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ACZ885

CACZ885X2205

A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety, and tolerability of ACZ885 (canakinumab) in patients with pulmonary sarcoidosis

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

Additional Manuals

Details for HRCT and [F-18]FDG-PET/CT imaging are described in the Parexel Imaging Investigator SOM.

Details on pulmonary function testing are described in the Biomedical Systems Centralized Spirometry, DLco, and Lung Volumes Procedure Manual.

For details on receipt, storage and handling of study medication please refer to the Pharmacy Manual.

For treatment assignment and randomization please refer to Cenduit Interactive Response Technology (IRT) Manual

Notification of serious adverse events

Refer to Section 9.2 of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the study lead).

Contact information is listed in the Site Operations Manual.

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List of abbreviations

γ-GT	Gamma-glutamyl transferase

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6MWT	6-minute walk test
[F-18]FDG-PET	fluorine-18 fluorodeoxyglucose positron emission tomography

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ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS/ERS	American Thoracic Society/European Respiratory Society
AUC	area under the curve
BAL	bronchoalveolar lavage
BDR	bioanalytical data report
BTPS	Body temperature, ambient pressure, saturated with water vapor
BUN	blood urea nitrogen
CAPS	cryopyrin-associated periodic syndromes
CD-ROM	compact disc – read only memory
CFR	Code of Federal Regulation
CK	creatinine kinase
cm	centimeters
CO_2	carbon dioxide

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CR	complete response
CRF	Case Report/Record Form (paper or electronic)
CRO	contract research organization
CT	computed tomography

CTC	Common Toxicity Criteria
CV	coefficient of variation
CXR	chest X-ray
DLco	diffusing capacity for carbon monoxide
DAR	dose administration record
EC	ethics committee
ECG	electrocardiogram
EDC	electronic data capture
ELISA	enzyme-linked immunosorbent assay
EOS	end of study visit
ePRO	electronic patient reported outcome

FCAS	familial cold autoinflammatory syndrome
FDA	Food and Drug Administration
FDG	fluorodeoxyglucose
FEF25-75	forced expiratory flow 25%-75% FEV_1 forced expiratory volume in 1 second
FEV3	forced expiratory volume in 3 seconds
FVC	forced vital capacity
FVC%	forced vital capacity (expressed as percent of normal expected value)
GCP	good clinical practice
h	hour
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRCT	high resolution computed tomography
i.v.	intravenous
IAC	infection adjudication committee
IB	investigator's brochure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	independent ethics committee

IL	interleukin
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IN	Investigator Notification
IRB	institutional review board
IRT	interactive response technology
ITF	image transmittal form
IUD	intrauterine device
IUS	intrauterine system
kg	kilograms
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LDH	lactate dehydrogenase
LFT	liver function test
LLN	lower limit of normal
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MAC	malignancy adjudication committee
MedDRA	medical dictionary for regulatory activities
mg	milligram(s)
ml	milliliter(s)
MMRC	Modified Medical Research Council
MRI	Magnetic resonance imaging
MWS	Muckle Wells syndrome
PA	posteroanterior
PD	pharmacodynamic(s)
PET	positron emission tomography
PFT	pulmonary function test
PK	pharmacokinetic(s)
PR	partial response
PRO	patient reported outcome
RA	rheumatoid arthritis
RBC	red blood cell(s)
REB	research ethics board
ROI	region of interest

RV	residual volume
s.c.	subcutaneous

SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
sJIA	systemic juvenile idiopathic arthritis
SOM	site operations manual
SUSAR	suspected unexpected serious adverse reaction
SUVmax	maximum standardized uptake value
TB	tuberculosis
TBL	total bilirubin
TLC	total lung capacity
ULN	upper limit of normal
ULQ	upper limit of quantification
VA	alveolar volume
VD	dead space volume
VT	tidal volume
WBC	white blood cell(s)

Pharmacokinetic definitions and symbols

C	The serum trough concentration during multiple dosing [mass / volume]
Cav	The observed average serum concentration following drug administration
CL	The systemic (or total body) clearance from plasma (or serum or blood) following intravenous administration [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
Vss	The volume of distribution at steady state following intravenous administration [volume]

Glossary of terms

Control drug	A study drug used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug.
Enrollment	Point/time of subject entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol).
Investigational drug	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with "investigational new drug" or "investigational medicinal product".
Investigational treatment	All investigational drug(s) whose properties are being tested in the study as well as their associated treatment controls. This includes any placebos, any active controls, as well as approved drugs used outside of their indication/approved dosage or tested in a fixed combination. Investigational treatment generally does not include other treatments administered as concomitant background therapy required or allowed by the protocol when used within approved indication/dosage.
Medication number	A unique identifier on the label of each study drug package in studies that dispense study drug using an IRT system.
Period	A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Stage	A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.
Study completion	Point/time at which the subject came in for a final evaluation visit or when study drug was discontinued whichever is later.
Study drug discontinuation	Point/time when subject permanently stops taking study drug for any reason; may or may not also be the point/time of premature subject withdrawal.
Study drug/treatment	Any drug (or combination of drugs) administered to the subject as part of the required study procedures; includes investigational drug, active drug run-ins or background therapy.

Subject	An individual who has consented to participate in this study. The term Subject may be used to describe either a healthy volunteer or a patient.
Subject number	A number assigned to each subject who enrolls in the study. When combined with the center number, a unique identifier is created for each subject in the study.
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified timepoints.

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Protocol synopsis

Protocol number	CACZ885X2205
Title	A multiple-dose, subject- and investigator-blinded, placebo-controlled, parallel design study to assess the efficacy, safety and tolerability of ACZ885 (canakinumab) in patients with pulmonary sarcoidosis
Brief title	Study of efficacy, safety and tolerability of ACZ885 (canakinumab) in patients with pulmonary sarcoidosis
Sponsor and Clinical Phase	Novartis Phase 2
Intervention type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to assess if inhibition of IL-1β by ACZ885 will improve lung function in association with reduction of tissue inflammation in patients with chronic sarcoidosis.
Primary Objective	To compare the effect of ACZ885 versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in the percent predicted forced vital capacity (FVC) at week 24
Secondary Objectives	To determine the effect of ACZ885 on decreasing the maximum standardized uptake value (SUVmax) ([F-18]FDG-PET) in nodules (nodal uptake regions) after 12 weeks of treatment, compared to placebo. To determine the effect of ACZ885 versus placebo on other parameters of pulmonary function testing in patients with sarcoidosis at 24 weeks compared to baseline. To determine the effect of ACZ885 versus placebo on HRCT of patients with sarcoidosis at 24 weeks compared to initial HRCT scan as measured by side-by-side comparison by blinded reviewers and HRCT scoring. To determine the effect of ACZ885 versus placebo on the 6-minute walk test distance of patients with sarcoidosis at 12 and 24 weeks compared to baseline To determine the effect of ACZ885 on additional [F-18]FDG-PET outcomes after 12 weeks of treatment compared to placebo To assess the safety and tolerability of ACZ885 in patients with sarcoidosis as measured by adverse events
Study design	This is a subject- and investigator-blinded, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the clinical efficacy of ACZ885 administered subcutaneously (s.c.) every four weeks for a total of 24 weeks.

Population	The study will randomize approximately 38 patients with radiological evidence of parenchymally involved, chronic pulmonary sarcoidosis of ≥1 year duration with persisting activity at baseline despite background therapy.
Inclusion criteria	• Male and female subjects ages 18 to 80 years of age (inclusive) • Subjects must weigh at least 50 kg to participate in the study • Able to communicate well with the investigator, to understand and comply with the requirements of the study • Disease duration of ≥1 year • Clinically active disease demonstrated either by a biopsy (any organ) or by bronchoalveolar lavage (lymphocytosis >15%, $CD4^+/CD8^+$ ratio >3.5, $CD103^+CD4^+/CD4^+$ ratio <0.2). Patients must also have all of the following criteria: ○ Modified Medical Research Council (MMRC) dyspnea scale ≥ 1 ○ Threshold FVC 50 - 90% of predicted ○ Evidence of parenchymal lung involvement by HRCT at screening or by historical radiological evidence
Exclusion criteria	• Diagnosis of pulmonary hypertension requiring treatment • Current inhaled use of tobacco products (urine cotinine level > 500 nanograms/mL) at screening • History of bleeding disorder • Extra-pulmonary sarcoidosis as primary treatment indication (e.g., involving brain, heart, eye and renal disease with significant hypercalcemia) • Any conditions or significant medical problems, which in the opinion of the investigator, immuno-compromises the patient and/or places the patient at unacceptable risk for immunomodulatory therapy, such as: ○ Absolute neutrophil count (ANC) < lower limit of normal (LLN) (1,500/µl) ○ Platelets < LLN – 75.0 x 10^9/L ○ Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection ○ Presence of human immunodeficiency virus (HIV) infection, active hepatitis B or hepatitis C infections based on screening lab result ○ Presence of active or latent tuberculosis (TB) Clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty's syndrome • Live vaccinations within 3 months prior to screening • Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial
	• Two treatment arms in a ratio of 1:1: canakinumab (ACZ885) versus placebo-controlled dose group

Efficacy/PD assessments	• Pulmonary function testing • [F-18]FDG-PET/CT • HRCT • Six-minute walk test (6MWT) • Serum IL-1β
Safety assessments	• Physical examination, including vital signs and height/weight • Hematology, clinical chemistry, urinalysis • Local tolerability of subcutaneous (s.c.) injections of canakinumab/ACZ885 • Electrocardiogram (ECG)
Other assessments	Corporate Confidential Information
Data analysis	The primary variable for the assessment of efficacy will be the change from baseline in the percent predicted FVC. It will be analyzed using a Bayesian model for repeated measurements. The model will investigate effects for baseline by time interaction, treatment by time interaction and PET positivity (yes/no) prior to randomization. Uninformative priors will be utilized to obtain the posterior estimates. The posterior probability that ACZ885 is better than placebo in terms of change from baseline in percent predicted FVC at 24 weeks will be calculated. If it is at least 90%, it will be considered a sign of efficacy of ACZ885 increasing FVC after 24 weeks of treatment in this patient population.
Key words	Pulmonary sarcoidosis, [F-18]FDG-PET/CT, IL-1β, canakinumab

1 Introduction

1.1 Background

Chronic sarcoidosis

Chronic sarcoidosis is a systemic disease characterized by development of granulomas, inflammation and accompanying fibrotic tissue reactions (Chen and Moller 2011). Although any organ can be affected, most common disease manifestations are found in lung, skin, and eye tissues. Chronic sarcoidosis is an orphan disease with an overall prevalence in US populations of 8/10,000. There exist ethnic differences in disease frequency and severity. The disease is more severe and frequent in African Americans than in those of Northern European descent (2.4% vs 0.85% lifetime risk) with risk of death up to 8%; (Swigris et al 2011).

There are no approved therapies for sarcoidosis. Corticosteroid use has long comprised the standard of care, with diverse and unapproved, secondary immunosuppressive usage (e.g., methotrexate, azathioprine) as needed, all of which are accompanied by treatment-related, severe adverse reactions (Baughman and Nunes 2012; Paramothayan et al 2008). Clinical trials in sarcoidosis with biological therapies targeting the adaptive immune response have not met expectations. The typical clinical course for chronic, active sarcoidosis patients is characterized by progressive and debilitating declines in lung function, with the primary causes of morbidity and mortality including pulmonary hypertension and fibrosis (Baughman and Lower 2011). Thus there is an unmet medical need in patients with chronic, active sarcoidosis for a disease modifying agent that induces resolution of granulomas and prevents deterioration or improves lung function.

The pathophysiology of sarcoidosis remains poorly understood but is suspected to be a host immunological response to an antigenic exposure. The role of T-lymphocytes in recognition of specific antigens and in the amplification of inflammatory responses has been well established. However, T-cell targeted therapeutics have not demonstrated substantial clinical benefits. Therefore, alternative therapeutic targets and disease mechanisms must be considered in this disease.

