NOVARTIS

Novartis Institutes for BioMedical Research

CMK389

Clinical Trial Protocol CCMK389X2201 / NCT04064242

A subject and investigator blinded, randomized, placebo-controlled, repeat-dose, multicenter study to investigate efficacy, safety, and tolerability of CMK389 in patients with chronic pulmonary sarcoidosis

Document type:	Amended Protocol Version
EUDRACT number:	2018-000381-11
Version number:	v08 (Clean)
Clinical Trial Phase:	II
Release date:	23-Jun-2022

Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct. Note: The SOM will not form part of the Clinical Study Report.

Notification of serious adverse events

Dear Investigator,

You must report a serious adverse event (SAE) (initial or follow-up) to Novartis as summarized below. Refer to Section 9.2 of the protocol for SAE criteria and additional requirements. See also page 2 of the Site Operations Manual (SOM) for further details on the method of reporting a SAE.

- Complete SAE report
- Submit SAE report to Novartis Chief Medical Office and Patient Safety (CMO&PS) **within 24 hours after awareness of the SAE**
- Notify the Novartis Medical Lead
- The fax number(s) and email address(es) are located in the SOM.

Table of contents

Commercially Confidential Information (CCI)

Commercially Confidential Information

Commercially Confidential Information

List of tables

Commercially Confidential Information

List of figures

List of abbreviations

6MWD	6-minute walk distance
6MWT	6-minute walk test
[^{18}F]FDG	fluorine-18 fluorodeoxyglucose
ADA	Anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS	American Thoracic Society
BMI	Body Mass Index
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulation
CK	creatinine kinase
CMO&PS	Chief Medical Office & Patient Safety
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSD	Clinical Status Determination
CSE	Clinical Status Evaluation
DAR	dose administration record
DLCO	Diffusion capacity of the lung for carbon monoxide
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
EOS	end of study
ERS	European Respiratory Society

FDA	Food and Drug Administration
FEV1	forced expiratory volume in one second
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
h	hour
HBsAG	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HRCT	high resolution computed tomography

i.v.	intravenous
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IG	immunogenicity
IgG1-LALA	human immunoglobulin IgG1 with fragment crystallizable region substitutions at leucine (L) $_{234}$ to alanine (A) and L_{235} to A
INR	International Normalized Ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine system
Commercially Confidential Information	
LDH	lactate dehydrogenase
Commercially Confidential Information	
MAR	missing at random
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
Commercially Confidential Information	
NCG	Non-caseating granuloma
NGS	Next Generation Sequencing
NIRT	Novartis Interactive Response Technology
NOAEL	no-observed-adverse-effect-level
PD	pharmacodynamic(s)
PET/CT	positron emission tomography/computed tomography
PFT	Pulmonary Function Test
PK	pharmacokinetic(s)
Commercially Confidential Information	
QTcF	Fridericia QT correction formula
RBC	red blood cell(s)
RoW	Rest of world
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
SUVmax	maximum standardized uptake value
SUVmean	mean standardized uptake value
TB	tuberculosis
TBL	total bilirubin

TCR	T cell receptor
ULN	upper limit of normal
ULOQ	upper limit of quantification
VA	Volume alveolar
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
WOCBP	Women of childbearing potential

Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma (or serum or blood) concentration-time curve from time zero to time 't' where t is a defined time point after administration [mass x time / volume]
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
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]
Ctrough	The lowest concentration reached by a drug before the next dose is administered
t1/2	the terminal elimination half-life [time]
Tmax	The time to reach the maximum concentration after drug administration [time]

Glossary of terms

Assessment	A procedure used to generate data required by the study
Control drug	A study drug (active or placebo) 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
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, and treatment follow-up) which applies across all arms of a study.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Patient	An individual with the condition of interest
Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Randomization number	A unique identifier assigned to each randomized subject
Run-in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's intervention or other treatment)
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.

Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer and does not allow any further collection of personal data

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

Protocol summary

Protocol number	CCMK389X2201
Full Title	A subject and investigator blinded, randomized, placebo-controlled, repeat-dose, multicenter study to investigate efficacy, safety, and tolerability of CMK389 in patients with chronic pulmonary sarcoidosis
Brief title	Study of efficacy, safety and tolerability of CMK389 in patients with chronic pulmonary sarcoidosis
Sponsor and Clinical Trial Phase	Novartis Phase II
Intervention type	Biologic
Study type	Interventional
Purpose and rationale	The purpose of this proof-of-concept study is to determine whether CMK389 displays the safety and efficacy profile to support further development in chronic pulmonary sarcoidosis
Primary Objective(s)	To assess the efficacy of CMK389 in subjects with chronic pulmonary sarcoidosis by looking at the change from baseline to end-of-treatment (16 weeks of treatment) in forced vital capacity (FVC)
Secondary Objectives	To assess the impact of CMK389 on a composite index of pulmonary physiology and exercise capacity from baseline to end-of-treatment To assess the safety and tolerability of CMK389 by evaluating adverse events, vital signs and routine safety laboratory results from baseline to end-of treatment To explore the impact of CMK389 observed with [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]-FDG-PET/CT) imaging (SUVmax and SUVmean) from baseline to week 16 To assess the impact of CMK389 on forced expiratory volume in one second (FEV1) and diffusion capacity (DLCO) between baseline and week 16 To assess the impact of CMK389 on 6 min walk distance between baseline and week 16 To assess the impact of CMK389 on steroid use (mg-days) for each arm between baseline and end-of-treatment To assess the pharmacokinetics of CMK389 after multiple doses in sarcoidosis patients at times specified at doses 1, 2, 3 and 4
Study design	This is a subject and investigator blinded, randomized, placebo-controlled, parallel-group, repeat-dose, multicenter, non-confirmatory study of the safety and efficacy of CMK389 administered intravenously every 4 weeks for a total of 4 doses in chronic pulmonary sarcoidosis patients. Approximately 66 patients will be randomized in a 1:1 ratio to receive either CMK389 or placebo. The expected total duration of participation for men and women of non-childbearing potential is approximately 38 weeks. For women of childbearing potential the expected duration of participation is approximately 46 weeks
Population	This study will recruit male and female patients 18 to 75 years of age with biopsy proven chronic pulmonary sarcoidosis diagnosed for > 1 year

Key Inclusion criteria	• Written informed consent must be obtained before any assessment is performed • Subjects must have a body mass index (BMI) at screening within the range of 18 - 46 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2 • Pulmonary Sarcoidosis present > 1 year prior to screening with a historical biopsy (from any organ or body part) confirming diagnosis prior to screening • Scadding stage II, III or IV as determined by the most recent chest x-ray obtained within 12 months prior to screening or at screening • HRCT extent of fibrosis <20% (confirmed by the central imaging reader) • Treatment with 5-15 mg/day prednisone (or prednisone equivalents) for ≥ 6 consecutive months prior to screening and with a minimum of 80% compliance with treatment each month as determined by the investigator. • Co-medication with methotrexate or azathioprine for ≥ 6 consecutive months prior to screening and with a minimum of 80% compliance with treatment each month as determined by the investigator (Note: hydroxychloroquine is allowed as background therapy but not required) • Able to perform reliable, reproducible pulmonary function test maneuvers per American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines
Key Exclusion criteria	• Diagnosis of significant pulmonary hypertension (WHO group 5) requiring pharmacological treatment • Active cardiac sarcoidosis requiring treatment. Inactive cardiac sarcoidosis or stable cardiac sarcoidosis not requiring treatment are permissible. • A known diagnosis of neurosarcoidosis • Forced vital capacity (FVC) <50% of predicted at screening (central read) • Modified British Medical Research Council (mMRC) dyspnea scale $\geq$ 3 at screening • Concomitant treatment with leflunomide, cyclophosphamide, mycophenolate, infliximab, etanercept, adalimumab, golimumab, ustekinumab, roflumilast, pentoxifylline, and abatacept within 12 weeks of screening. • Prior treatment with rituximab, canakinumab, anakinra, and tocilizumab • Current smokers, defined as inhaled use of tobacco products • Any conditions or significant medical problems which, in the opinion of the investigator in consultation with the sponsor, immunocompromises the patient and/or places the patient at unacceptable risk for immunomodulatory therapy • Contraindication to FDG-PET scan investigations such as severe claustrophobia or uncontrolled diabetes • History or current diagnosis of ECG abnormalities indicating significant risk of safety for patients participating in the study. • A diagnosis of Lofgren's syndrome • A history of pancreatitis • Other pulmonary disease (i.e., asthma, bronchiectasis, COPD, etc.) unrelated to sarcoid as determined by the investigator

Study treatment	• Two treatment arms in a ratio of 1:1: CMK389 versus placebo-controlled dose group
Pharmacokinetic assessments	• Serum CMK389 concentrations
Efficacy/PD assessments	• Spirometry • DLCO • Six-minute walk test • [^{18}F]FDG-PET/CT • mMRC dyspnea scale
Key safety assessments	• Physical examination, including vital signs and height/weight • Hematology, clinical chemistry, urinalysis • Electrocardiogram (ECG) • Serious Adverse Events and Adverse Events • 2-hour post-dose observation period for monitoring of acute infusion or hypersensitivity reactions.
Other assessments	Commercially Confidential Information
Data 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 FVC by time interaction, prior sarcoidosis immunosuppressant therapy (stratification factor) and baseline prednisone dose. The correlation among the repeated measures collected on the same subject will be assessed via an unstructured covariance matrix. The stratification factor may be removed in case of strata with low sample sizes impacting on the convergence of the model. Uninformative priors will be utilized to obtain the posterior estimates. Baseline is defined as Day 1. The posterior probability that CMK389 is better than placebo in terms of change from baseline in percent predicted FVC at 16 weeks will be calculated. If it is at least 90%, it will be considered a sign of efficacy of CMK389 in this patient population. Commercially Confidential Information
Key words	Chronic pulmonary sarcoidosis

1 Introduction

1.1 Background

Unmet Medical Need

Sarcoidosis is a multi-system inflammatory disease of unknown etiology characterized by the formation of non-caseating granulomatous (NCG) inflammation in various organs. NCG contain a core of monocyte-derived epithelioid histiocytes and multi-nucleated giant cells; the outer rim consists of CD4+T cells, regulatory T cells, B cells and fibroblasts (Dastoori et al 2013; Newman 2000).

