or continued.

12) Section 7.2.3 According to Protocol: Clarification of the definition of this population.

13) Section 7.4: Sample size was updated to be consistent with the Study Abstract and Study Design sections.

15.3 Protocol Amendment 3, [redacted]

Text revisions resulting from this amendment are incorporated into the body of Protocol Amendment 3. Major changes to the protocol are described below:

1) The phone and fax number of the medical monitor was updated.

2) Study abstract and Blinding Section 4.4: Clarification that MedImmune will be unblinded after the primary analysis. In addition the Abstract was edited to be consistent with the body of the text of the protocol.

3) Section 5.3.2 Clinical Laboratory Tests: Urine dipsticks have been provided to the sites, the original text was corrected.

4) Section 5.3.2 Clinical Laboratory Tests: Glucose had previously been omitted in error, Albumin was corrected to Protein/Albumin.

5) Section 6.4.1 Interruption of Dosing: Text was added to allow the sponsor to discontinue dosing.

6) Section 6.4.2 Study Stopping Criteria: Was updated bullet 4 to be consistent with MedImmune standard text.

7) Section 6.2.5 Recording of Events of Hepatic Function Abnormality and Section 6.3.3.3. Hepatic Function Abnormality were added to be consistent with other MedImmune protocols.

8) Section 7.3.3 Clarification of the analysis of exploratory biomarkers.

9) Abstract, Section 4.4 and Section 7.4 was updated to clarify the personnel that remain blinded at the primary efficacy analysis (Day 85)

10) Section 7.4.1 was added to be consistent with the Abstract.

Appendix 1 Classification and Suggested Treatments for Acute Hypersensitivity Reactions

Severity of Symptoms	Treatment	Investigational product
Mild (Grade 1) Localised cutaneous reactions such as mild pruritus, flushing, rash, dizziness, headache, ≤ 20 point change in systolic blood pressure	• Evaluate subject, including close monitoring of vital signs • At the discretion of the investigator, treat subject, for example with − Antihistamine (eg, diphenhydramine HCL) oral or IV − Paracetamol/acetaminophen 500-1000 mg − Corticosteroids topical or systemic	• Discontinue future administration of investigational product; OR, at the discretion of the investigator, continue investigational product administration and pretreating subject 1.5-0.5 hours prior to investigational product administration, for example with − Antihistamine (eg, chlorpheniramine) 10 mg − Paracetamol/acetaminophen 500-1000 mg
Moderate (Grade 2) As above generalised rash or urticaria, palpitations; chest discomfort, shortness of breath, hypo- or hypertension with > 20 point change in systolic blood pressure. Drug fever > 38°	− Treatment as for Mild (Grade 1) − Normal saline (~500 ml)	• Management as for Mild (Grade 1) • If moderate event recurs in the same subject, discontinue future investigational product administration
Severe (Grade 3) or Symptomatic bronchospasm with or without urticaria, hypotension with ≥ 40 point change in systolic blood pressure, wheezing, angioedema, or stridor **Life threatening (Grade 4)** Defined as a reaction that is life threatening and requires pressor and/or ventilator support or shock associated with acidemia and impairing vital organ function due to	• Evaluate subject, including close monitoring of vital signs • Maintain airway, oxygen if available • Treat subject immediately, for example with − Adrenaline/epinephrine 1:1000, 0.5-1.0 mL for bronchospasm, hypotension unresponsive to IV fluids, or angioedema. Dose and route as per local standard of care (e.g. SC for mild cases and IM for more severe cases) − Secure IV access, normal saline (~500 to 1000 IV) − IV corticosteroids (eg. such as hydrocortisone 100-200 mg or methylprednisolone 20-40 mg) − If wheezing treat for asthma − Antihistamine (eg. chlorpheniramine 10mg IV)	• It is recommended to measure mast cell tryptase serum level within maximum 12 hours of the event or a serum sample to be collected and kept at -20C for the future analysis. • Discontinue future investigational product administration

Severity of Symptoms	Treatment	Investigational product
tissue hypoperfusion	− Paracetamol/acetaminophen 500-1000 mg • Call emergency medical transport for transport to hospital if − Grade 3 wheezing, hypotension or angioedema is unresponsive to single dose of adrenaline/epinephrine − Grade 4 − At the discretion of the investigator	