A role for IL-1β in sarcoidosis

IL-1β is a pro-inflammatory cytokine produced by a variety of cell types, particularly mononuclear phagocytes, in response to injury, infection and inflammation. In sarcoidosis, the IL-1β has been shown to be an important contributor to maintaining macrophage and T cell alveolitis and epithelioid cell granuloma formation (Hunninghake 1984). Epithelioid cells, the predominant cell type within sarcoid granulomas, have been shown to strongly express IL-1β (Devergne et al 1992). In addition, 70-95% of bronchoalveolar lavage (BAL) macrophages from sarcoidosis patients demonstrate cytoplasmic staining of IL-1β (Chilosi et al 1988). Clinical relevance is suggested by studies showing that the degree of sarcoidosis inflammation measured by gallium scan and lymphocytic alveolitis correlates with spontaneous and stimulated IL-1β release by alveolar macrophages (Hunninghake 1984; Steffen et al 1993; Yamaguchi et al 1988; Barth et al 1989). Finally, IL-1β is known to induce and enhance

granuloma formation *in vitro* and *in vivo* and to be involved in associated anergy (Kobayashi et al 1985; Kasahara et al 1989; Terao et al 1993). Thus, IL-1β represents a potential therapeutic target for sarcoidosis.

Therapeutic targeting of IL-1β and the inflammasome

ACZ885 (canakinumab) is a high affinity, fully human, monoclonal anti-human IL-1β antibody of the IgG1/κ isotype that is designed to bind to human IL-1β, blocking the interaction of this cytokine to its receptors, thus functionally neutralizing the bioactivity of this cytokine.

Canakinumab is currently marketed under the name Ilaris® for treatment of adults and children aged 4 years and older that have a condition known as cryopyrin-associated periodic syndromes (CAPS), including familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS). Ilaris® is also approved for the symptomatic treatment of acute gouty arthritis attacks and for the treatment of active systemic juvenile idiopathic arthritis (sJIA) in children 2 years of age and older. For further details please refer to the investigators' brochure (IB).

IL-1β is recognized as one of the principal pro-inflammatory cytokines in a variety of inflammatory conditions (Dinarello et al 2012), including those involving autoinflammation and the inflammasome.

The inflammasome is a multiprotein oligomer that is expressed in myeloid cells as a component of the innate immune system. Inflammasomes can be triggered by a variety of activators and processes, resulting in an inflammatory cascade that includes cleavage by caspase-1 of pro-IL-1β and pro-IL-18 into their active forms, along with triggering of other inflammatory processes. Over the last few years, there has been an increasing body of literature about the efficacy of targeting IL-1β in a wide spectrum of autoinflammatory conditions. Autoinflammatory disorders can be distinguished from autoimmune disorders by disease mechanisms involving innate immune regulation of cytokines and neutrophilic inflammation rather than adaptive immune responses involving antibodies and lymphocytes. Inflammasome-mediated diseases include rare orphan diseases classified together within the condition of hereditary periodic fevers. Another disease in which the inflammasome plays a key role is gouty arthritis. These conditions have in common either conditions or mutations that result in increased inflammasome activation, resulting in chronically recurring inflammation.

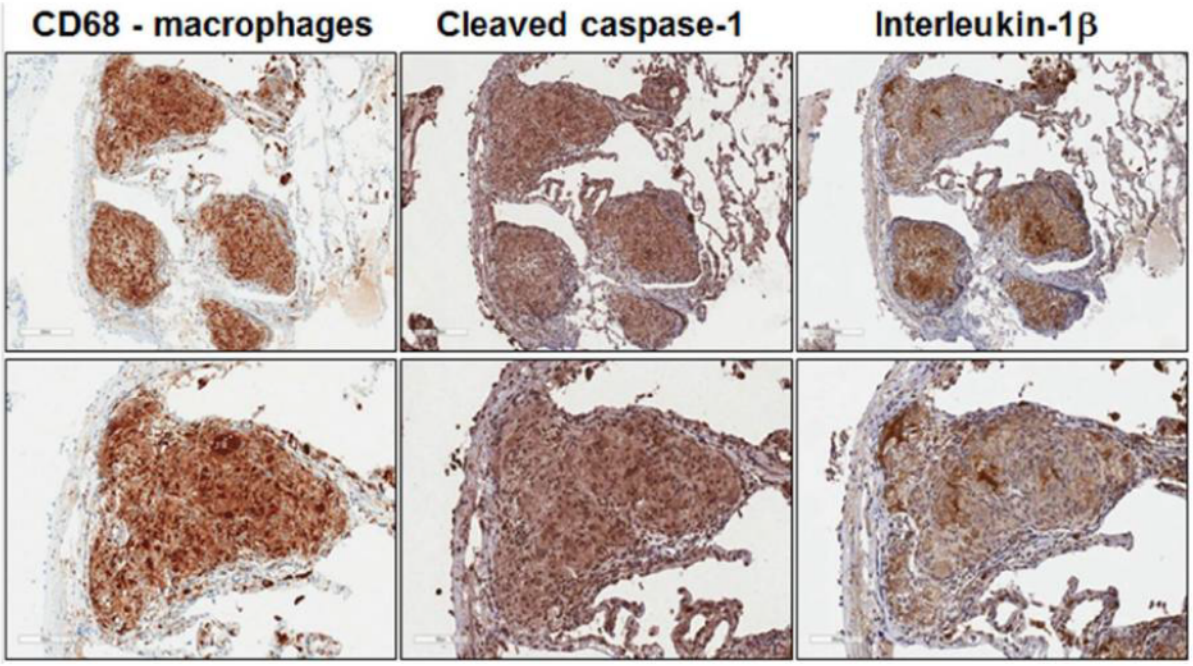
Sarcoidosis as an inflammasome-mediated disease

Using unbiased, molecular profiling approaches guided by pathway signatures from recent canakinumab trials in other diseases, we discovered unanticipated evidence for significant involvement of the inflammasome as a generator of IL-1β in sarcoidosis; a disease heretofore primarily regarded as driven largely by cell-mediated immune processes. Confirmatory studies examining lung and skin lesional tissues or *ex vivo* cells from patients with chronic sarcoidosis provided further evidence for inflammasome and IL-1β activation in diseased tissues. In the representative Figure 1-1 below, serial sections from an untreated sarcoidosis patient with highly active, multi-organ disease demonstrate strong, co-localizing staining of pulmonary granulomas for macrophages (CD68+), activated inflammasome

(cleaved caspase-1) and its downstream product IL-1β. Functional assays with *ex vivo* BAL cells from sarcoidosis patients and normal healthy controls revealed elevated non-stimulated and stimulated IL-1β levels in sarcoidosis-derived specimens with correlations to disease activity. Finally, neutrophils, an important component of autoinflammatory disorders, also play a role in sarcoidosis pathophysiology. Neutrophil chemotaxis, phagocytosis and numbers in sarcoidosis patients have been shown to correlate to disease activity and prognosis (Ziegenhagen et al 2003; Tutor-Ureta et al 2006; Schmekel et al 1985; Drent et al 1999; Turner-Warwick et al 1986). Additional indicators of neutrophil activity, such as IL-8 and esterase are also elevated in sarcoidosis patients with correlations to disease activity (Car et al 1994; Loza et al 2011; Hind et al 1988).

The above evidence supports that inflammasome activity is upregulated in sarcoidosis patients and may play a role in disease activity. Thus, IL-1β pathway interruption with canakinumab is anticipated to confer therapeutic benefit.

Figure 1-1 Immunohistochemistry staining of sarcoidosis lung biopsy tissue



Representative staining in serial sections of biopsy tissue from a sarcoidosis patient with highly active disease in need of immune suppressive treatment. CD68 is a marker for macrophages. Cleaved caspase-1 is indicative of inflammasome activation. Positive staining represented by the color brown.

1.2 Nonclinical data

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1.3 Clinical data

1.3.1 Human safety and tolerability data

As of 30 June 2016, an estimated 10,900 patients have received canakinumab treatment in 66 Novartis-sponsored investigational clinical trials and 17 investigator-initiated trials in a wide spectrum of IL-1β driven diseases such as CAPS, mild asthma, psoriasis, wet age-related macular degeneration, gouty arthritis, type 2 diabetes mellitus, rheumatoid arthritis (RA), and sJIA. Health authority approvals for Ilaris® have been granted for CAPS, gouty arthritis and sJIA. The post- marketing cumulative patient exposure since the first launch of the product is estimated to be approximately 8,588 patient treatment-years. The doses administered i.v. ranged from 0.3 mg/kg to 10 mg/kg or a fixed dose of 600 mg, and from 0.5 mg/kg to 9 mg/kg s.c. or fixed doses of 5 mg to 300 mg s.c. The frequency of dosing ranged from a single dose to weekly repeated administration. Every four weeks s.c. dosing of 4 mg/kg up to

300 mg is approved by the FDA in sJIA. Canakinumab has a long half-life, averaging approximately 4 weeks in man and has been well-tolerated by patients at all dose levels investigated. So far the duration of exposure to canakinumab is more than 4 years for the first 4 MWS patients enrolled in the CACZ885A2102 trial. Final and preliminary data from completed clinical studies demonstrate efficacy as well as good safety in patients with CAPS, sJIA, RA and gouty arthritis. The details of the SAEs and AEs of the completed studies and relevant details of the SAEs of the ongoing studies are summarized in the latest version of the IB. Adverse events in unblinded studies ranged from mild to moderate in severity and included upper respiratory tract infections, nasopharyngitis and otitis, headache, nausea, diarrhea, and asthenic conditions.

Immunogenicity has not proved to be a significant concern for canakinumab. Canakinumab studies across multiple indications and dosing regimens have demonstrated that the incidence of treatment-emergent ADA development remains very low, in the range of 0.3% to 2.9%. Furthermore, there have been no clinical consequences evident for these detected antibodies.

1.3.2 Human pharmacokinetic data

Canakinumab has the expected pharmacokinetics of an IgG1-type antibody with a low volume of distribution (VSS=6.0 L) and low clearance that is dependent on body weight (e.g., CL=0.174 L/day in a a CAPS patient of body weight 70 kg, 0.11 L/day in a SJIA patient of body weight 33 kg and 0.23 L/day in a gout patient of body weight 93 kg). Half-lives vary between 21 and 30 days. Within the dose range studied, the pharmacokinetics of canakinumab were linear. The systemic exposure parameters, AUC and Cmax, increase in proportion to dose over the dose range of 0.30 to 10.0 mg/kg given as i.v. infusion and from 150 mg to 300 mg when administered as an s.c. injection. The absolute bioavailability of s.c. canakinumab is 70%. A mathematical model to characterize the binding kinetics of canakinumab to IL-1β has been created. The model successfully fits the patient data and allows estimation of canakinumab clearance and volumes of distribution, together with IL-1β rate of release and half-lives.

1.3.3 Human pharmacodynamic data

Canakinumab binds to and inactivates IL-1β and blocks downstream events of IL-1β signaling, including IL-1β production, IL-1β pathway-related gene activation, elevation of acute phase proteins. Corporate Confidential Information and C-reactive protein (CRP), and mobilization of neutrophils and platelets from bone marrow.

Normally undetectable, serum IL-1β becomes detectable in humans when complexed with canakinumab. These IL-1β/canakinumab complexes are biologically inactive and have been utilized in all clinical studies as a surrogate PD marker because their increase reflects the reduction of free IL-1β levels caused by binding to canakinumab.

1.4 Study purpose

This study is designed as a proof-of-concept study to assess if inhibition of IL-1β by canakinumab will improve lung function in association with attenuation of tissue inflammation in patients with chronic sarcoidosis, therefore allowing further development of the compound for treatment of this disease population.