The incidence of sarcoidosis in the U.S. has been estimated at 10-36/100,000; with variability dependent upon ethnic background. U.S. mortality increased by 3% per year, during the period between 1988 and 2007; with the primary causes of morbidity and mortality being pulmonary hypertension, pulmonary fibrosis and heart failure (secondary to sarcoidosis) (Chen and Moller 2011). The overall risk of death from sarcoidosis in the U.S. is 8%; mortality rates are 10-fold higher in African-Americans and Asians, as compared to Caucasians.

Sarcoidosis most often impacts the lungs, skin or eyes; but may affect other tissues and organ systems. In two-thirds of cases, sarcoidosis presents as an asymptomatic, self-limited disease, incidentally detected on a routine chest radiograph; in such cases, complete remission of sarcoidosis is typically observed within the first 2 years after diagnosis (Iannuzzi et al 2007). The remainder of patients with sarcoidosis develops a persistent form of the disease that can last for 2 or more years; spontaneous remission is rare within this cohort. Spontaneous remission is even rarer in patients who present with cutaneous sarcoidosis, sinus manifestations, or fibrotic lung changes.

Currently, there are no FDA/EMA-approved therapies for sarcoidosis. Standard therapy consists of non-specific immunosuppression with corticosteroids and/or a cytotoxic agent (such as methotrexate or azathioprine). However, the benefit of these interventions has not been fully proven by randomized-controlled interventional studies (Chen and Moller 2011). Additionally, such non-specific immunosuppressant agents carry the burden of severe adverse reactions associated with chronic administration and the long-term benefit remains unclear.

In addition, rigorous evaluations of anti-TNF agents in the treatment of sarcoidosis have shown mixed results and their utility in the treatment of this disease remains in question (Baughman et al 2006; Utz et al 2003). Recent investigation of an anti-IL-12/23 mAb (Benson et al 2011) demonstrated a lack of efficacy (Baughman et al 2013; Judson et al 2013).

Rationale for IL-18 Antagonism in Sarcoidosis

The etiology of sarcoidosis is poorly understood. However, the oligoclonal, restricted T cell receptor (TCR) rearrangement of T cells in sarcoidosis suggests response to a “specific” antigen. It has been suggested that sarcoidosis is triggered by serum amyloid A (AA) in response to mycobacterial infection (Chen and Moller 2011; Gupta et al 2012); other possible triggers include common bacterial, viral or fungal infections; dusts and metals. Granulomatous inflammation develops around the nidus of antigenic material (e.g., serum amyloid, bacteria, etc.). In response, the innate immune cells engulf, then display, the antigenic material on the

surface of MHC class I and class II molecules. This triggers an adaptive immune system response with T cells, polarized toward the expression of T_H1-affiliated cytokines (Romagnani 2006). The T_H1-polarized cytokine response orchestrates the formation of NCG associated with sarcoidosis.

IL-18 is a pleiotropic pro-inflammatory cytokine which, in synergy with IL-12, increases IL-18 receptor expression. Activation of the IL-18 receptor by IL-18 induces MyD88, IRAK, TRAF6, NF-κB and other downstream signaling pathways that are pivotal for maximal generation of IFN-γ and induction of polarized T_H1 responses (Okamura et al 1995; Yoshimoto et al 1998).

CMK389

CMK389 is a fully human, IgG1-LALA, high affinity monoclonal antibody that has been shown to selectively bind to IL-18 and potently inhibit IL-18 activity.

CMK389 is expected to neutralize the bioactivity of IL-18, thereby reducing NCG formation and the tissue damage associated with excessive IFN-γ-driven immune responses.

Commercially Confidential Information

Thus, CMK389 is proposed for the treatment of chronic, persistent pulmonary sarcoidosis.

1.2 Nonclinical data

Commercially Confidential Information

Commercially Confidential Information

1.3 Clinical data

1.3.1 Human safety and tolerability data

Commercially Confidential Information

Commercially Confidential Information

1.3.2 Human pharmacokinetic data

Commercially Confidential Information

1.3.3 Human pharmacodynamic data

Commercially Confidential Information

1.4 Study purpose

The purpose of this proof-of-concept study is to determine whether CMK389 displays the safety and efficacy profile to support further development in chronic pulmonary sarcoidosis.

2 Objectives and endpoints

2.1 Primary objective(s)

Primary objective(s)	Endpoints related to primary objective(s)
• To assess the efficacy of CMK389 in subjects with chronic pulmonary sarcoidosis	• Change in forced vital capacity, % of predicted, (FVC%) between baseline and Week 16, between CMK389 and placebo.

2.2 Secondary objective(s)

Secondary objective(s)	Endpoints related to secondary objective(s)
• To assess the impact of CMK389 on steroid use (mg days)	• Difference in steroid usage for each arm of the study between baseline and end of treatment
• To assess the impact of CMK389 on a composite index of pulmonary physiology and exercise capacity	• Proportion of patients who deteriorate from baseline to Week 16, defined as: relative reduction in FVC ≥ 10% or relative reduction in FEV1 ≥ 10% or relative reduction of DLCO ≥ 15% or relative reduction of 6MWD ≥ 50 m

Secondary objective(s)	Endpoints related to secondary objective(s)
• To explore the impact of CMK389 observed with [^{18}F]-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]-FDG-PET/CT) imaging	• Change in [^{18}F]-FDG-PET/CT (SUVmax and SUVmean) from baseline and Week 16
• To assess the pharmacokinetics of CMK389	• Pharmacokinetic parameters (Cmax/End of infusion, Ctrough) of CMK389
• To assess the safety and tolerability of CMK389	• Adverse events, vital signs and routine safety laboratory results.
• To assess the impact of CMK389 on pulmonary physiology	• Change in forced expiratory volume in one second (FEV1) and diffusion capacity for carbon monoxide (DLCO) between baseline and Week 16
• To assess the impact of CMK389 on exercise capacity	• Change in 6-minute walk distance (6MWD) between baseline and Week 16

2.3 Exploratory objective(s)

Commercially Confidential Information

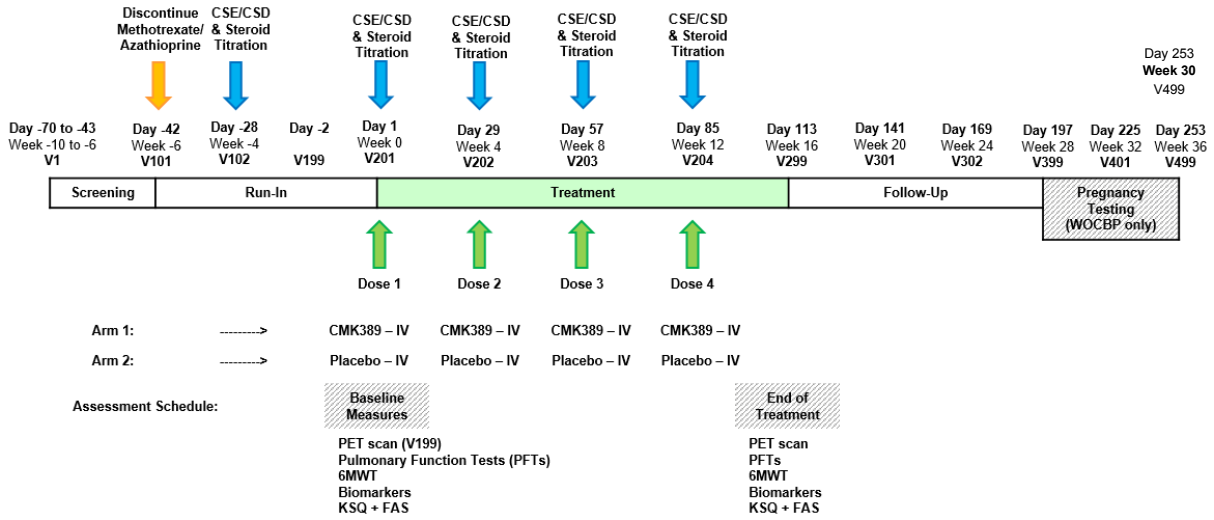
3 Investigational plan

3.1 Study design

This is a subject and investigator blinded, randomized, placebo-controlled, parallel-group, repeat-dose, multicenter, non-confirmatory study of CMK389 in chronic pulmonary sarcoidosis. This study will investigate the safety and efficacy of 10 mg/kg CMK389 administered intravenously (i.v.) every 4 weeks for a total of 4 doses, versus placebo (Figure 3-1). After obtaining signed informed consent, a screening epoch of 28 days will be used to assess subject eligibility. The population will consist of patients with biopsy-proven pulmonary sarcoidosis, in Scadding stages II, III, or IV as determined by the most recent chest

x-ray. A high resolution computed tomography (HRCT) scan (historical or performed at screening (**Day -70 to -43**)) will be reviewed to select subjects with minimal fibrosis (< 15% reticular markings on a volumetric basis). Eligible patients must be treated with 5-15 mg daily prednisone (or equivalent) and methotrexate or azathioprine for ≥ 6 months prior to screening. Hydroxychloroquine is allowed as background therapy but not required. Approximately 66 subjects will be randomized in a 1:1 ratio to receive CMK389 or placebo. Randomization will be stratified by prior sarcoidosis immunosuppressant therapy (azathioprine or methotrexate).