2 Study objectives and endpoints

2.1 Primary objective

Primary objective	*Endpoints related to primary objective*
• To compare the effect of ACZ885 versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in the percent predicted forced vital capacity (FVC) at week 24	• Change from baseline in percent predicted FVC at week 24

Rationale for Primary Outcome

FVC has been shown in sarcoidosis patients to correlate with mortality risk and is the most often used functional outcome in sarcoidosis studies, providing a benchmark for comparison against previously tested agents (Baughman et al 2012). Based on published results with corticosteroids, significant clinical responses by spirometry in sarcoidosis patients can be detected as early as 24 weeks, with maximum effect shown by 52 weeks (Baughman et al 2013).

2.2 Secondary objectives

Secondary objectives	*Endpoints related to secondary objectives*
• To determine the effect of ACZ885 on decreasing the maximum standardized uptake value (SUVmax) [F-18]FDG-PET in nodules (nodular uptake regions) after 12 weeks of treatment, compared to placebo.	• Percent change from initial scan in [F-18]FDG-PET SUVmax at week 12
• To determine the effect of ACZ885 versus placebo on other parameters of pulmonary function testing (i.e., absolute FVC, FEV1, FEV1/FVC, FEV3,FEF25-75, FEV3/FVC, FEV6, TLC, RV, RV/TLC, DLco and post-bronchodilator FEV1/reversibility) in patients with sarcoidosis at 24 weeks compared to baseline	• Lung function testing results at 24 weeks compared to baseline
• To determine the effect of ACZ885 versus placebo on HRCT of patients with sarcoidosis at 24 weeks compared to initial HRCT scan as measured by side-by-side comparison by blinded reviewers and HRCT scoring	• HRCT results at 24 weeks compared to HRCT initial scan measured by blinded reviewers and HRCT scoring
• To determine the effect of ACZ885 versus placebo on the 6-minute walk test (6MWT) distance of patients with sarcoidosis at 12 and 24 weeks compared to baseline	• 6MWT results at week 12 and 24 compared to baseline

Secondary objectives	***Endpoints related to secondary objectives***
• To determine the effect of ACZ885 on additional [F-18]FDG-PET outcomes (i.e., SUVmean, SUVpeak and volume of the lesions) after 12 weeks of treatment compared to placebo	• Percent change from initial scan in additional [F-18]FDG PET outcomes at week 12
• To assess the safety and tolerability of ACZ885 in patients with sarcoidosis as measured by adverse events (AEs)	• Adverse events in patients taking ACZ885 compared to placebo

Rationale for imaging with HRCT and FDG PET/CT in screening and/or secondary outcomes

High resolution computed tomography (HRCT) is used in this study for both screening and for clinical outcome measurements. Standard plain chest radiographic views are frequently used in the diagnostic and staging processes for sarcoidosis patients. However, the chest radiographic scores (Scadding stages 0-IV) have limited value in predicting severity of pulmonary involvement and are relatively insensitive as a disease marker in therapeutic trials. HRCT (without contrast agent) provides superior resolution of lung morphology when compared to chest radiography or even conventional CT. HRCT can detect parenchymal disease in patients with normal chest radiographs or demonstrate more extensive disease in patients having only focal abnormalities on chest radiographs (Batra 1993; Drent et al 2003). Typical HRCT features of sarcoid parenchymal abnormalities include nodular densities, patchy areas of ground glass opacities, irregular linear opacities, end-stage fibrosis and honeycomb appearance. The nodules found on HRCT have been shown to likely represent confluent interstitial granulomas. Signs of distortion on HRCT are consistent with the development of fibrosis. Sequential HRCTs have shown that nodules and patchy ground glass densities are reversible, whereas honeycombing and lung distortion suggest irreversible fibrosis. Moreover, HRCT abnormalities have been reported to correlate better than radiographic stage to pulmonary functional parameters and serum biomarkers. Of particular note, relationships have been noted between HRCT findings and BAL neutrophil numbers, a marker of disease activity. HRCT correlations with other sarcoidosis disease activity markers have also been found, including BAL total cell count and serum levels of sIL-2R.

This study will use highly sensitive [F-18]FDG-PET/CT imaging to provide early evidence for effective decrease in IL-1β-driven inflammation on ACZ885 treatment. [F-18]FDG-PET/CT detects increased inflammation-associated metabolic activity in sarcoidosis with sensitivity of 90-100%, and decreases in [F-18]FDG-PET/CT at 24 weeks compared to baseline have been correlated with improvements in FVC over this time period (Keijsers et al 2008; Milman et al 2012; Adams et al 2014) with evidence of improvement by

serial [F-18]FDG-PET detected in sarcoid patients reported as early as 1-2 months (Brudin et al 1994; Braun et al 2008; Imperiale et al 2013). In addition, evidence suggests that low dose prednisone therapy does not appreciably alter [F-18]FDG-PET tracer uptake evaluated in a second, follow up scan while high dose (e.g., 40 mg/d) does result in PET signal reduction (Brudin et al 1994). We postulate rapid reduction in inflammasome activity upon ACZ885 treatment, and a temporally associated decrease in [F-18]FDG-PET is expected by 12 weeks. However, detectable clinical signs of improvement in pulmonary function are anticipated to require additional time after cessation of tissue inflammation by the experimental treatment. Hence, the endpoint related to pulmonary function assessment occurs later at 24 weeks. In consideration of evidence suggesting that patients with FDG PET tracer uptake in parenchymal lung tissues have active disease more likely to improve with effective intervention versus no changes in patients with negative PET findings (Keijsers et al 2011; Vorselaars et al 2015), patients in this study will undergo stratification at randomization based on baseline FDG PET/CT results. In addition, later analyses for this study will also stratify patients for the presence of lung parenchymal PET tracer uptake at baseline.

Rationale for other secondary outcomes

Full pulmonary function tests include spirometry (FVC, FEV1, FEV1/FVC, FEF25-75, FEV3/FVC, FEV6, lung volumes (TLC, RV, RV/TLC) and gas diffusion (DLco) to allow further characterization of the patients' response to treatment. Emerging evidence suggests that sarcoidosis involves a component of small airways disease caused by constriction by peri-bronchiolar granulomatous inflammation (Davies et al 2000). Therefore, the following spirometry measures: FEV3, FEV3/FVC, 1-(FEV3/FVC) will be performed to assess small airway disease. (Burgel et al 2011). The Investigator needs to pay special attention to capture the FEV3 data (not always captured by traditional software; may be captured by saving the flow volume loop).

The 6MWT (including distance walked, changes in oxygenation, and Borg Questionnaire) is a practical and simple assessment of functional capacity, reflective of activities of daily living (Enright 2003) that has been increasingly applied to assess various lung diseases, including interstitial lung diseases other than sarcoidosis where it has proved useful for both predicting mortality and monitoring response to therapy. Its application in sarcoidosis studies has been more limited (Baughman et al 2007) and results should be interpreted in recognition of the multi-factorial nature of the disease (Baughman and Lower 2011).

2.3 Exploratory objectives

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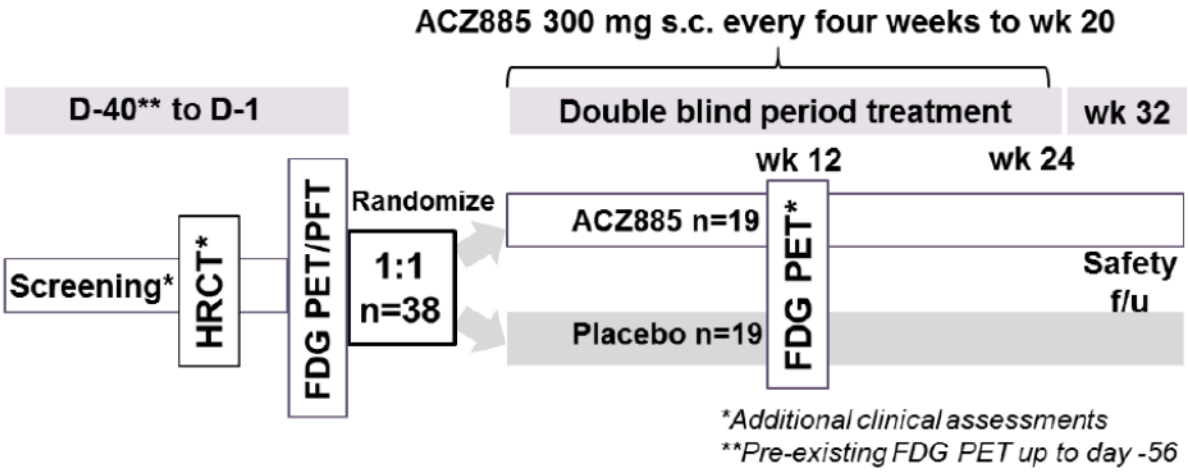
3 Investigational plan

3.1 Study design

Figure 3-1 Study Design scheme



This is a 32-week, subject- and investigator-blinded, randomized, placebo-controlled, parallel-group, non-confirmatory study to assess the clinical efficacy of ACZ885 administered subcutaneously (s.c.) in 6 injections given 28 days apart (Figure 3-1). The study will randomize approximately 38 patients (targeting 30 completers) with evidence of parenchymal involvement and histologically proven, chronic pulmonary sarcoidosis of ≥1 year duration with persisting activity at baseline despite background therapy as determined by clinical history, radiologic evidence (e.g. HRCT, MRI or chest x-ray), spirometry and MMRC dyspnea scale assessments. Randomization will be stratified by positive PET parenchymal tracer uptake (yes/no). Acceptable background therapy includes a stable regimen of prednisone ≤15 mg/day and/or no more than one immune suppressive agent (i.e., methotrexate, azathioprine, leflunomide or hydroxychloroquine).

Re-screening of subjects may be allowed with the consultation of the Sponsor's medical expert.

For each subject, there will be a maximum 40-day screening period. Screening is valid for 40 days from the time of the first screening assessment. [F-18]FDG-PET/CT scans obtained locally at the study site within 8 weeks of randomization will be acceptable for baseline assessment prior to receiving the first injection of ACZ885. However, any prior [F-18]FDG-PET/CT imaging must also have been done without changes in treatment during the subsequent period leading up to study randomization.

Subjects who meet the eligibility criteria at screening will undergo evaluation of full baseline clinical and biomarker assessments prior to injection. Baseline assessments including safety laboratory evaluations and pulmonary function tests will not be available prior to dosing and for those measures eligibility criteria will be determined based on the screening results. Enrolled subjects will be randomized at a 1:1 ratio to receive treatment with either ACZ885 or placebo. On Days 1, 29, 57, 85, 113 and 141 patients will be administered s.c. dosing with ACZ885 at 300 mg or corresponding placebo treatment. All patients will return to the study center for safety and pharmacokinetic (PK) checks on an every four week basis at which time they will receive either study treatments depending on treatment arm. Additionally, patients will undergo clinical assessments that include pulmonary function tests with lung volumes, DL_{CO}, 6MWT, and clinical outcome assessments as outlined in the Assessment Schedule.

At week 12, a second [F-18]FDG-PET/CT will be obtained. In addition, functional clinical measures Corporate Confidential Information will take place at this time point. The final dosing will take place on week 20, followed by a visit on week 24 Corporate Confidential Information Corporate Confidential Information . Also included at the week 24 visit is the second HRCT assessment. Patients return for the end of study (EOS) visit at week 32.

A follow-up visit or phone call for SAEs must be performed 30 days following early discontinuation, or 8 weeks after last injection of study drug, whichever is later. If anaphylactic reactions occur after injection, two more immunogenicity samples (at the time of the event and 8 weeks later) need to be taken. Any patient who discontinues the study early will complete the Week 32, EOS visit. Patients discontinuing after week 12 will also undergo a second HRCT assessment at this visit, as assessed on a case-by-case basis by the Sponsor.

3.2 Rationale for study design

A randomized, placebo-controlled, subject and investigator blinded approach is used to eliminate potential bias in reporting safety and clinical efficacy data in this first exploratory study in sarcoidosis patients.

The patient exclusion criteria of background prednisone dosing >15 mg/day is justified because chronic high dose steroids (e.g., 40 mg/day) have been reported to attenuate the [F-18]FDG-PET signal while low dose steroids do not have this effect (Brudin et al 1994).

3.3 Rationale for dose/regimen, route of administration and duration of treatment

The dose of ACZ885 (canakinumab) selected for the current proof-of-concept trial is 300 mg s.c. every four weeks. This dose will ensure optimal tissue penetration for suppressing the established granulomatous inflammation over time and allow for tissue repair and recovery of organ functionality. The current label for canakinumab (Ilaris®) indicates a standard starting dosage of 2 or 4 mg/kg up to 150 mg s.c. every 8 weeks and allows for every 8 weeks dosing up to 8 mg/kg for CAPS patients ≤40 kg and up to 600 mg s.c. for those patients >40 kg if a satisfactory clinical response has not been achieved 7 days after treatment start. Every 4 week s.c. dosing up to 300 mg is indicated for patients with systemic juvenile idiopathic arthritis. RA patients, a relatively comparable patient population to sarcoidosis in terms of age range and inflammatory levels, have been treated with 300 mg s.c. up to 184 weeks (studies CACZ885A2201, E1 & E2) at every 2 weeks for the first 12 weeks and every 4 weeks thereafter. This dosing regimen was well-tolerated, without dose-dependent differences in AE incidence compared to every 4 weeks dosing of 150 mg s.c.

ACZ885 administered s.c. has an approximate bioavailability of 70% compared to i.v. administration. However, there are likely to be differential, organ-dependent tissue levels of ACZ885, with lung tissue penetration expected to be 10-15% of the systemic exposure (Wang et al 2008, Shah et al 2012, Shah et al 2013). Analysis of a recent failed trial of the TNF-α inhibitor golimumab in chronic sarcoidosis patients suggested insufficient dosing may have been a factor (Judson et al 2014). Thus, higher dosing of ACZ885 is desired for initial clinical testing of IL-1β blockade, a novel therapeutic target for this disease process.

The duration of every 4-week dosing to week 20 is based on the expected time of 24 weeks required for detecting functional improvement in the clinical outcome of change in percent of predicted FVC for this patient population.

In summary, in order to optimally assess the potential for ACZ885 in its first trial in sarcoidosis patients, an every 4-week dosing at 300 mg s.c. is justified to reach adequate circulating and tissue levels within the target organs for the anticipated duration required for a meaningful change in the lung inflammation and in the subsequent clinical outcomes.

3.4 Rationale for choice of comparator

In this study, the placebo to ACZ885 will be used as comparator to provide objective evidence of potential AEs and other safety data as well as clinical efficacy generated from patients exposed to ACZ885.

3.5 Rationale for choice of background therapy

Patients will continue on stable background therapy as established prior to study entry, thereby justifying potential treatment with placebo. Subjects will be maintained on their pre-existing stable medical regimen for treatment of preexisting medical conditions, including sarcoidosis.

3.6 Purpose and timing of interim analyses/design adaptations

Corporate Confidential Information

3.7 Risks and benefits

ACZ885 has not been previously administered with therapeutic intent to patients with active, chronic sarcoidosis. Therefore, no statement can be made at this time on the actual clinical benefits of ACZ885 in this patient population. However, given the mechanism of action of ACZ885 and the relevant inflammatory pathways involving IL-1β as discussed in the background (Section 1.1), there is a reasonable expectation that a therapeutic response can be achieved with the compound in sarcoidosis.

Overall, the development program with ACZ885 has demonstrated a good safety and tolerability profile as evidenced by a low number of study discontinuations for AEs, predominantly mild injection site reactions and no specific target organ toxicity. The AEs profile is characterized by non-specific gastrointestinal and central nervous system events, and infections predominantly of the upper respiratory tract, in some instances serious, with all infections responding to standard therapy.

The available toxicology, efficacy, safety, tolerability, lack of detectable immunogenicity and efficacy data in MWS, RA, sJIA and gouty arthritis, further support the clinical development of canakinumab in diseases in which IL-1β is likely to have a predominant role. However, since preventing IL-1β receptor signaling may alter immunologic responsiveness in unanticipated ways, patients receiving ACZ885 will be closely monitored for clinical and laboratory indicators of immune suppression and immune dysregulation, such as infection including opportunistic infections (recognizing that blocking IL-1β may mask fever and blunt the inflammatory response to infection), blood cells count abnormalities (including neutropenia), and development of malignancies, autoimmune manifestations and hypersensitivity reactions.

The total radiation whole body effective dose in this protocol will be less than 25 mSv; 14 mSv from HRCT scanning and 11 mSv from [F-18]FDG-PET/CT scans, including attenuation correction scans. In larger patients, a higher injected [F-18]FDG activity may be required but the total radiation exposure in these patients will not exceed 30 mSv. This amount of radiation is considered to be a moderate risk, category III (ICRP62) and is balanced against the substantial societal benefit gained from the trial. If patients have a historical [F-18]FDG-PET/CT scan that can be used as baseline scan, then only the follow up scan will be conducted as part of the clinical protocol.

As part of the spirometry assessment at Visits 101 and 107, a single dose of short-acting bronchodilators (SABA) salbutamol/albuterol will be administered. For more information please refer to product information (SmPC/USPI).

Women of child bearing potential should be informed that taking the study drug may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the subject will not reliably comply, they should not be entered in the study.

There may be unknown risks of ACZ885 which may be serious and unforeseen.

3.7.1 Blood sample volumes

A maximum of 350 mL of blood is planned to be collected over a period of approximately 38 weeks, from each subject as part of the study. Additional samples for monitoring of any safety findings would be in addition to this. This is not considered to be a risk for this population.

Timings of blood sample collection are outlined in the Assessment Schedule, Section 8.2.

A summary blood log is provided in the Site Operations Manual, together with instructions for all sample collection, processing, storage and shipment information.

See Section 8.9 regarding the potential use of residual samples.

4 Population

This study will recruit patients with chronic active pulmonary sarcoidosis as defined by disease duration ≥1 year with evidence of persistent or progressive parenchymal changes as characterized by radiological evidence. A total of approximately 38 patients will be randomized to participate in the study. The sample size will be re-estimated at the interim analysis and number of randomized patients may be increased up to a maximum of 90.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria.

Subject selection is to be established by checking through all inclusion/exclusion criteria at screening and first baseline prior to the first injection. Safety laboratory evaluations and pulmonary function tests taken at first baseline will not be available prior to first injection, and screening values should be used for inclusion in the study. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criterion excludes a subject from enrollment into the study.

4.1 Inclusion criteria

Pulmonary sarcoidosis patients eligible for inclusion in this study must fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female subjects ages 18 to 80 years of age (both inclusive)
3. Subjects must weigh at least 50 kg to participate in the study
4. Able to communicate well with the investigator and to understand and comply with the requirements of the study.
5. Disease duration of ≥1 year
6. Clinically active disease demonstrated either by a biopsy (any organ) or by bronchoalveolar lavage (lymphocytosis >15%, $CD4^+/CD8^+$ ratio >3.5, $CD103^+CD4^+/CD4^+$ ratio <0.2) (Heron et al 2008). Patients must also have all of the following criteria:
   - MMRC dyspnea scale ≥1
   - Threshold FVC 50 - 90% of predicted (Pellegrino et al 2005, Vorselaars et al 2015)
   - Evidence of parenchymal lung involvement by HRCT at screening or by historical radiological evidence (e.g. CT, MRI or x-ray)

4.2 Exclusion criteria

Pulmonary sarcoidosis patients fulfilling any of the following criteria are <u>not</u> eligible for inclusion in this study:

1. History of known hypersensitivity to canakinumab
2. Current inhaled use of tobacco products (urine cotinine level > 500 nanograms/mL) at screening
3. Use of other investigational drugs at the time of enrollment, or within 5 half-lives of enrollment, or until the expected PD effect has returned to baseline, whichever is longer, or longer if required by local regulations
4. Previous exposure to concomitant treatment according to the following criteria:
   a. Prednisone >15 mg/day or changes in prednisone dose in the 8 weeks prior to screening
   b. More than one immune-modulator (i.e., methotrexate, azathioprine, leflunomide, hydroxychloroquine) or changes in their dosing levels within 12 weeks of randomization. Refer to Section 5.2, 'Prohibited treatments' for additional details
   c. Mycophenolate use within 12 weeks of randomization

5. Prior treatment with any biologic drug targeting the immune system within 180 days of randomization or history of any previous use of rituximab
6. Diagnosis of pulmonary hypertension requiring treatment
7. History of bleeding disorder
8. Extra-pulmonary sarcoidosis as primary treatment indication (e.g., involving brain, heart, eye and renal disease with significant hypercalcemia)
9. Any conditions or significant medical problems which in the opinion of the investigator immune-compromise the patient and/or places the patient at unacceptable risk for immunomodulatory therapy, such as:
    - Absolute neutrophil count (ANC) <LLN (1,500/µl)
    - Thrombocytopenia CTCAE v4.03 Grade 1: Platelets <LLN (75.0 x 10^9/L)
    - Any active or recurrent bacterial, fungal (with exception of onychomycosis) or viral infection
    - Presence of human immunodeficiency virus (HIV) infection, active hepatitis B or hepatitis C infections based on screening lab results
    - Presence of active or latent tuberculosis (TB). If historical Tb result is available, Tb status needs to be confirmed pre-randomization as determined by screening laboratory measurements.
    - Clinical evidence or history of multiple sclerosis or other demyelinating diseases, or Felty's syndrome
10. Live vaccinations within 3 months prior to screening
11. Current severe progressive or uncontrolled disease, which in the judgment of the clinical investigator renders the patient unsuitable for the trial
12. Inability or unwillingness to undergo repeated venipuncture (e.g., because of poor tolerability or lack of access to veins)
13. Donation or loss of blood (amount depending on age and weight, 10-20% or more of volume, within 8 weeks prior to first dosing, or longer if required by local regulation
14. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases
15. Contraindications to FDG-PET scan investigations, such as severe claustrophobia or uncontrolled diabetes
16. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test

17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using basic methods of contraception during dosing of investigational drug. ***Basic contraception methods include:***
    - Total abstinence from heterosexual intercourse (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
    - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps). For UK: with spermicidal foam/gel/film/cream/vaginal suppository
    - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS)

    In case of use of oral contraception women should be stable on the same pill for a minimum of 3 months before taking study drug

    Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g., age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.
18. History of drug or alcohol abuse within the 12 months prior to dosing, or evidence of such abuse as indicated by the laboratory assays

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

5 Restrictions for Study Subjects

During recruitment, screening/informed consent review, and baseline visit, the subjects must be informed and reminded of the following restrictions:

5.1 Contraception requirements

Please refer to exclusion criteria (Section 4.2) for details of contraception requirements for the study.

5.2 Prohibited treatment

Use of the treatments displayed in the table below are NOT allowed during the screening period or after the start of study treatment due the concern for increased potential immunosuppressant-related conditions. These are prohibited for the duration of the study until 30 days after the last study visit.

Table 5-1 Prohibited treatment

Medication	Action to be taken
Biologic drugs targeting the systemic immune system (e.g., TNF-α blockers, anakinra, rituximab, abatacept, tocilizumab)	Discontinue study drug
Live vaccines (within 90 days of study drug dosing)	Discontinue study treatment; if live vaccines are given after screening but prior to study drug administration, the subject may be enrolled after 90 days have passed since vaccine administration if the subject continues to meet eligibility criteria upon re-screening
Systemic immune suppressive drugs, except for the following: prednisone ≤15 mg/d and/or no more than one of the following cytotoxic drugs: methotrexate, azathioprine, leflunomide or hydroxychloroquine, provided dosing of these listed medications has remained unchanged in a 12 week period prior to randomization and remains unchanged throughout study period	Any acute dosing of immune suppressive drugs may require discontinuation of study treatment and participation and will have to be evaluated with Sponsor on a case-by case basis

5.3 Dietary restrictions and smoking

There are no specific dietary restrictions except for those required when preparing for PET scanning. Subjects are not allowed to participate in the trial if they smoke.