Figure 3-1 Study Design Schematic



Run-in Epoch

A 6-week run-in epoch will commence on **Day -42**. First, eligible patients will discontinue methotrexate and azathioprine. Hydroxychloroquine will be allowed to continue as background therapy. Then, on **Day -28** (2 weeks after discontinuation of methotrexate or azathioprine), patients will undergo a full safety assessment, a "Clinical Status Evaluation (CSE)", and enter into a steroid (prednisone or equivalent; see Table 17-1-Appendix 3) titration algorithm. CSE will consist of a 6-minute walk test, spirometry assessments, and an assessment of dyspnea (Modified Medical Research Council [mMRC] breathlessness scale). The CSE serves as an additional safety evaluation and will serve to establish the patient's current clinical status (Clinical Status Determination [CSD]) as compared to their status at Day -42 (Figure 3-2). The CSE will be performed at each subsequent visit, prior to the titration of steroids, and the CSD will guide selection of the next dose of steroids (Figure 3-3). Steroid titration will continue through the run-in epoch; and steroid titration will also continue through the treatment epoch. Patients with CSD of "improved" or "stable" will decrease steroid dose by 1-step on the dosing scale (Figure 3-4). (Note: To prevent Addisonian crisis, steroids will not be tapered below a physiologic dose (2.5 mg/day); and steroid tapering will follow a very slow regimen, as per protocol – i.e., modest decreases in dose, no more frequent than every four weeks). Patients with CSD of "deteriorating" will be ineligible to continue the study (if "deteriorating" is determined during the run-in epoch); or they will increase their steroid dose by 1-step (if "deteriorating" is

determined during the treatment epoch). [^{18}F]-FDG PET/CT will be performed prior to the first dose (**Day -2 (± 1)**) and again at the end of the treatment epoch (**Day 113**).

Figure 3-2 Clinical Status Evaluation (CSE) and Clinical Status Determination (CSD)

	Clinical Status Evaluation (CSE)		
Parameters	Change since Day -42 (V101)		
	Better	Same	Worse
6MWT	↑ 50m	Δ = ± (<50)m	↓ 50m
FVC	+10% relative Δ	-15% < relative Δ < +10%	-15% relative Δ
FEV_1	+10% relative Δ	-15% < relative Δ < +10%	-15% relative Δ
MMRC dyspnea score	-1 point	No change	+1 point

Clinical Status Determination (CSD)	Improved	Stable	Deteriorating
	3 or more parameters "Better"	Does not meet criteria for "Improved" or "Deteriorating"	2 or more parameters "Worse" or Δ MMRC is ≥ 2 points

Figure 3-3 Patient pathway as determined by clinical status

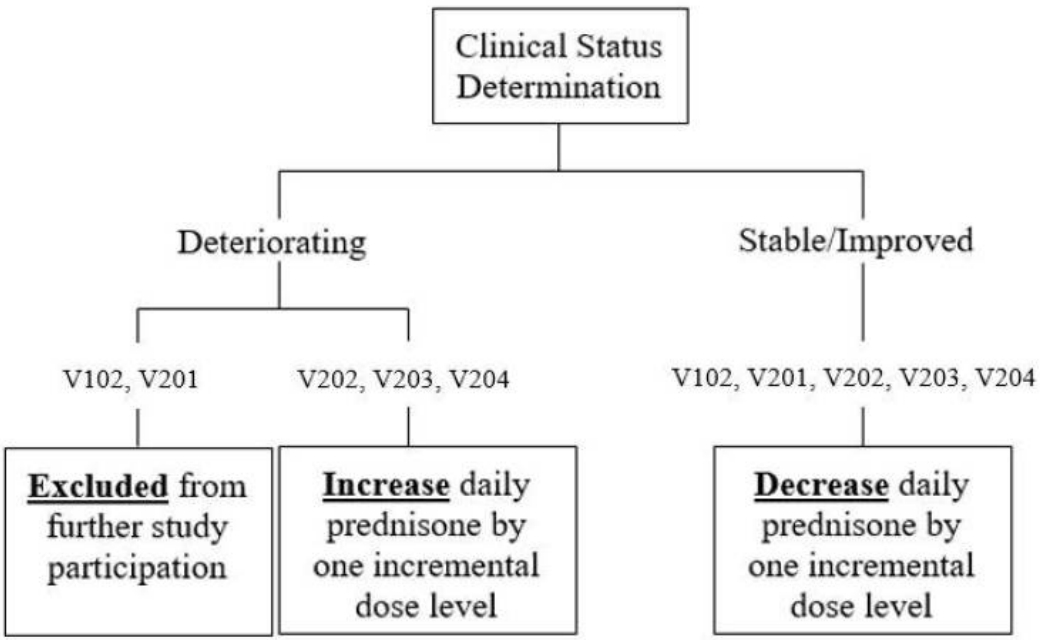


Figure 3-4 Steroid dose levels

Incremental dose-steps of corticosteroid co-medication (mg/day):

← ← ← *decreasing dose level* ← ← ←

Prednisone (equivalent)	2.5 *	5-6	7-8	9-13	14-15 *

→ → → *increasing dose level* → → →

* Prednisone (or equivalent) cannot be less than 2.5 mg/day or more than 15 mg/day during the Run-In and Treatment epochs.

Treatment Epoch

A 16-week treatment epoch will commence on Day 1. Patients with a CSD of "deteriorating" at this visit will be ineligible to continue in the study. Patients with a CSD of "improved" or "stable" will decrease steroid dose by 1-step. (Note: Steroids will not be tapered below 2.5 mg/day) Then, the patients will be randomized to receive CMK389 or placebo, stratified by prior sarcoidosis immunosuppressant therapy (Stratum 1: azathioprine or Stratum 2: methotrexate).

During the treatment epoch, steroid dose will be guided by the results of CSE/CSD (Figure 3-3). During the treatment epoch, adverse events will be monitored on an ongoing basis. Monthly visits are scheduled to assess safety and efficacy. Physical exam, vital signs, blood draw (safety labs, pharmacokinetic [PK] samples, CCI), spirometry, 6MWT, mMRC and CCI will be performed during the treatment epoch every 4 weeks or as described in the Assessment Schedule (Table 8-1).

Every effort should be put in place to adhere to this algorithm, but in cases where the Investigator feels that, during the Treatment Epoch, a subject's increase in steroids outside of the specified incremental dose-steps indicated or re-initiation of methotrexate or azathioprine is clinically indicated, this therapy can be started/adjusted. All the actual treatments should be reported in the CRF and all the PD parameters collected after therapy adjustment will be excluded from the primary analysis.

Safety Follow-up Epoch

After the treatment epoch, the safety follow-up epoch will last 12 weeks. This enables the assessment of safety in adults with sarcoidosis for ~5 half-lives following the last administration of CMK389. During the safety follow-up epoch, physical exam, adverse events, safety labs, PK and CCI samples, CCI will be collected every four weeks. During the safety follow-up epoch, treatment for sarcoidosis will be guided by the Investigator; if necessary, methotrexate and/or azathioprine may be reintroduced and corticosteroid doses may be adjusted.

Pregnancy Testing Period (WOCBP only)

Due to hypothetical effects on the fetus (see Section 3.2), WOCBP will be followed for an additional 8 weeks after EOS #1 (V399) (or 24 weeks total after their last treatment with CMK389) to ensure that they continue to use highly effective contraception.