5.4 Other restrictions

On study days when spirometry will be performed, patients should refrain from the following:

- Using of bronchodilators for at least 6 hours for short-acting β-2 agonist and at least 48 hours for long-acting β-2 agonist prior to spirometry testing
- Drinking alcohol for 4 hours prior to spirometry testing
- Participating in strenuous activity for 30 min prior to spirometry testing
- Wearing clothes that substantially restrict full chest and abdominal expansion
- Eating a large meal within 2 hours of testing

On study days when [F-18]FDG-PET/CT scan is performed, patients should:

- Refrain from alcohol consumption and vigorous sports activities 24 hours prior to the measurement
- Be well-hydrated and fasted 4 hours prior to administration of radiotracer
- Have a blood glucose level below 11 mmol/L (200 mg/dL)

6 Treatment

6.1 Study treatment

Details on the storage and management of study medication, randomization and instructions for prescribing and taking study treatment are outlined in Section 3 of the Site Operations Manual.

6.1.1 Investigational treatment and control drugs

The investigational drug, ACZ885 (canakinumab) 150 mg/ 1mL and matching placebo liquid in vials will be prepared by Novartis and supplied to the Investigator as blinded subject packs.

6.1.2 Additional study treatment

- [F-18]fluorodeoxyglucose ([F-18]FDG) PET tracer will be produced under GMP. [F-18]FDG PET has approved New Drug Application in the US and marketing authorities in the EU for certain indications. [F-18]FDG will be sourced locally.
- Salbutamol/Albuterol will be used during the spirometry testing and will be sourced locally.

6.2 Treatment arms

Subjects will be assigned to one of the following two treatment arms in a ratio of 1:1. Study treatments are defined as:

- Doses of 300 mg ACZ885 s.c. every four weeks
- Doses of placebo to match the 300 mg ACZ885 s.c. every four weeks

6.3 Treatment assignment and randomization

All eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. Subjects will undergo stratification based on baseline [F-18] FDG-PET/CT results. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of investigational treatment to be dispensed to the subject. The randomization number will not be communicated to the caller.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of treatment arms to randomization numbers. Once a

patient is deemed eligible for enrollment into the study and ready for dosing, the next lowest available randomization number will be assigned. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug.

6.4 Treatment blinding

This is a subject- and investigator-blinded study; subjects, investigator staff, and persons performing the assessments will remain blind to the identity of study treatments according to the specifications provided in Table 6-1.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

Randomization data are kept strictly confidential, and are accessible only to authorized personnel, until unblinding of the trial as described in the blinding table (Table 6-1). The clinical team may communicate unblinded interim analysis results (e.g., information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

No further dissemination of interim results should occur, in particular not with individuals involved in treating the study's subjects or assessing clinical data (e.g., ECGs, images, symptoms) obtained in the study.

Unblinding will occur in the case of patient emergencies (see Section 6.7), at the time of interim analysis and at the conclusion of the study.

Site staff

Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site (see Section 6.7).

Sponsor staff

The following unblinded sponsor roles are required for this study:

Unblinded sample analyst(s) (PK/PD/IG)

The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

The study statistician will be able to access the randomization list for interim analyses and is allowed to share unblinded information with the rest of the clinical team as appropriate for internal decision purposes, as outlined in Table 6-1. For example, unblinded summaries and unblinded individual data can be shared with the team for interim analyses.

Study programmers and other personnel involved in study data analysis (e.g., biomarker expert) are allowed to access treatment assignment information for the purpose of conducting interim analyses.

Table 6-1 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	Interim Analysis & dose escalation
Subjects/Patients	B	B	UI	B
Site staff	B	B	UI	B
Unblinded site staff (see text for details)	NA	NA	NA	NA
Drug Supply and Randomization Office	UI	UI	UI	UI
Unblinded sponsor staff (see text for details)	UI	UI	UI	UI
Statistician/statistical programmer/data analysts	B	B	UI	UI
Independent committees used for assessing interim results	NA	NA	NA	NA
All other sponsor staff not identified above	B	B	UI	UI

B Remains blinded

NA Not applicable

UI Allowed to be unblinded on individual patient level

6.5 Treating the subject

ACZ885 will be administered to the subject via the following route of administration (s.c. injection) at the investigational site. See the Site Operations Manual for further details.

Sponsor qualified medical personnel will be readily available to advise on trial-related medical questions or problems.

6.6 Permitted dose adjustments and interruptions of study treatment

Scheduled dosing of study drug may be delayed by up to 5 days if subjects present with conditions that require withholding of study drug, e.g., evidence for active infection (treated or untreated) or acute abdominal pain. Outside of this 5-day window, the dose will be considered missed. These changes must be recorded on the Dosage Administration Record CRF. The 5-day window for those subjects requiring study drug to be withheld until resolution is in addition to the defined +/-5 day visit window, therefore subjects can be no more than 10 days outside of the scheduled visit. Subjects must maintain at least 21 days between visits.

Subjects who are unable to generate the requisite number of reproducible spirometry maneuvers at baseline will be allowed an additional 5 days beyond the 40-day screening period, if necessary, for repeat spirometry prior to dosing. All other baseline measures should be repeated at the same visit as the first dose administration.

Subjects are able to miss no more than one dose administration. All missed dose administrations must be discussed with the Sponsor to determine if the subject should be discontinued from further study treatment.

6.7 Emergency breaking of assigned treatment code

Emergency treatment code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the study monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT in case of emergency. The investigator will need to provide:

- protocol number
- study drug name (if available)
- subject number

The investigator must provide oral and written information to inform the subject how to contact his/her backup in cases of emergency when he/she is unavailable to ensure that un-blinding can be performed at any time and instructions for contacting the local Novartis CPO (or any entity to which it has delegated responsibility for emergency code breaks) to the subject in case an emergency treatment code break is required at a time when the investigator and backup are unavailable.

6.8 Treatment exposure and compliance

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with ACZ885, as detailed in Section 8.7.

6.9 Recommended treatment of adverse events

There is no treatment that can reverse the activity of ACZ885. Given that ACZ885 is an IgG1 isotype monoclonal antibody, plasmapheresis may be of value in removing ACZ885 from the body. Potential adverse events should therefore be treated symptomatically at the discretion of the Investigator. Medication used to treat AEs must be recorded on the concomitant medications/significant non-drug therapies eCRF.

6.10 Rescue medication

In the context of this study, rescue medications are defined as those medications used acutely to directly manage medical signs or symptoms related to the subject's underlying sarcoidosis. Addition or alteration of immunosuppressant or corticosteroid therapy for or by a patient during the study are not allowed and may require his or her termination from study participation. If a patient is withdrawn from the study, the Week 32 EOS visit should be completed.

Non-sarcoidosis flares (bronchitis)

Patients with sarcoidosis may experience episodes of bronchitis that do not indicate worsening of their disease. Production of yellow-green sputum is a characteristic of bronchitis. Treatment details are at the discretion of the investigating physician. First line treatment is typically with antibiotics. Unresponsive patients may require the addition of a short course of corticosteroids. This may result in the patient being withdrawn from the trial (See Table 5-1) in which case the Week 32 EOS visit should be completed.

Acute pulmonary exacerbations of sarcoidosis (APES)

APES are defined as acute worsening of pulmonary signs and symptoms in patients with known sarcoidosis not explained by another cause, combined with a decline in spirometry (≥10% decrease from previous baseline FVC and/or FEV1, present for at least one month (Panselinas and Judson 2012). Patients' signs and symptoms of APES typically respond to corticosteroids. This may result in the patient being withdrawn from the trial (See Table 5-1) in which case the Week 32 EOS visit should be completed.

Use of rescue medication must be recorded on the concomitant medications/significant nondrug therapies CRF.

6.11 Concomitant treatment

The investigator must instruct the subject to notify the study site about any new medications he/she takes after the subject was enrolled into the study.

Common potential concomitant medications in this study population are anticipated to include topical corticosteroids or systemic corticosteroids at ≤15 mg/d prednisone or equivalent, and/or up to one of the following systemic immune-modulating drugs: methotrexate, azathioprine, leflunomide or hydroxychloroquine.

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study must be recorded on the concomitant medications/significant non-drug therapies CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

7 Study completion and discontinuation

7.1 Study completion and post-study treatment

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes their EOS visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

A follow-up visit or phone call for SAEs must be performed 30 days following early discontinuation, or 8 weeks after last injection of study drug, whichever is later. The phone call for SAEs is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 9.2 and the Site Operations Manual. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Individual subject withdrawal

Subjects may voluntarily discontinue from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

Any patient who discontinues the study early will complete the Week 32 EOS visit. For those patients discontinuing after Week 12, the volumetric and HRCT exam should also be included as assessed on a case-by-case basis by the Sponsor.

If a subject discontinuation occurs for any reason, the Investigator must make every effort to determine the primary reason for a subject's discontinuation from the study and record this information on the CRF.

The investigator should discontinue study treatment for a given subject or discontinue the subject from study if, on balance, he/she believes that continuation would be detrimental to the subject's well-being.

If a liver or renal event occurs, follow guidelines outlined in Appendix 1 and Appendix 2 regarding discontinuation of study treatment.

Study treatment must be permanently discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy
- Severe allergic reaction or anaphylaxis following administration of the study drug
- Non-compliance as defined by missing more than one dose administration
- Emergence of the following adverse events:
  - Serious infections combined with neutropenia CTCAE v4.03 grades ≥1 (ANC <1.5 x 10^9/L)
  - Confirmed diagnosis of latent or active TB
  - Onset of any malignancy

- Any of the following laboratory abnormalities confirmed to be sustained by repeat assessment within 7 days after initial lab assessment:
  - Neutropenia CTCAE v4.03 grades ≥2
  - Thrombocytopenia CTCAE v4.03 grade 4
- Use of prohibited treatment as per Table 5-1.
- Any other protocol deviation that results in a significant risk to the patient's safety

The appropriate personnel from the site and Novartis will assess whether study treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

Subjects who discontinue study treatment should NOT automatically be considered withdrawn from the study. See Section 8 for the required assessments of these subjects after discontinuation of study treatment.

7.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a subject does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study-related contact **and** does not allow analysis of already obtained biologic material.

If a subject withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

7.4 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g., dates of telephone calls, registered letters, etc. A subject should not be considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

All subjects will undergo regular monitoring at scheduled visits for safety and tolerability, including adverse events, throughout the duration of the study. If significant risk to the study subjects is identified, the study may be put on hold or terminated based on a full safety review.

The study will be stopped if any of the following criteria are met, and no further dosing pending a full safety review:

- An overt change in the rate of incidence of expected drug-related serious adverse events such as infections, opportunistic infections, hypersensitivity, white blood cell (WBC) or platelet count decreases as compared to the rates described in the current version of the IB.

- New unexpected serious adverse events considered related to canakinumab in more than 3 individuals on active therapy.