3.2 Rationale for study design

The rationale for key elements of this study are as follows:

- **Placebo controls:** The placebo group is used to define the natural history of disease under the study's conditions. Comparison of placebo to the active group provides the most rigorous test of efficacy. Since no drugs are currently approved for the treatment of sarcoidosis, inclusion of a placebo arm is considered to be ethical; and the risk-benefit of placebo treatment is considered to be favorable. (Note: the potential benefits of alternative treatments, such as TNF inhibitors, are unproven/unknown, risk-benefit of alternative treatments are unfavorable, and such treatments are prohibited by this protocol).
- **Randomization:** Randomization is used to avoid "selection bias" in the assignment of subjects to treatment groups. Randomization also serves to balance the treatment groups with respect to many known and unknown confounding variables; and randomization forms the basis of assumptions for our statistical tests.
- **Blinding:** Conscious and unconscious biases are avoided ("detection bias" and "reporting bias", pertaining to outcome assessment) by ensuring that patients and investigators are unaware of treatment assignment.
- **Run-in epoch:** During this epoch, adjustments are made to background therapy in an effort to harmonize all the patients before commencement of the treatment epoch.
- **Discontinuation of methotrexate and azathioprine during the run-in epoch:** In clinical practice, immunosuppressants are often interrupted while the patient is closely observed for evidence of clinical change. This protocol mimics the immunosuppressant interruption that is frequently employed in clinical practice. This design allows a more robust evaluation of the efficacy of CMK389 while minimizing the potentially masking effects of immunosuppressant therapy.
- **Steroid titration algorithm:** Judicious titration of corticosteroids is common practice for a patient with sarcoidosis who is doing well; conversely, the dose of steroids is typically increased for a patient with sarcoidosis who is doing poorly. Within the context of this clinical trial, adjustment of steroids will be allowed. However, to avoid the introduction of "performance bias" by individual sites and investigators, all steroid titrations will be performed according to the rules of a pre-determined algorithm.

  To prevent Addisonian crisis, steroids will not be tapered below a physiologic dose (2.5 mg/day); and steroid tapering will follow a very slow regimen, as per protocol.
- **Pregnancy Testing Period (WOCBP only):** IL-18 is expressed at the maternal-fetal interface (Tokmadzić et al 2002) and could potentially play a role, with other cytokines, in the pro-inflammatory events of early pregnancy such as ovulation, implantation decidual remodeling and placentation as well as contributing to the pro-inflammatory response promoting parturition (Laskarin et al 2005; Wilson et al 2004). However, there is also a pathogenic role of enhanced levels of pro-inflammatory cytokines, including IL-18, in

pregnancy, with reported links to preterm labor, recurrent abortion, intrauterine growth retardation, pre-eclampsia and spontaneous fetal resorption (El-Kabarity and Naguib 2011; Chau et al 2016). IL-18 knockout mice show no alteration in litter size, sex ratio, and weight gain and no structural abnormalities (Takeda et al 1998). IL-18 knockout mice develop hyperphagy, obesity and insulin resistance at 6 months of age (Netea et al 2006), which represents a theoretical risk to the neonate, although post-natal exposure to CMK389 through maternal transfer will be much shorter duration in humans relative to lifespan than in mice. Hence CMK389 treatment could have both positive and negative impacts on pregnancy. This represents a hypothetical risk to the developing fetus.

Commercially Confidential Information

Therefore, WOCBP will be followed up to 24 weeks after their last treatment with CMK389 to ensure that highly effective contraception is used and fetal risks are avoided.

Commercially Confidential Information

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

The selection of dose, 10 mg/kg, for CMK389 is based on identification of the "maximum feasible dose",

Commercially Confidential Information

Additionally, based on the prediction of nonclinical modeling and simulation, monthly dosing at 10 mg/kg would have a near complete inhibition (>90%) of interferon gamma release in humans. Therefore, 10 mg/kg, the highest dose, is selected to maximize the chances for detecting efficacy in this proof-of-concept trial.

Monthly 10 mg/kg repeat-dosing is planned to achieve trough drug concentrations that are above (~50-fold) the EC80 (7.4 nM) of the in vitro whole blood assay for the inhibition of IFN-gamma release. Four monthly repeated doses of CMK389 at 10 mg/kg are anticipated to result in a peak concentration (~440 µg/mL)

Commercially Confidential Information

3.4 Rationale for choice of comparator

In this study, the placebo to CMK389 will be used as comparator to provide objective evidence of potential AEs and other safety data as well as clinical efficacy and PD data generated from patients exposed to CMK389.

3.5 Rationale for choice of background therapy

There are no FDA/EMA-approved therapies for sarcoidosis. It is common practice for patients to be treated with non-specific immunosuppressants: corticosteroids, with or without the

addition of a cytotoxic agent (such as methotrexate, azathioprine, or hydroxychloroquine). Due to potential confounding factors and the absence of proven efficacy, methotrexate and azathioprine will be discontinued during the run-in epoch. However, corticosteroid medications and hydroxychloroquine will be allowed as background therapy during this study, in order to test the efficacy of CMK389 in a "real-world" setting.

3.6 Purpose and timing of interim analyses/design adaptations

Commercially Confidential Information

3.7 Risks and benefits

Potential benefit:

- There is no proven direct medical benefit for subjects who will participate in this study. However, the patient's participation in this study will facilitate and advance research in the field of drug development for the treatment of sarcoidosis, which is still a significant unmet medical need (Section 1.1).

Potential risk:

- Commercially Confidential Information

- **Based on clinical observation:** Commercially Confidential Information Therefore, to date, no specific risks have been identified through clinical observation.
- **Based on mechanism of action (i.e., drug class):** CMK389 is an immunosuppressant; therefore patients undergoing treatment with CMK389 are theoretically at risk for infection. CMK389 is a biologic compound; therefore patients who receive CMK389 are theoretically at risk of acute infusion and/or hypersensitivity reactions.
- **Based on COVID-19 pandemic:** CMK389 has been shown to selectively bind to IL-18 and potently inhibit IL-18 activity. Blocking IL-18 may impair the innate and cytotoxic immune responses that play a role in viral clearance. IL-18 contributes to antiviral immune responses by promoting IFN-γ production by T cells, natural killer cells, and natural killer T cells and supports the induction of cytotoxic T cells. Impaired cytotoxic T cell responses may impair the killing of virus-infected cells. However, data generated to-date to assess the impact of CMK389 on immune function support a lack of a broad immunosuppressive effect.

CMK389 is not expected to impair the production of viral-specific antibodies, including those against SARS-CoV-2. The inflammasome and the pivotal mediators IL-1β, IL-18, and NLRP3 contribute to the hyper-inflammatory response that results in severe pulmonary tissue damage after initial SARS-CoV and SARS-CoV-2 infections. Patients with severe COVID-19 and respiratory failure have elevated levels of IL-1β and its downstream cytokine IL-6, as well as IFN-γ and CCI , both downstream markers of IL-18 pathway activation. Hence, blocking IL-18 with CMK389 could theoretically play a protective role in suppressing the hyper-inflammatory response to these viruses.

Novartis is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements should be applied in the countries that are affected by the COVID-19 pandemic. The Novartis clinical trial team will review the situation in each participating country and work with Investigators to continue to ensure the safety of participants during the conduct of the trial. A benefit/risk assessment has been made and has been determined to not significantly change for the participants that are planned to be enrolled in the proposed clinical trial. As the COVID-19 situation evolves, Investigators must use their best judgement to minimize risk to participants during the conduct of the study.

Risk mitigation strategy:

- The risk to subjects in this trial will be minimized by adherence to the eligibility criteria, close clinical monitoring, and compliance with criteria for treatment interruption outlined in the protocol (Section 7.2).
- Drug-drug interactions are unlikely with biologics, however, sites and patients must strictly observe and adhere to the list of prohibited medications listed in the protocol (Section 5.2).
- Women of childbearing potential must be informed that taking the study treatment 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 requirements outlined in Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered into or continue in the study.
- Patients with current, active or latent infection are excluded from this study. In addition, investigators will remain vigilant for signs of intercurrent infections (i.e., nausea, vomiting, fever, rash, confusion, or muscle aches).

Risk of Imaging Procedures:

The total radiation effective dose in this protocol will be less than 15 mSv; 4 mSv from HRCT scanning and 11 mSv from [^{18}F]FDG-PET/CT scans, including attenuation correction scans. In large and obese patients, a higher injected [^{18}F]FDG activity may be required but the total radiation exposure in these patients will not exceed 20 mSv. This amount of radiation is considered to be a moderate risk, category III (ICRP 1991) and is balanced against the substantial societal benefit gained from the trial.

Miscellaneous:

There may be unknown risks of CMK389 which may be serious.

3.7.1 Blood sample volumes

A maximum of 493 mL of blood is planned to be collected over a period of 9 months, from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule (Section 8.1).

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and Central Laboratory Manual.

See Section 8.9 regarding the potential use of residual samples.

4 Population

The investigator must ensure that all subjects being considered for the study meet the below eligibility criteria. No additional criteria should be applied by the investigator in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site prior to randomization.

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

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

4.1 Inclusion criteria

Subjects 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 18-75 years of age inclusive at screening
3. Subjects must have a body mass index (BMI) at screening within the range of 18 - 46 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2
4. Pulmonary Sarcoidosis present > 1 year prior to screening with a historical biopsy (from any organ or body part) confirming diagnosis prior to screening

5. Scadding stage II, III or IV as determined by the most recent chest x-ray obtained within 12 months prior to screening or at screening (confirmed by the investigator)
6. HRCT extent of fibrosis <20% (confirmed by the central imaging reader) on an HRCT obtained within 12 months prior to screening or at screening
7. Treatment with 5-15 mg/day prednisone (or prednisone oral equivalents) for ≥ 6 consecutive months prior to screening and with a minimum of 80% compliance with treatment each month as determined by the investigator.
8. Co-medication with methotrexate or azathioprine for ≥ 6 months prior to screening and with a minimum of 80% compliance with treatment each month as determined by the investigator (Note: hydroxychloroquine is allowed as background therapy but not required)
9. Able to perform reliable, reproducible pulmonary function test maneuvers per American Thoracic Society/European Respiratory Society (Culver et al 2017; Miller et al 2005; Graham et al 2017) guidelines
10. Able to communicate well with the investigator, to understand and comply with the requirements of the study

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study:

1. History of hypersensitivity to the study drug, or to drugs of similar chemical classes (i.e., IgG-1 related biologic agents)
2. Diagnosis of significant pulmonary hypertension (WHO group 5) requiring pharmacological treatment
3. Active cardiac sarcoidosis requiring treatment. Inactive cardiac sarcoidosis or stable cardiac sarcoidosis not requiring treatment are permissible.
4. A known diagnosis of neurosarcoidosis
5. Forced vital capacity (FVC) <50% of predicted at screening (central read)
6. Modified British Medical Research Council (mMRC) dyspnea scale ≥ 3 at screening
7. Concomitant treatment with leflunomide, cyclophosphamide, mycophenolate, infliximab, etanercept, adalimumab, golimumab, ustekinumab, roflumilast, pentoxifylline, and abatacept within 12 weeks of screening
8. Any prior treatment with rituximab, canakinumab, anakinra, and tocilizumab
9. Use of other investigational drugs within 5 half-lives of screening, or until the expected PD effect has returned to baseline, whichever is longer; or longer if required by local regulations
10. Current use of any inhaled substance, including but not limited to tobacco, marijuana products and the use of any electronic cigarette or vaping device (note that respiratory inhalers or nebulizers for delivery of prescribed medication for pulmonary sarcoidosis are allowed).
11. Any conditions or significant medical problems which, in the opinion of the investigator and in consultation with the sponsor, immunocompromises the patient and/or places the patient at unacceptable risk for immunomodulatory therapy
12. Any one of the following screening values of complete blood count laboratory values:

- Hemoglobin levels below 8.0 g/dL
- Total leukocyte count less than 2,000/μL
- Platelets <100.0 x 10^9/L
- Absolute neutrophil count (ANC) <1.5 x 10^9/L

13. Active viral, bacterial or other infections requiring systemic treatment at the time of screening, or within 3 months from screening in case of a known or suspected COVID-19 infection, unless resolution is confirmed radiographically as determined by the Investigator.
14. History of primary or secondary immunodeficiency, or a positive Human Immunodeficiency Virus (HIV) (Enzyme-linked Immunosorbent Assay (ELISA) and Western blot) test result at screening
15. Positive hepatitis B surface antigen (HBsAg) with concurrent negative hepatitis B surface antibody (anti-HBs); or positive total hepatitis B core antibody (anti-HBc) with concurrent negative anti-HBs; or positive hepatitis C antibody (anti-HCV) unless it can be documented that the patient has received highly-effective HCV-specific antiviral therapy, HCV RNA levels are measured, and HCV RNA is undetectable at least 12 weeks after the conclusion of HCV-specific antiviral therapy; i.e., any acute or chronic infection with hepatitis B or hepatitis C
16. Evidence of active or latent tuberculosis (TB) infection, as determined by Quantiferon test at screening (Note: if Quantiferon test is indeterminate, it may be repeated once. Two indeterminate Quantiferon tests will be considered as evidence of TB infection. Furthermore, after anti-TB treatment, patients with history of or latent TB may become eligible according to national guidelines)
17. Receipt of live/attenuated vaccine within a 1 month period before first dose of CMK389 (V201)
18. Contraindication to FDG-PET scan investigations such as severe claustrophobia or uncontrolled diabetes
19. History of confirmed malignancy of any organ system (other than localized carcinoma of the skin (for example: basal, squamous) or in situ cervical carcinoma), treated or untreated, within 5 years of screening, regardless of whether there is evidence of local recurrence or metastases
20. 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
21. Women of childbearing potential (WOCBP) (see definition below), unless they are using highly effective methods of contraception during dosing and for an additional 6 months after the last dose (infusion)

Women of childbearing potential

WOCBP are defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partner have been sterilized by vasectomy or other means.

Women of non-childbearing potential

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (i.e. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks prior to screening. 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 childbearing potential.

Highly effective contraception methods include:

- Total abstinence (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
- Male/female sterilization
- Use of oral, injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception

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

22. Other history or current diagnosis of ECG abnormalities not due to cardiac sarcoidosis at screening as determined by the investigator and based on the totality of the safety information to indicate significant safety risk. The following should be considered by the investigator in guiding the determination as part of the overall assessment, but should not be considered in isolation:
    - PR > 200 msec
    - QRS complex > 120 msec
    - QTcF > 450 msec (males)
    - QTcF > 460 msec (females)
23. Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
24. Significant illness which has not resolved within two weeks prior to initial dosing
25. Donation or loss of 400 mL or more of blood within eight weeks prior to initial dosing, or longer if required by local regulation
26. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which may jeopardize the subject in case of participation in the study. The investigator should make this determination in consultation with the sponsor and in consideration of the subject's medical history and/or clinical or laboratory evidence.
27. Clinical Status Determination (CSD) of "deteriorating" at Day-28 (V102) or Day 1 (V201)

28. A diagnosis of Lofgren's syndrome
29. History of pancreatitis
30. Other pulmonary disease (i.e.. asthma, bronchiectasis, COPD, etc.) unrelated to sarcoid as determined by the investigator
31. Active drug or alcohol abuse (as defined by the investigator) within 3 months prior to screening.

5 Restrictions for Study Subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

5.1 Contraception requirements

Women of childbearing potential must be informed that taking the study treatment 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 outlined in Section 4.2 (Exclusion Criteria). If there is any question that the subject will not reliably comply, they should not be entered or continue in the study.

5.2 Prohibited treatment

Use of the following treatments are NOT allowed in the timeframes reported in Table 5-1.

Commercially Confidential Information

5.3 Dietary restrictions and smoking

Use of any inhaled substance, including but not limited to tobacco or marijuana products or use of any electronic cigarette or vaping device is not allowed during the study. Respiratory inhalers or nebulizers for delivery of prescribed medication for pulmonary sarcoidosis are allowed.

Patients will be asked to not eat or drink anything (except water) for 8 hours before completing the chemistry and fasting lipid panel assessment at each applicable visit.

5.4 Other restrictions

No strenuous physical exercise is allowed within 30 minutes of Spirometry and DLCO assessments.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the Pharmacy Manual.

6.1.1 Investigational treatment and control drug(s)

Table 6-1 Overview of study medication

Study Drug	Formulation	Appearance	Unit dose	Packaging	Provided by
CMK389	Powder for Solution for Infusion	a white to off-white lyophilisate	150 mg powder in a 6 mL glass vial	open label bulk	Novartis

6.1.2 Bio-batch retention samples

Not applicable

6.1.3 Additional study treatment

No additional treatment beyond investigational drug and placebo control drug are included in this trial.

Pre-medication (prior to infusion of CMK389) with corticosteroids, NSAIDs and paracetamol is not allowed.

Note: in the event of hypersensitivity reaction, refer to Section 6.9.

6.2 Treatment arms

Subjects will be assigned to one of the following 2 treatment arms in a ratio of 1:1.

Study treatments are defined as:

- four doses of CMK389 10 mg/kg i.v. (one dose q4 weeks)
- four doses of matching placebo i.v. (one dose q4 weeks)

6.3 Treatment assignment and randomization

Randomized treatment will be assigned to individual subjects by way of a randomization number, which will be in the range of 5101-5200, 5201-5300, for the 2 strata (azathioprine or methotrexate), respectively.

The randomization number is only used to identify which treatment the subjects have been randomized to receive. The Subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see 'Subject numbering' section in the SOM.

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 randomization list will be produced by the NIRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

Randomization will be stratified by prior sarcoidosis immunosuppressant therapy (azathioprine or methotrexate).

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator blinded study. Subjects and investigators will remain blinded to study treatment throughout the study, except where indicated below.

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, and odor.

Site staff

With the exception of an unblinded pharmacist, all site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study. See Section 7.2 for details on early discontinuation. For detailed information about the scheduled unblinding of subjects, please refer to the SOM.

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).

Drug product will be supplied as open label bulk so an unblinded pharmacist who is independent of the study team will be required in order to maintain the blind. This unblinded pharmacist will receive the treatment allocation from the NIRT system. Appropriate measures must be taken by the unblinded pharmacist to ensure that the treatment assignments are concealed from the rest of the site staff.

Sponsor staff or delegate

The following unblinded sponsor roles are required for this study:

Unblinded clinical staff managing drug re-supply to site

Unblinded sample analyst(s) (PK, CCI)

Commercially Confidential Information

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 trial team (CTT) as appropriate for internal decision purposes, as outlined in Table 6-2. 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 CCI are allowed to access treatment assignment information for the purpose of conducting interim analyses.

The CTT is allowed to share unblinded results with other sponsor staff (e.g. decision boards) as required for internal decision making on the study or the project at the time of interim analyses while the study is ongoing.