7.6 Early study termination by the sponsor

The investigator must contact the IRT to register the subject's discontinuation from the study and/or investigational treatment. The study can be terminated by Novartis at any time for medical or ethical reasons, and/or in accordance with the respective contractual terms. Should this be necessary, the subject should be seen as soon as possible and treated as a prematurely withdrawn subject as described in Section 7. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing institutional review boards (IRBs) and/or ethic committees (ECs) of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment Schedule

Epoch	Screening	Treatment							
Study Phase	Screening	Treatment Period[2]							End of Study[3]
Visit Numbers[1]	1	101	102	103	104	105	106	107	199
Study Day(s)	40 to 0 -40 +0	1	29 -5 +5	57 -5 +5	85 -5 +5	113 -5 +5	141 -5 +5	169 -5 +5	224 -5 +5
Informed consent	S								
Inclusion / exclusion criteria	S	S							
Medical history/current medical conditions	X								
Demography	X								
Physical examination	S	S	S	S	S	S	S	S	S
Smoking history	X								
Tuberculosis Blood Test	S								
Hepatitis and HIV Screen	S								
Urine drug screen and cotinine test	S								
Pregnancy test[4]	X	X							X
Hematology	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X	X	X	X	X	X	X	X
Urinalysis[5]	X	X	X	X	X	X	X	X	X
Body height	X								
Body weight	X				X				
Body temperature	X	X	X	X	X	X	X	X	X
Blood pressure[6]	X	X	X	X	X	X	X	X	X
Spirometry	X		X	X	X	X	X		X
Spirometry Reversibility Test		X[7]						X	
Diffusing Capacity (DLCO)		X	X	X	X	X	X	X	X

Epoch	Screening	Treatment							
Study Phase	Screening	Treatment Period[2]							End of Study[3]
Visit Numbers[1]	1	101	102	103	104	105	106	107	199
Study Day(s)	40 to 0 -40 +0	1	29 -5 +5	57 -5 +5	85 -5 +5	113 -5 +5	141 -5 +5	169 -5 +5	224 -5 +5
Lung Volumes		X	X	X	X	X	X	X	X
MMRC dyspnea scale	X								
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6MWT (including O2 Saturation %, Pulse Rate, Borg Questionnaire)[8]	X	X	X	X	X	X	X	X	X
ECG evaluation	X	X			X			X	X
Volumetric CT and HRCT[9]	X							X	
Fasting glucose[10]	X				X				
[F-18]FDG-PET/CT[11]	X				X				
Randomization		X							
Study drug administration[12]		X	X	X	X	X	X		
Pharmacodynamic blood collection		X	X	X	X	X	X	X	
Pharmacokinetic blood collection		X	X	X	X	X	X	X	
Immunogenicity blood collection		X			X			X	
Corporate Confidential Information									
Blood collection for pharmacogenetics		X							
Whole blood collection for pharmacogenomics (RNA PAXgene tubes)		X			X			X	
Adverse events	X								
Serious adverse events	X								
Concomitant therapies	X								
Study completion information									X

[1] Visit structure given for internal programming purpose only
[2] A window of ±5 days is allowed for the treatment visits, but the interval between 2 doses must be at least 21 days
[3] All patients who discontinue early must complete the EOS Visit. For those discontinuing after week 12, the volumetric and HRCT exam should also be included as assessed on a case-by-case basis by the Sponsor
[4] Limited to females of childbearing age. Serum testing is done at screening and urine test is done predose at Day 1 and at the EOS
[5] If the dipstick result is positive for protein, nitrite, leukocytes and/or blood, the sample should be sent for microscopic analysis of WBC, red blood cell count (RBC) and casts
[6] Vital signs taken after resting in a sitting position for at least 3 minutes
[7] For subjects at baseline who are unable to generate reproducible spirometry maneuvers, an additional 5 days beyond the 40 day screening window will be allowed for the subjects to return for repeat spirometry.
[8] Oxygen saturation %, pulse rate, and Borg Questionnaire score will be recorded before the test. Oxygen saturation %, pulse rate, Borg Questionnaire score, and distance walked will be recorded at the end of the test. 6MWT should occur after ECGs have been completed. Pulse rate should be taken after sitting for at least 3 minutes.
[9] The screening HRCT should be completed as the last assessment for eligibility criteria. If patients have evidence of parenchymal involvement of disease from historical radiological evidence (e.g. CT, MRI or x-ray), then baseline HRCT can be performed at same time as the [F-18]FDG-PET/CT. At each time point, two scans will be collected: 1 HRCT scan and 1 lower dose volumetric CT scan.
[10] The [F-18]FDG-PET/CT requires a blood glucose level below 11 mmol/L. The measurement is performed by finger prick at site the same day [F-18]FDG-PET/CT is performed
[11] For baseline, [F-18]FDG-PET/CT results obtained within 8 weeks of randomization will be accepted. The [F-18]FDG-PET/CT at baseline should always be conducted after all other assessments are done and patient found eligible unless a previous result was used or sponsor agreement was obtained. It should not be done post-randomization.
[12] All assessments for a given visit should be completed before study drug is administered

8.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent. If the subject is capable of doing so, he/she should indicate assent by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

8.3 Subject screening

In general, it is permissible to re-screen a subject; however, each case must be discussed and agreed with the Sponsor's medical lead on a case-by-case basis.

Patient re-screening will be allowed in the study in the event of a delay in treatment, e.g., in the event of a washout period of more than 28 days. However, the screening HRCT cannot be repeated and re-screening may not occur if planned dosing will not take place within 8 weeks of these screening imaging assessments.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: date of birth, age, sex, race, predominant ethnicity.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses, and not symptoms, will be recorded.

The following should be recorded on the respective CRF page:

- Relevant medical history/current medical conditions
- Prior and current medications / significant non-drug therapies
- Response to treatment with previous drug therapies (e.g., corticosteroids, methotrexate, azathioprine, TNF-α blockers)

8.4.1 Hepatitis screen, HIV screen, tuberculosis screen

All subjects will be screened for HIV, hepatitis B and C, and tuberculosis. See the Site Operations Manual for details.

8.4.2 Alcohol test, drug screen, urine cotinine

All subjects will be screened for substances of abuse and cotinine. See the Site Operations Manual for details.

8.5 Efficacy/Pharmacodynamics

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the Study Operations Manual. Assessments will be performed/samples collected at the timepoints defined in the Assessment Schedule.

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

8.5.1 Clinical Outcome Assessments (COAs)

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8.5.2 Imaging

Details for HRCT and [F-18]FDG-PET/CT imaging are described in the Parexel Imaging Investigator SOM.

To avoid unnecessary radiation, all screening activities except imaging needs to be completed prior to HRCT scan for eligibility. Evaluation by HRCT for eligibility must be completed prior to the patient undergoing baseline [F-18]FDG-PET/CT. Patients with historical radiologic evidence of parenchymal disease involvement (either HRCT or historical chest x-ray) can be used for eligibility, allowing the HRCT baseline assessment to be performed along with [F-18]FDG-PET/CT on same visit day without waiting for HRCT screening result.

8.5.2.1 [F-18] FDG-PET/CT

In this study, [F-18]FDG-PET/CT imaging will provide early evidence for anti-inflammatory effects of IL-1β blockade by ACZ885 on the sarcoidosis process. [F-18]FDG-PET/CT has been shown to detect lung parenchymal involvement at any chest x-ray (CXR) stage, including therapy-resistant disease, and can also provide information on extra-pulmonary disease. Lung fluorodeoxyglucose (FDG) uptake in sarcoidosis has been shown by PET imaging to correlate with important sarcoidosis BAL biomarkers, including percentage neutrophils and CD4:CD8 ratio. In two previous sarcoidosis trials, the [F 18]FDG-PET/CT endpoint was shown to be decreased by 53-55% on treatment (Keijsers et al 2008; Milman et al 2012). Improvements in FVC over a 24 week period have been correlated with decreases in [F-18]FDG-PET/CT compared to baseline, with evidence of improvement by serial [F-18]FDG-PET/CT detected in sarcoid patients reported as early as 1-2 months (Brudin et al 1994; Braun et al 2008; Imperiale et al 2013). Furthermore, [F-18]FDG-PET/CT imaging was able to predict subsequent decreases in FVC and DLco (Sobic-Saranovic et al 2013; Vorselaars et al 2015).

In this study, all patients will undergo whole-body head to mid-thigh [F-18]FDG-PET/CT imaging on a state-of-the-art, 3D PET/CT scanner with a reconstructed resolution of ≤5 mm. Subjects with glucose levels above 11 mmol/L (200 mg/dL) should have their scan delayed or be rescheduled as appropriate. The blood glucose level measured prior to the radiotracer administration should be recorded in the image transmittal form (ITF). Subjects will have the radiotracer administered through an i.v. line, whereafter they will be positioned comfortably in a supine position to rest for 60 min, while the radiotracer distributes through the body. Near the end of this 60 min rest, subjects will be asked to void their bladder prior to the scanning procedure. A whole body low-dose attenuation CT will be acquired with a whole body effective dose of 1.5 mSv. Maximum injected radioactivity dose 200 MBq will result in a whole body effective dose of 4 mSv (ICRP 2008). Higher [F-18]FDG activities may be required in large or obese patients to ensure sufficient imaging quality, but it will not exceed 350 MBq. One further imaging scan will be performed at week 12 according to the schedule on enrolled patients with results quantitatively compared to baseline findings using centralized quantitative reading. Detailed information will be provided in the Parexel Imaging Investigator SOM. Total injected activity and body weight will be recorded and used to

compute standardized uptake values. The total dose for all PET/CT scanning (excluding HRCT) in this protocol will be maximally 11 mSv, or 16 mSv in larger or obese patients requiring a higher [F-18]FDG injected dose.

8.5.2.2 Volumetric CT and HRCT

HRCT will be utilized in this study for assessing therapeutic response at Week 24.

At the time points specified in the schedule, an HRCT scan of the lung without contrast agent will be acquired at full inspiration according to parameters as listed in a separate imaging acquisition manual. In addition to the lung assessment by HRCT, Corporate Confidential Information Corporate Confidential Information and require an additional, full expiratory low-dose CT. Thus, subjects will undergo a total of 2 HRCT scans and two lower dose volumetric CT scans.

With 4 CT scans planned for subjects during this study, the total whole body effective dose per subject from the CT scanning (excluding [F 18]FDG-PET/CT) will be maximally 14 mSv. In all subjects, the baseline and follow-up HRCT scan should be performed where possible on the same scanner, although scans on the PET/CT scanner may be used if they are determined to be comparable with follow-up scans on a different scanner.

8.5.3 Six-minute walk test (6MWT)

The 6-minute walk test (6MWT) is a simple, economical and reproducible test that measures how many meters a person can walk in 6 minutes. Repeated measurement of the 6MWT over time has been used in studying numerous musculoskeletal, pulmonary, and cardiovascular conditions and is a validated outcome in investigational drug trials.

Patients will be instructed by the test administrator using a script and established testing protocol. The testing should be conducted on an individual basis (patient and testers) with no additional audience or support other than that of the trained personnel conducting the test. If a walking aid is required at baseline, patients will be asked to use the least assistive walking aid that in their opinion will enable them to complete the 6MWT safely. Patients should be encouraged to use the same walking aid when performing all tests throughout the study.

A change in walking aid to perform the test is permitted if required for safety reasons (e.g., deterioration of balance). The testing should occur at approximately the same time of the day as the baseline assessment to prevent any possible diurnal variations. The same test administrator should perform all repeat tests on a patient whenever possible to reduce technician-related differences in test performance.

In circumstances where the test is interrupted for reasons other than patient fatigue the test may be repeated once, preferably on the same day (with a minimum 60 minute rest period). If re-testing on the same day is not possible, the test may be repeated as soon as possible, but within 2-3 days of the original attempt.

Patients resting values of oxygen saturation (%), heart rate (bpm), and Borg Questionnaire score will be recorded before the test. Oxygen saturation (%), heart rate (bpm), distance walked (meters), and Borg Questionnaire score will be recorded at the end of the 6MWT. Requirement of rescue medications, including supplemental oxygen therapy, and any adverse events occurring during the 6MWT will be recorded. If a patient is on chronic oxygen therapy,

supplemental oxygen will be allowed during the 6MWT; however, the same level/rate of supplemental oxygen should be maintained through the initial 6MWT and all subsequent trials. Complete details of course set-up, test administration, equipment and recording into the eCRF are described in the Site Operations Manual.

8.5.4 Serum IL-1β

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8.5.5 Pulmonary function testing

For details on pulmonary function testing please refer to below sections and the Biomedical Systems Centralized Spirometry, DLco and Lung Volumes Procedure Manual.