All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

Table 6-2 Blinding levels

Role	Time or Event			
	Randomization list generated	Treatment allocation & dosing	Safety event (single subject unblinded)	
Subjects/Patients	B	B	UI	
Site staff	B	B	UI	
Unblinded site staff (see text for details)	B	UI	UI	
Drug Supply and Randomization Office	UI	UI	UI	CCI
Unblinded sponsor staff (see text for details)	B	UI	UI	
Statistician/statistical programmer/data analysts	B	B	UI	
All other sponsor staff not identified above	B	B	UI	

B Remains blinded

UI Allowed to be unblinded on individual patient level

6.5 Treating the subject

CMK389 will be administered to the subject via i.v. infusion for approximately one hour at the study site. See the pharmacy 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

Study treatment dose adjustments and/or missed doses are not permitted.

For instructions regarding infusion interruptions, refer to the Pharmacy Manual.

6.7 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when knowledge of the assigned treatment 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 NIRT. 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 NIRT at any time in case of emergency. The investigator will need to provide:

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

In addition, 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.

An assessment will be done by the appropriate site personnel and sponsor after an emergency unblinding to assess whether or not study treatment should be discontinued for a given subject and, if applicable, whether the subject can continue with follow up assessments.

6.8 Treatment exposure and compliance

Subjects will receive all study medication at the Investigator site. Study medication will be administered by site personnel, compliance will be ensured by appropriate training of site personnel. The date and time of administration of study drug will be recorded in the dosage administration record section of the eCRF.

6.9 Recommended treatment of adverse events

Acute infusion or hypersensitivity reactions: Study participants are required to undergo observation for a minimum of two hours post-infusion prior to leaving the site (or longer if deemed necessary by the Investigator). In the event of an acute infusion or hypersensitivity reaction, the investigator should consider the criteria for treatment discontinuation (Section 7.2), and the patient should be treated with antihistamines and glucocorticoids. Depending on severity, patients may also require supplemental oxygen, volume expansion, catecholamines and transfer to an intensive care setting. Plasmapheresis to decrease the systemic concentration of CMK389 may be considered dependent on the patient's condition. Patients should be observed for at least four hours after resolution of signs and symptoms; and those who have experienced severe infusion reactions should be closely observed for 24 hours after resolution because of the risk for a biphasic episode.

Infections: In the event of an infection, the investigator should consider the criteria for treatment discontinuation (Section 7.2), as well as consider early treatment with specific antimicrobial therapy on the basis of clinical diagnosis or suspicion thereof (e.g., antiviral treatment for herpes simplex or zoster) in consultation with infectious disease experts, as appropriate.

Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

6.10 Rescue medication

Use of rescue medication is not allowed in the context of this study. Therefore, if the investigator believes that continuation of the study is potentially detrimental to a patient's health, such patient should be withdrawn from the study.

6.11 Concomitant treatment

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 section of the 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.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

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.

The study is considered completed when the last subject completes their End of Study (EOS) visit, for males and women not of childbearing potential (EOS#1 V399) and for WOCBP (EOS#1 V399 and EOS#2 V499), 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.

All SAEs reported during this time period must be reported as described in Section 9.2 and the SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

7.2 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time.

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

Study treatment must be discontinued under the following circumstances:

- Subject is non-compliant with study treatment, as defined by missing any dose
- Subject withdraws consent
- Pregnancy
- Severe infection
- Use of a prohibited treatment as outlined in Table 5-1
- Any situation in which study participation might result in a safety risk to the patient.
- Severe allergic reaction or anaphylaxis, as defined by Sampson criterion #1 (Sampson et al 2006) (Table 7-1), following administration of the study drug
- Any protocol deviation that results in a significant risk to the subject'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 or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent. Where possible, they should return for the assessments indicated for EOS#1 (V399) in the Assessment Schedule (Table 8-1). WOCBP should also complete urine pregnancy tests at home every 4 weeks after the last dose received, for 40 weeks. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, email, letter) should be made to contact them.

Table 7-1 Sampson Criterion #1 for diagnosing anaphylaxis

Criteria #1	Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
	AND AT LEAST ONE OF THE FOLLOWING
a.	Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b.	Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

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 allow further collection of personal data

In this situation, the investigator should make a reasonable effort (e.g. telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table (Table 8-1).

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the informed consent form.

For EU and RoW: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

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 discontinue or 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 cannot be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

7.5 Study Stopping rules

The study will be paused for a full safety review in the event of:

- 2 or more drug-related SAEs are reported
- 3 or more patients experience infectious complications of at least moderate severity related to study drug
- 3 or more patients experience the same (or similar) unexpected severe AE related to study drug
- 2 or more patients experience a hypersensitivity reaction related to study drug
- 2 or more patients experience a severe infusion reaction related to study drug

Any restart of the study following a full safety review will require notification to health authorities or submission and approval of a substantial amendment, whichever is appropriate based on local requirements.

7.6 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/ risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. Should this be necessary, subjects must be seen as soon as possible and treated as a prematurely discontinued subject. 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 IRBs/IECs of the early termination of the trial.

8 Procedures and assessments

8.1 Assessment schedule

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible.

Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

Table 8-1 Assessment Schedule

Epoch	Screening	Run-in			Treatment Period													Safety Follow-up		
Visit Name	Screening	Run-in			Treatment Period													Follow-Up		End of Study #1
Visit Numbers[1]	1	101	102	199	201			202			203			204			299	301	302	399
Days	-70 to -43	-42 ±1	-28 ±1	-2 ±1	1			29 ±3			57 ±3			85 ±3			113 ±3	141 ±3	169 ±3	197 ±3
Time (post-dose)	-	-	-	-	0min[2]	60min	180min	0min[2]	60min	180min	0min[2]	60min	180min	0min[2]	60min	180min	-	-	-	-
Informed consent	X																			
Commercially Confidential Information																				
Inclusion / Exclusion criteria	X		X		X															
Medical history/current medical conditions	X																			
Concomitant therapies	X																			
Demography	X																			
Physical Examination	S	S	S		S[3]			S			S			S			S	S	S	S
Body Weight	X																X			X
Body Height	X																			
Smoking history	X																			
Cotinine test	S																			
Hepatitis and HIV Screen	S																			
Tuberculosis status[4]	S																			
Pregnancy and assessments of fertility	X[5]				S[3, 6]			S[6]			S[6]			S[6]			S[6]	S[6]	S[6]	X[5]
Clinical Chemistry[7]	X		X		X[3]			X			X			X			X	X	X	X

Epoch	Screening	Run-in			Treatment Period												Safety Follow-up		
Visit Name	Screening	Run-in			Treatment Period												Follow-Up		End of Study #1
Visit Numbers[1]	1	101	102	199	201			202			203			204			299	301	302	399
Days	-70 to -43	-42 ±1	-28 ±1	-2 ±1	1			29 ±3			57 ±3			85 ±3			113 ±3	141 ±3	169 ±3	197 ±3
Time (post-dose)	-	-	-	-	0min[2]	60min	180min	0min[2]	60min	180min	0min[2]	60min	180min	0min[2]	60min	180min	-	-	-	-
Hematology	X		X		X[3]			X			X			X			X	X	X	X
Urinalysis	X		X		X[3]			X			X			X			X	X	X	X
Fasting Lipid Panel	X		X		X[3]			X			X			X			X	X	X	X
Body Temperature	X	X	X		X[3]			X			X			X			X			X
Blood Pressure and Pulse Rate	X	X	X		X[3]			X			X			X			X			X
ECG evaluation	X				X[3]												X			X
Chest x-ray[8]	S																			
High Resolution CT of Chest (HRCT)[9]	X																			
[^{18}F]FDG-PET/CT				X													X[10]			
Fasting glucose[11]				X													X[10]			
6-Minute Walk Test		X	X		X[3]			X			X			X			X			
mMRC dyspnea scale	X	X	X		X[3]			X			X			X						

Commercially Confidential Information

Spirometry	X	X	X		X[3]			X			X			X			X			
Diffusion Capacity (DLCO)					X[3]			X			X			X			X			
Clinical Status Determination Form[12]			X		X[3]			X			X			X						

Epoch	Screening	Run-in			Treatment Period													Safety Follow-up		
Visit Name	Screening	Run-in			Treatment Period													Follow-Up		End of Study #1
Visit Numbers[1]	1	101	102	199	201			202			203			204			299	301	302	399
Days	-70 to -43	-42 ±1	-28 ±1	-2 ±1	1			29 ±3			57 ±3			85 ±3			113 ±3	141 ±3	169 ±3	197 ±3
Time (post-dose)	-	-	-	-	0min[2]	60min	180min	0min[2]	60min	180min	0min[2]	60min	180min	0min[2]	60min	180min	-	-	-	-
Randomization					X															
Discontinue Sarcoidosis Immunosuppressant Therapy[13]		X																		
Steroid Titration[14]			X		X			X			X			X						
Study drug administration					X			X			X			X						
2h post-dose observation period					S			S			S			S						
PK blood collection CCI					X[16]	X[17]	X[18]	X[16]	X[17]		X[16]	X[17]		X[16]	X[17]	X[18]	X	X	X	X
Adverse Events	X																			
Study/Epoch completion information	X			X													X			X

Commercially Confidential Information

Epoch	**Pregnancy Testing Period (WOCBP Only)[22]**	
Visit Name	**Pregnancy Testing (WOCBP Only)**	**End of Study #2**
Visit Numbers[1]	**401**	**499**
Days	**225 ±3**	**253 ±3**
Pregnancy and assessments of fertility	S[6]	S[6]
Serious Adverse Event - Only Pregnancies Reported[23]	X	X
Study/Epoch completion information		X

[X] Assessment to be recorded in the clinical database or received electronically from a vendor

S- source documentation at the study site

[1] Visit structure given for internal programming purpose only

[2] Unless specified otherwise, assessments at 0 min should be done pre-dose

[3] Can be done at Day -1 instead of Day 1 if needed.