8.5.5.1 Diffusing Capacity (DL_{CO})

Diffusion capacity for carbon monoxide (DL_{CO}) will be determined according to ATS guidelines (MacIntyre et al 2005). Measurements will include DL_{CO} and alveolar volume (V_A). DL_{CO} is determined by measuring the uptake of carbon monoxide from the lung over a breath-holding period. V_A represents an estimate of lung gas volume into which CO is distributed and then transferred across the alveolar capillary membrane making it critical in the measurement of DL_{CO}. V_A is typically measured simultaneously with CO uptake by calculating the dilution of an inert tracer gas (e.g., argon, methane, or helium). In normal subjects, the sum of V_A and V_D (dead space volume) closely matches the total lung capacity (TLC) determined by plethysmography. However, in cases of poor gas mixing in patients with obstructed airways, tracer gas dilution is markedly reduced leading to V_A values that are significantly less than those expected based on actual total thoracic gas volumes. Additional information for obtaining DL_{CO} is provided in the Pulmonary Function Tests Manual.

8.5.5.2 Lung Volumes

A body plethysmograph will be used to measure Functional Residual Capacity (FRC), Inspiratory Capacity (IC), Total Lung Capacity (TLC), and Residual Volume (RV). All plethysmography evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of the measurement of lung volumes (Wanger et al 2005). Additional information for conduct of plethysmography will be provided in the Biomedical Systems Centralized Spirometry, DLco and Lung Volumes Procedure Manual.

8.5.5.3 Spirometry

Spirometry testing will be performed according to the American Thoracic Society guidelines (Miller et al 2005a; Miller et al 2005b) at screening to assess patients' eligibility for the study and as detailed in the assessment schedule. Eligibility criteria are based on FVC in percent of predicted, stratified by gender, age, height, and race (Pellegrino et al 2005).

The spirometry equipment used during the trial must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guidelines (Miller et al 2005b).

The same spirometry equipment should be used for all assessments performed by a subject. A limited number of staff, as designated by the investigator, will evaluate all patients at all visits throughout the entire trial. Where possible the same technician should perform all maneuvers for an individual subject. All staff conducting the spirometry tests must have received appropriate training, which must be documented.

Results from FVC, FEV1, FEV3 and FEV6 tests are highly dependent on effort and cooperation from the subject. Thus, throughout the maneuver, enthusiastic coaching of the subject is required.

All clinic visits will start in the morning. The following spirometry measurements will be taken: forced vital capacity (FVC); absolute and FVC% (forced vital capacity, expressed as a percentage of the normal expected value) and forced expiratory volume in one second (FEV1). Additional spirometry data to be captured include FEF25-75, FEV1/FVC, FEV3/FVC and FEV6.

For all clinic spirometry assessments, three acceptable maneuvers should be performed for each time-point. All spirometry maneuvers should be performed in sitting position whilst wearing nose clips. The FEV_1 and FVC values recorded in the CRF must be the highest values measured irrespective of whether or not they occur on the same curve. All displaceable volumes will be reported in liters (L) at the following conditions: normal body temperature (37° C), ambient pressure, saturated with water vapor (BTPS).

Additional information for conduct of spirometry evaluations is provided in the Biomedical Systems Centralized Spirometry, DLco and Lung Volumes Procedure Manual.

8.5.5.4 Spirometry Reversibility Test

Two spirometry evaluations will be performed at Visit 101 and Visit 107, the first prior to use of salbutamol/albuterol, the second performed after intake of salbutamol/albuterol. The initial spirometry assessment will be performed after a wash-out period of at least 6 hours for a short-acting β-2 agonist and at least 48 hours for a long acting β-2 agonist. After the initial spirometry assessment salbutamol/albuterol is administered, and the second spirometry assessment is performed within 30 min of administration. Investigators should follow the reversibility procedures cited in the ATS/ERS guidelines above with regard to bronchodilator use. The primary spirometry readout will be the post-bronchodilator FVC.

Reversibility (%) will be calculated as follows:

(FEV1 (post bronchodilator) – FEV1 (pre-bronchodilator) x 100)/FEV1 (pre-bronchodilator)

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the Assessment Schedule detailing when each assessment is to be performed.

8.6.1 Physical examination

See the Site Operations Manual for details.

8.6.2 Vital signs

- Blood pressure (BP)
- Pulse
- Body temperature (same method of measurement should be used throughout study)

8.6.3 Height and weight

- Height
- Body weight

8.6.4 Laboratory evaluations

In the case where a laboratory assessment that is listed in the inclusion/exclusion criteria is outside of a protocol-specified range at screening and/or at the initial baseline, the assessment may be repeated once prior to randomization. If the repeat value remains outside of protocol-specified ranges, the subject is excluded from the study.

In the case where a laboratory range is not specified by the protocol, but is outside the reference range for the laboratory at screening and/or initial baseline, a decision regarding whether the result is of clinical significance or not shall be made by the investigator and shall be based, in part, upon the nature and degree of the observed abnormality. The assessment may be repeated once prior to randomization.

In all cases, the investigator must document in the source documents the clinical considerations (i.e., result was/was not clinically significant and/or medically relevant) in allowing or disallowing the subject to continue in the study.

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differentials (e.g., neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured.

Clinical chemistry

Albumin, alkaline phosphatase (ALP), total bilirubin, bicarbonate/CO2, calcium, cholesterol, chloride, creatinine, CK, γ-GT, glucose, LDH, inorganic phosphorus, lipase, amylase, magnesium, potassium, total protein, AST, ALT, sodium, triglycerides, urea/BUN and uric acid.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

Urinalysis

A semi-quantitative "dipstick" evaluation for the following parameters will be performed: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

Microscopy, WBC, RBC and casts will also be assessed in case of an abnormal dipstick test.

8.6.5 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

- PR interval, QRS duration, heart rate, RR, QT, QTc

The Fridericia QT correction formula (QTcF) calculated with the RR interval expressed in seconds should be used for clinical decisions.

Clinically significant abnormalities should be recorded on the relevant medical history/current medical conditions CRF page prior to informed consent signature and on the Adverse Events page thereafter. Clinically significant findings must be discussed with the Sponsor.

8.6.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile will have pregnancy testing. See the Assessment Schedule for timing of the protocol required pregnancy testing; additional pregnancy testing may be performed to meet local requirements. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

If additional pregnancy testing is needed per local requirements, those additional results will be kept as source documentation only.

8.6.7 Immunogenicity (Anti-ACZ885 Antibodies)

To assess potential immunogenicity, serum samples for determination of anti-ACZ885 antibodies (ADA) will be collected during the study (see Assessment Schedule).

Follow instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing, and shipment.

In the case of an anaphylactic reaction occurring after injection, a sample will be taken at the time of the event and 8 weeks later. An immunogenicity positive subject at the end of the study will be followed up for three months.

Immunogenicity analytical method

An ELISA based method will be used for the detection of potential ADA formation. The detailed method description to assess immunogenicity will be described in the bioanalytical raw data of the study and in the respective Bioanalytical Data Report (BDR).

8.6.8 Local tolerability (subcutaneous injections)

Local tolerability at the sites of s.c. injections will be evaluated by the investigator. Any local reactions should be observed until they have disappeared. An assessment of severity (i.e., none, mild, moderate, severe) of the following signs and symptoms: pain, redness, swelling, induration, hemorrhage and itch, and the exact location of any local reaction will be recorded in the eCRF.

8.7 Pharmacokinetics

PK samples will be collected at the timepoints defined in the Assessment Schedule according to the instructions outlined in the Central Laboratory Manual regarding sample collection, numbering, processing and shipment. See Section 8.9 regarding the potential use of residual samples.

In order to better define the PK profile, the timing of the PK sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol.

Pharmacokinetic parameters

Concentrations will be expressed in mass per volume units. Missing values or those below the limit of quantification will be indicated in the data listings and treated as zero in data presentations and calculations.

For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

A previously utilized and validated mixed effects modeling approach may be used to characterize the exposure-related PK parameters (i.e., AUC and CL) of canakinumab. These results may be reported in a separate report from the final CACZ885X2205 clinical study report.

8.8 Other assessments

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8.9 Use of residual biological samples

Residual blood and lesional biopsy samples may be used for another protocol-specified endpoint.

9 Safety monitoring

9.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign including abnormal laboratory findings, symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the study treatment are also considered an adverse event irrespective if a clinical event has occurred. See Section 9.5 for an overview of the reporting requirements.

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination finding, laboratory test finding, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver- and kidney-related events are included in Appendix 1 and Appendix 2, respectively.

Pre-existing medical conditions/diseases (i.e., Medical History(ies)) are considered AEs if they worsen after providing written informed consent.

Adverse events must be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to study treatment
3. Its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved must be reported.
4. Whether it constitutes a SAE (see Section 9.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding investigational treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g., further observation only)
- investigational treatment dosage increased/reduced
- investigational treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- hospitalization/prolonged hospitalization (see Section 9.2 for definition of SAE)

6. Its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown).

Information about common side effects already known about the investigational drug can be found in the IB. Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the investigational drug, the interventions required to treat it, and the outcome.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

9.2 Serious adverse event reporting

9.2.1 Definition of SAE

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, including planned imaging procedures.
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent form
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, e.g., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (see Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (see Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the CRF; SAEs also require individual reporting to Novartis Drug Safety & Epidemiology (DS&E) as per Section 9.2.2.

9.2.2 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Note: SAEs reported by subjects deemed to be screen failures must be reported to Novartis as outlined here with appropriate information also captured in the CRFs as specified in the Site Operations Manual.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Follow- up information provided must describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not (if applicable) and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the IB or package insert (new occurrence) and is thought to be related to the study treatment, a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an IN to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Follow the detailed instructions outlined in the Site Operations Manual regarding the submission process for reporting SAEs to Novartis. Note: SAEs must be reported to Novartis within 24 hours of the investigator learning of its occurrence/receiving follow-up information.

9.3 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Appendix 1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, ALP and γGT) to confirm elevation within 48-72 hours

These liver chemistry repeats should always be performed using the central laboratory, with the results provided via the standard electronic transfer. If results will not be available from the central laboratory within 24 hours, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results reported in the CRF.

- If the initial elevation is confirmed, close observation of the subject will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug refer to Section 7.2 (Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include:

- Repeating liver chemistry tests two or three times weekly. Testing should include ALT, AST, ALP, PT/INR, and γGT. If total bilirubin is elevated > 2 x ULN, fractionation into direct and indirect bilirubin is required. To rule out muscular origin of transaminase elevations, CPK should be measured along with liver chemistry tests. Frequency of re-testing can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic. Re-testing should be continued up to resolution.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases.
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Exclusion of underlying liver disease, as specified in Table 15-3.
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF.

9.4 Renal safety monitoring

Every renal laboratory trigger or renal event must be followed up by the investigator or designated personnel at the trial site. Recommended follow-up assessments are listed in Appendix 2.

9.5 Reporting Medication errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient/subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

All study treatment errors and uses outside of what is foreseen in the protocol will be collected in the dose administration record (DAR) CRF. Study treatment errors are only to be reported to Novartis Drug Safety and Epidemiology department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the AE CRF irrespective of the misuse/abuse being associated with an AE/SAE. In addition, all instances of misuse or abuse must be reported to Novartis Drug Safety and Epidemiology. As such, instances of misuse or abuse are also to be reported using the SAE form/CRF. Table 9-1 summarizes the reporting requirements.

Table 9-1 Summary of reporting requirements for medication errors

Treatment error type	Document in Dose Administration (DAR) CRF	Document in AE CRF	Complete SAE form/CRF
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see Section 9.1 and Section 9.2, respectively.

9.6 Pregnancy reporting

To ensure patient safety, each pregnancy in a subject on study drug must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The study drug must be discontinued, though the subject may stay in the study, if she wishes to do so. All assessments that are considered as a risk during pregnancy must not be performed. The subject may continue all other protocol assessments.

Pregnancy must be recorded on a Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatments.

Any SAE experienced during pregnancy and unrelated to the pregnancy must be reported on an SAE Report Form.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.7 Early phase safety monitoring

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

10 Data review and database management

10.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

10.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the Investigator will receive copies of the subject data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and Assessment schedule and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

10.3 Database management and quality control

The CRO, working on behalf of Novartis, reviews the data entered into the eCRFs by investigational staff for completeness and accuracy and instructs the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Imaging-related data will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes and data in reference to dispensing of study drug(s) to the subject and all IRT recorded dosage changes will be tracked using Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the COAR Analytics NIBR Franchise Head and the relevant NIBR TA Head.