[4] Determined by QuantiFERON TB-Gold test

[5] Serum pregnancy test

[6] Urine pregnancy test

[7] Chemistry panel must be done under fasting conditions at all visits

[8] Only for patients who don't have an historical chest x-ray within 12 months from screening

[9] HRCT at screening should be performed after all other screening assessments for eligibility. A historical HRCT obtained within 12 months prior to screening may be used instead and sent to the central reader for analysis.

[10] Fasting glucose and [^{18}F]FDG-PET/CT must be done on a different day than the other assessments of V299 or after all other V299 assessments are completed on the same day.

[11] The [^{18}F]FDG-PET/CT requires a blood glucose level below 11 mmol/L. The measurement is performed by finger prick at site before [^{18}F]FDG-PET/CT is performed

[12] Clinical Status Determination includes the following: 6-minute walk distance, FVC, FEV1 and mMRC dyspnea score. Complete the form (found in the SOM) and use as a guide for CSE

[13] Discontinue methotrexate and azathioprine

[14] Patients with CSD of "deteriorating" will be ineligible to continue the study (during the run-in epoch); or they will increase steroid dose by 1-step (during the treatment epoch). See study design Section 3.1

Commercially Confidential Information

[16] pre-dose (within 2 hours prior to infusion)

[17] In the event that the infusion must be lengthened beyond 60 minutes, then this sample is collected at the end of the infusion (+ 5 minutes)

[18] +/- 60 minutes

[19]

[20] Commercially Confidential Information

[21]

[22] Pregnancy tests done at home by the patient and results collected over the phone by site staff. Pregnancy tests may be done at the clinical site instead of at-home during the Pregnancy Testing Period (WOCBP only) if required per local regulations. See SOM for more details about these visits

[23] See Section 9.6 Pregnancy Reporting

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 applicable, in cases where the subject's representative gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form.

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

Novartis will provide to investigators a proposed informed consent (ICF) form that complies with the ICHE6 GCP guideline and regulatory requirements and is considered appropriate for this study. The informed consent form will also include a section related to optional future research which will require a separate signature if the subject agrees to future research. The procedures set out in the main consent form concerning the storage, maintenance of privacy, and release of the data or specimens for the main study will also be adhered to for any future research. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and then must be discussed with the subject.

Ensure subjects are informed of the contraception requirements outlined in the Section 4.2 (Exclusion criteria) and in Section 5.1 (Contraception requirements).

Commercially Confidential Information

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

Refer to the SOM for a complete list of ICFs included in this study.

8.3 Subject screening

Screening assessments (e.g., clinical laboratory assessments or Pulmonary Function Tests (PFTs)) may be repeated one time at the discretion of the Investigator if there are questionable results or if abnormalities are felt to be due to inherent variability of the test procedure.

In general, it is permissible to re-screen a subject once if s/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor.

If a subject must be rescreened for study entry, results from previous screening assessments may be used, as long as the screening windows for those assessments are met and all spirometry data used for subject qualification are derived from a single day. If any PFTs are to be repeated, only the tests that are felt to be questionable should be repeated (i.e., spirometry, DLCO).

Initial screening HRCT and chest x-ray (including historical ones) are valid and can be used in case of re-screening up to 365 days after the initial assessment date if the subject does not report clinically significant changes in PFTs or symptoms (qualitative or quantitative) as determined by the Investigator.

Information on what data should be collected for screening failures is outlined in the SOM.

8.4 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgment, the test abnormality occurred prior to the informed consent signature.

8.4.1 Concomitant therapies

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.

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.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact Novartis before randomizing a subject or, if the subject is already enrolled, to determine if the subject should continue participation in the study.

For eligible patients, the investigator must have previous records of steroid treatment and immunosuppressant therapy, such as prednisone and either methotrexate or azathioprine, for the treatment of sarcoidosis.

8.4.2 Discontinue Sarcoidosis Immunosuppressant Therapy

During the run-in epoch eligible patients will discontinue methotrexate and azathioprine. The patient's immunosuppressant therapy may be restarted after V299 is completed, at the Investigator's discretion.

8.4.3 Tuberculosis status

Determination of tuberculosis (TB) status will be required before administration of study treatment and should be determined at screening by Quantiferon TB Gold test. Note: if Quantiferon test is indeterminate, it may be repeated once. Two indeterminate Quantiferon tests will be considered as evidence of TB infection. Furthermore, after anti-TB treatment, patients with history of or latent TB may become eligible according to national guidelines.

Any significant findings will be recorded in the "Relevant medical/history/Current medical conditions" section of the eCRF.

8.4.4 Hepatitis and HIV Screen

All subjects will be screened for HIV, Hepatitis B and C. See the SOM for details.

8.4.5 Inclusion / Exclusion criteria

The investigator must ensure that all subjects being considered for the study meet the inclusion and exclusion criteria. No additional exclusions should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all inclusion/exclusion criteria at screening, V102 and V201. A relevant record (e.g. checklist) must be stored with the source documentation at the study site. Deviation from any entry criterion excludes a subject from enrolment into the study. The investigator or his/her deputy must promote compliance to inclusion/exclusion criteria for the duration of the study.

8.4.6 Medical history/current medical conditions

Relevant medical history and current medical conditions will be recorded on the CRF until signature of the informed consent.

Where possible, diagnoses and not symptoms will be recorded.

Any event or change in the subject's condition or health status occurring prior to informed consent will be reported in the Relevant medical history / Current medical conditions section of the CRF.

8.4.7 Smoking history

Smoking history including usage status, type of substance used, amount consumed and date stopped will be collected.

8.4.8 Cotinine test

All subjects will be screened for cotinine. See SOM for details.

8.5 Efficacy / Pharmacodynamics

Commercially Confidential Information

8.5.1 6-Minute Walk Test

A standardized six-minute walk test (6MWT) will be carried out by a trained technician in accordance with the guidelines (Holland et al 2014). See SOM for details.

8.5.2 Patient Reported Outcomes (PROs)

Commercially Confidential Information

mMRC dyspnea scale

The mMRC Dyspnea Scale is a widely used, rapidly administered, 5-point scale based on degrees of various physical activities that precipitate breathlessness (Bestall et al 1999; Mahler and Wells 1988). Patients read the descriptive statements and then select the number which best fits his or her shortness of breath. The mMRC dyspnea scale is a component of the study inclusion criteria and will be used in patient screening. mMRC dyspnea score is also used during the patient's Clinical Status Evaluation (CSE). See SOM for additional details.

Commercially Confidential Information

8.5.3 Diffusion Capacity (DLCO)

Diffusion capacity will be determined according to ATS guidelines (Graham et al 2017). Measurements will include DLCO and Volume alveolar (VA). DLCO will be over read by pulmonary function testing vendor. Additional information is provided in the SOM.

Commercially Confidential Information

8.5.5 Steroid Titration

The Clinical Status Evaluation (CSE) serves as a safety evaluation and will serve to establish the patient's clinical status (Clinical Status Determination [CSD]) (Figure 3-2). CSE will be performed at visits (V102, V201, V202, V203, and V204) prior to the titration of steroids, and

the CSD will guide selection of the next dose of steroids (Figure 3-3). Titration will continue throughout the run-in and treatment epochs. Patients with CSD of "improved" or "stable" will decrease steroid dose by 1-step on the dosing scale (Figure 3-4). Patients with CSD of "deteriorating" will be ineligible to continue the study (during the run-in epoch or at V201); or they will increase steroid dose by 1-step (during the treatment epoch).

8.5.6 Spirometry

Spirometry testing will be performed according to the ATS guidelines (Miller et al 2005); (Culver et al 2017) at screening to assess patients' eligibility for the study and as detailed in the Assessment schedule (Section 8.1).

The spirometry equipment will be supplied to each site for the study. 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. Information on the procedure can be found in the SOM.