DNA samples (optional):

To maximize confidentiality, all samples and the information associated with these samples will be double-coded to prevent the exposure of the subject's identity. This double-coding process allows Novartis to go back and destroy the sample at the subject's request. In addition, sample information is stored in one secured database while genetic data is stored in an independent, secured database.

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

10.5.1 Infection Adjudication Committee

An independent Infection Adjudication Committee (IAC) has been formed on a program level and will review pertinent data from this trial.

The mission of the IAC is to independently and blindly review, evaluate and categorize reports of serious infection events across all potential indications and therapeutic areas in the canakinumab development program.

The members and procedures of the IAC are detailed in the IAC Charter.

10.5.2 Malignancy Adjudication Committee

An independent Malignancy Adjudication Committee (MAC) has been formed on a program level and will review pertinent data from this trial.

The mission of the MAC is to independently and blindly review, evaluate and categorize reports of malignancy events across all potential indications and therapeutic areas in the canakinumab development program.

The members and procedures of the MAC are detailed in the MAC Charter.

11 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

11.1 Analysis sets

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects that received any study drug and that have no protocol deviations with relevant impact on PD data.

11.2 Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, and any other relevant information will be listed by treatment group and subject.

11.3 Treatments

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

11.4 Analysis of the primary variable(s)

The primary aim of the study is to compare the effect of ACZ885 versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in the percent predicted FVC at week 24.

11.4.1 Variable(s)

The primary variable will be the change from baseline in percent predicted FVC after 24 weeks of treatment.

11.4.2 Statistical model, hypothesis, and method of analysis

The change from baseline in percent predicted FVC will be analyzed using a Bayesian model for repeated measurements. The model will investigate effects for treatment by time (included as a class variable) interaction, baseline by time interaction and PET positivity (yes/no) prior to randomization. Uninformative priors will be utilized to obtain the posterior estimates.

The posterior probability that ACZ885 is better than placebo in terms of change from baseline in percent predicted FVC at 24 weeks will be calculated. If it is at least 90%, it will be considered a sign of efficacy of ACZ885 in increasing FVC after 24 weeks of treatment in this patient population.

At the interim analysis, the posterior probability that ACZ885 is worse than placebo in terms of change from baseline in percent predicted FVC at week 12 will be calculated. If it is at least 60%, the study may be stopped for futility.

11.4.3 Handling of missing values/censoring/discontinuations

The primary analysis will consider patients with partial data (for instance without a 24 week assessment but with at least one post baseline assessment available). Estimates of the missing values will be derived by the model that are valid under the missing at random (MAR) assumption.

11.4.4 Sensitivity analyses

Not applicable.

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

11.5.1.1 [F-18]

The [F-18]FDG-PET/CT imaging data will be analyzed to identify the max standardized uptake values in the following categories:

- A maximum of 5 focal nodal uptake regions (mediastinal, hilar)
- A maximum of 5 focal regions of uptake in lung parenchyma
- A maximum of 5 extra-thoracic focal uptake regions on the whole body scan

[F-18]FDG-PET/CT mean

- A region of lung parenchyma, unaffected by focal lesion uptake

The mean of the SUVmax (resp. SUVmean) for each category will be taken to obtain one SUVmax value (resp. SUVmean) per patient / time point / category.

The mean percent change from baseline in SUVmax in the nodules after 12 weeks of treatment will be analyzed using ANCOVA with baseline SUVmax as a covariate and treatment and PET positivity (yes/no) as factors.

The same analysis as for the percent change from baseline in SUVmax in the nodules will be performed for the percent change from baseline in SUVmax in the lung parenchyma and the extra-thoracic regions, where available. It will also be repeated for SUVmean in the parenchyma.

The percentage of patients with at least 50% reduction of SUVmax in nodules will be analyzed via logistic regression with baseline SUVmax as a covariate and treatment and PET positivity (yes/no) as factors.

Also the change in the individual lung nodules will be examined, using a discretized scale of complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) as in the oncology European Organization for Research and Treatment of Cancer criteria for [F-18]FDG-PET/CT. The proportion of individual responders and non-responders will be determined, based on PET. Patients who discontinue for lack of efficacy will be treated as a separate category in this summary.

The correlation between changes from initial FDG-PET scan in SUVmax and changes from baseline in FVC, FEV1, COAs, 6MWT distance will be assessed with graphical methods.

11.5.1.2 High resolution computed tomography (HRCT)

Change in HRCT scoring from initial scan to 24 weeks will be analyzed, using a regression model with baseline HRCT score as a covariate and treatment and PET positivity (yes/no) as factors. The HRCT scans will be evaluated using an HRCT scoring system quantifying various features such as: BVB: thickening or irregularity of the bronchovascular bundle; PC: parenchymal consolidation (including ground-glass opacifications); ND: intraparenchymal nodules; LS: septal and nonseptal lines; PL: focal pleural thickening; LN: enlargement of the mediastinal lymph nodes. The score for the lung will be determined using a scoring system similar to previous published literature (Oberstein et al 1997; Ors et al 2013).

In addition, HRCT results will be evaluated for worsening, improvement, or stable outcome by 2 blinded assessors in side-by-side comparison. Results will be summarized in a shift table.

11.5.1.3 Other secondary variables

Data from other pulmonary function tests and 6MWT will be listed and summarized. Graphical representations of the pulmonary function test endpoints over time will be presented.

11.5.2 Safety

11.5.2.1 Vital signs

All vital signs data will be listed by treatment, subject, and visit and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit.

11.5.2.2 ECG evaluations

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit.

11.5.2.3 Clinical laboratory evaluations

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

11.5.2.4 Adverse events

All information obtained on adverse events will be displayed by treatment and subject. The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

11.5.3 Pharmacokinetics

11.5.4 Pharmacokinetic/pharmacodynamic interactions

The relationship between PK and efficacy/PD parameters may be investigated using graphical methods and simple regression models.

11.5.5 Other assessments

Not applicable.

11.6 Analysis of exploratory variables

Statistical analysis for exploratory variables will be described in the statistical analysis plan.

11.6.1 Exploratory biomarkers

11.7 Sample size calculation

The sample size is determined by calculations with respect to the Bayesian analyses (Fisch et al 2014) (based on uninformative priors) of the change from baseline in the percent predicted FVC after 24 weeks of treatment. With 15 patients per group providing data at week 24 and assuming a standard deviation of 9% (Judson et al 2014), there is approximately 80% power to meet the efficacy criterion, if the true effect of ACZ885 over placebo is 7%.

Under the same assumption for the standard deviation, there is l0% probability of meeting the efficacy criterion if the true treatment difference is 0% (type I error rate).

11.8 Power for analysis of key secondary variables

Not applicable.

11.9 Interim analyses

Corporate Confidential Information

12 Ethical considerations

12.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming

his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

12.3 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

13 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented.

13.1 Protocol Amendments

Any change to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, provided the Health Authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 9 (Safety Monitoring) must be followed and the Study Lead informed.

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15 Appendix 1: Liver Event definitions and follow-up requirements

Table 15-1 Liver Event definitions

Definition	Thresholds
Potential Hy's law cases	• ALT or AST > 3 × ULN and TBL > 2 × ULN without initial increase in ALP to > 2 × ULN
ALT or AST elevation with coagulopathy	• ALT or AST > 3 × ULN and INR > 1.5 (in the absence of anticoagulation)
ALT or AST elevation accompanied by symptoms	• ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash, or eosinophilia
Isolated ALT or AST elevation	• ALT or AST > 8 × ULN • 5 x ULN < ALT/AST ≤ 8 x ULN • 3 x ULN < ALT/AST ≤ 5 x ULN
Isolated ALP elevation	• ALP > 2 × ULN (in the absence of known bone pathology)
Others	• Any clinical event of jaundice (or equivalent term) • Any adverse event potentially indicative of liver toxicity

Table 15-2 Actions required for Liver Events

Criteria	Actions required
Potential Hy's Law case	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance
ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	
Isolated ALT or AST elevation > 5 to ≤ 8 × ULN	• If confirmed, consider interruption or discontinuation of study drug • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Complete CRFs per liver event guidance
Isolated ALT or AST elevation > 3 to ≤ 5 × ULN (patient is asymptomatic)	• Monitor liver chemistry tests two or three times weekly

Criteria	Actions required
Isolated ALP elevation	• Repeat liver chemistry tests within 48-72 hours • If elevation is confirmed, measure fractionated ALP; if >50% is of liver origin, establish hepatic causality • Complete CRFs per liver event guidance
Any AE potentially indicative of liver toxicity	• Consider study treatment interruption or discontinuation • Hospitalize if clinically appropriate • Complete CRFs per liver event guidance

Table 15-3 Exclusion of underlying liver disease

Disease	Assessment
Hepatitis A, B, C, E	• IgM anti-HAV; HBSAg, IgM anti-HBc, HBV DNA; anti-HCV, HCV RNA, IgM & IgG anti-HEV, HEV RNA
CMV, HSV, EBV infection	• IgM & IgG anti-CMV, IgM & IgG anti-HSV; IgM & IgG anti-EBV
Autoimmune hepatitis	• ANA & ASMA titers, total IgM, IgG, IgE, IgA
Alcoholic hepatitis	• Ethanol history, gGT, MCV, CD-transferrin
Nonalcoholic steatohepatitis	• Ultrasound or MRI
Hypoxic/ischemic hepatopathy	• Medical history: acute or chronic CHF, hypotension, hypoxia, hepatic venous occlusion. Ultrasound or MRI.
Biliary tract disease	• Ultrasound or MRI, ERCP as appropriate.
Wilson disease	• Caeruloplasmin
Hemochromatosis	• Ferritin, transferrin
Alpha-1-antitrypsin deficiency	• Alpha-1-antitrypsin

16 Appendix 2: Specific Renal alert criteria and actions

Table 16-1 Specific Renal alert criteria and actions

Criteria	Action required
Serum creatinine (sCr) increase 25 – 49% compared to baseline	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider hospitalization and specialized treatment
Protein-creatinine or albumin-creatinine ratio increase ≥ 2-fold or new onset dipstick proteinuria ≥ 1+ or Albumin-creatinine ratio (ACR) ≥ 30 mg/g or ≥ 3 mg/mmol; or Protein-creatinine ratio (PCR)≥ 150 mg/g or >15 mg/mmol	• Consider causes and possible interventions • Assess serum albumin & serum protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset glucosuria on urine dipstick (unless related to concomitant treatment, diabetes)	Assess & document: • Blood glucose (fasting) • Serum creatinine • Urine albumin-creatinine ratio
New hematuria on dipstick	Assess & document: • Urine sediment microscopy • Assess sCr and urine albumin-creatinine ratio • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

Additional specialized assessments are available to assess renal function or renal pathology. (Note: In exceptional cases when a nephrologist considers a renal biopsy, it is strongly recommended to make specimen slides available for evaluation by Novartis to potentially identify project-wide patterns of nephrotoxicity.)

Whenever a renal event is identified, a detailed subject history and examination are indicated to identify, document and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5 min rest, with an appropriate cuff size)
- Signs and symptoms such as fever, headache, shortness of breath, back or abdominal pain, dysuria, hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other potential causes of renal dysfunction, e.g., dehydration, hemorrhage, tumor lysis

Table 16-2 Follow-up of renal events

Action	Follow up
Assess*, document and record in the Case Report Form (CRF) or via electronic data load. Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc) in the CRF.	• Urine dipstick and sediment microscopy • Blood pressure and body weight • Serum creatinine, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Monitor subject regularly (frequency at investigator's discretion) until:	• Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.

*Urine osmolality: in the absence of diuretics or chronic kidney disease this can be a very sensitive metric for integrated kidney function that requires excellent tubular function. A high urinary osmolality in the setting of an increase in sCr will point toward a "pre-renal" cause rather than tubular toxicity.