8.5.7 FDG-PET/CT

In this study, [^{18}F]FDG-PET/CT imaging will provide early evidence for anti-inflammatory effects of IL-18 blockade by CMK389 on the sarcoidosis process. [^{18}F]FDG-PET/CT has been shown to detect lung parenchymal involvement at any chest X-ray stage, including therapy-resistant disease, and can also provide information on extra-pulmonary disease. Lung FDG-PET uptake in sarcoidosis has been shown to correlate with important sarcoidosis BAL biomarkers, including percentage neutrophils and CD4:CD8 ratio. In two previous sarcoidosis trials, the [^{18}F]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 [^{18}F]FDG-PET/CT compared to baseline, with evidence of improvement by serial [^{18}F]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, [^{18}F]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 [^{18}F]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. 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. A maximum injected radioactivity dose of 200 MBq will result in a whole body effective dose of 4 mSv (ICRP 2008). Higher [^{18}F]FDG doses and/or extended scanning time may be required in large or obese patients to ensure sufficient imaging quality but the injected activity will not exceed 350 MBq. One further imaging scan will be performed at week

16 according to the schedule on enrolled patients and the results compared to baseline findings using centralized quantitative reading. Detailed information will be provided in a separate [^{18}F]FDG-PET/CT imaging manual. Total injected activity and body weight will be recorded and used to compute standardized uptake values (SUVs). The total radiation dose for all PET/CT scanning (excluding HRCT) in this protocol will be maximally 11 mSv (or 16 mSv if [^{18}F]FDG injected dose is 350 MBq). In all subjects, the baseline and follow-up PET/CT scan (at week 16) should be performed where possible on the same scanner.

Refer to the Imaging Acquisition Guidelines and Imaging Investigator Site Operations Manual for [^{18}F]FDG-PET/CT.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers. Incidental findings are beyond the scope of central imaging vendor. If an investigator/radiologist recognizes any incidental finding in the images during the course of conducting the clinical trial, the investigator should follow up as part of his/her duty of care to ensure the safety and wellbeing of the participant.

8.6 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with the Assessment schedule (Section 8.1) detailing when each assessment is to be performed.

8.6.1 Adverse Events

Safety assessments are specified below; methods for assessment and recording are specified in the SOM, with Assessment schedule (Section 8.1) detailing when each assessment is to be performed. The safety assessments include:

- Adverse events, vital signs, physical exams, safety labs (hematology, chemistry, urinalysis), and electrocardiogram (ECG).
- CSE (Section 8.6.3)

8.6.2 Body Temperature

Body temperature will be measured at multiple time points during the study. The same method of measurement should be used throughout study. Please refer to the Assessment schedule (Section 8.1).

8.6.3 Clinical Chemistry

The fasting chemistry panel will include: albumin, alkaline phosphatase, total bilirubin, calcium, chloride, serum bicarbonate, creatinine, creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), α-amylase, γ- glutamyltransferase (GGT), glucose, sodium, potassium, inorganic phosphorus, total protein, lactate dehydrogenase (LDH), magnesium, blood urea nitrogen (BUN), uric acid, lipase and serum ketones.

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

Please refer to the Assessment schedule (Section 8.1).

8.6.4 Blood Pressure and Pulse Rate

Blood pressure and pulse rate will be recorded at multiple time points during the study. Please refer to the Assessment schedule (Section 8.1) and the SOM for additional information.

8.6.5 ECG evaluation

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

ECG parameters will include: PR interval, QRS duration, heart rate, RR interval, QT interval, QTcF. The Fridericia QT correction formula (QTcF) calculated with the RR interval expressed in seconds should be used for clinical decisions.

Clinically significant abnormalities must be reported in the AE CRF.

8.6.6 Hematology

The hematology panel will include: hemoglobin, hematocrit, red blood cell (RBC) count, white blood cell (WBC) count with differentials (e.g. neutrophils, basophils, eosinophils, monocytes, lymphocytes) and platelet count will be measured. Please refer to the Assessment schedule (Section 8.1) and SOM.

8.6.7 Pregnancy and assessments of fertility

Pregnancy Testing

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Serum pregnancy testing is required at Screening (V1) and EOS#1 (V399). Urine pregnancy testing is required at V201, V202, V203, V204, V299, V301, V302 and for an additional 8 weeks (V401, and EOS#2 V499; for all urine pregnancy testing, record the results in source documentation at the study site).

See the Assessment schedule (Section 8.1), for timing of the protocol required pregnancy testing*. A positive urine pregnancy test requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative.

*Additional pregnancy testing might be performed if requested per local requirements.

Refer to Section 9.6 for details on Reporting Pregnancy.

Assessments of Fertility

Refer to Section 4.2 for criteria to determine women that are not of childbearing potential.

Medical documentation of oophorectomy, hysterectomy, or bilateral tubal ligation must be retained as source. Subsequent hormone level assessment to confirm the woman is not of childbearing potential must also be available as source documentation in the following cases:

- surgical bilateral oophorectomy without a hysterectomy
- reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at Screening.

8.6.8 Physical Examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

8.6.9 Urinalysis

A urine sample (approx. 30 mL) will be obtained midstream in order to avoid contamination with epithelial cells and sediments, and to allow proper assessments.

Semi-quantitative 'dipstick' evaluation of the urine for the following parameters will be performed centrally: specific gravity, pH, glucose, protein, bilirubin, ketones, nitrite, leukocytes and blood.

If the dipstick result is positive for nitrite, leucocytes and/ or blood, the sample will be sent for culture and for microscopic analysis of white blood cells, red blood cells and casts.

8.6.10 Body Weight and Height

Body weight and height will be recorded at multiple time points during the study. Refer to the Assessment schedule (Section 8.1).

8.7 Pharmacokinetics

PK samples will be collected at the time points defined in the Assessment schedule (Section 8.1). Follow instructions outlined in the Site Operations 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 SOM. If patients experience suspected immunologically-related AE such as infusion-related reaction, hypersensitivity, cytokine release syndrome and anaphylaxis (as defined by Sampson criterion #1; Sampson et al 2006), an unscheduled PK blood sample should be obtained as close as possible to the event occurrence. The date and time of the last dose and the time of PK blood draw should be recorded.

An ELISA based assay will be used to analyze the CMK389 concentration in PK samples.
Commerically Confidential Information

PK samples will be obtained and evaluated in all subjects, all samples will be analyzed except the placebo group.

Commerically Confidential Information

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

The following PK parameters will be determined using the actual recorded sampling times and non-compartmental analysis using Phoenix WinNonlin: Ctrough, Cmax, Tmax, and if feasible AUC0-t, AUCinf, t1/2, Vz and CL from CMK389 serum concentration-time data.

The linear trapezoidal rule will be used for AUC calculation. Regression analysis of the terminal plasma elimination phase for the determination of t1/2 will include at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase will be less than 0.75, no values will be reported for t1/2, AUCinf and CL.

8.7.1 PK blood collection

For PK assessment, pre-dose blood samples will be collected before each dose administration. Blood samples will also be collected at designated time points after dosing.

For details on PK blood collection and processing, labeling, and shipment instructions, see laboratory manual.

The exact clock time of dosing, as well as actual sample collection date and time will be entered on the PK blood collection summary page of the CRF. Sampling problems will be noted in the relevant field of the CRF.

8.8 Other assessments

Commercially Confidential Information

As outlined in Section 4.1 Inclusion Criteria, investigator must assess the Scadding stage II, III or IV as determined by the most recent chest x-ray obtained within 12 months prior to screening. If necessary, the chest x-ray may be obtained during screening. Original x-ray film, appropriately labeled, will be archived at study site.

8.8.2 High Resolution CT of Chest

An HRCT scan of the lung will be completed at screening to assess reticular pattern for the purpose of fulfilling eligibility criteria. The HRCT scans, without contrast agent, will be acquired at full inspiration according to parameters as listed in a separate imaging acquisition manual. Inclusion scans will be read by a central reader (expert radiologist) contracted through imaging vendor. The total whole body effective dose per subject from the HRCT scanning (excluding [^{18}F]FDG-PET/CT) will be maximally 4 mSv.

An historical HRCT obtained within 12 months from screening may also be sent to the central reader for over-read.

Refer to the Imaging Acquisition Guidelines and Imaging Investigator Site Operations Manual for HRCT details and requirements for historical HRCT.

The coded medical images will be used primarily for analysis as described in this protocol; however, the images may also be used for the development and evaluation of new analysis methods directly related to the area of research that this study covers. Incidental findings are beyond the scope of central imaging vendor. If an investigator/radiologist recognizes any incidental finding in the images during the course of conducting the clinical trial, the investigator should follow up as part of his/her duty of care to ensure the safety and wellbeing of the participant.

Commercially Confidential Information

8.8.4 Fasting lipid panel

A fasting lipid panel will be performed, measuring cholesterol, direct LDL, HDL cholesterol, LDL cholesterol, and triglycerides.

Sample(s) will be collected at the timepoint(s) defined in the Assessment schedule (Section 8.1). Detailed instructions for sample collection, numbering, processing and shipment will be provided in the Central Lab Manual.

Commercially Confidential Information

8.9 Use of residual biological samples

Residual blood and urine samples may be used for another protocol specified endpoint.

Commercially Confidential Information

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 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.

AEs of Special Interest comprise hypersensitivity reactions such as serum sickness and anaphylaxis (as defined by Sampson criterion #1; Sampson et al 2006).

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.

Adverse events should 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
    a. Adverse events will be primarily assessed and graded according to the “Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials”. A copy of the Toxicity Grading Scale can be found in the Investigator Portal.

b. For any adverse event not listed in the "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials", the adverse event will be assessed and graded according to the "Common Terminology Criteria for Adverse Events", version 5.0 (CTCAE v5.0). A copy of the CTCAE Grading Scale can be found in the Investigator Portal.
c. For infusion-related reactions, event will also be assessed and graded according to the CTCAE v5.0

2. Its relationship to the study treatment
   - Yes or
   - No
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)

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications. 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.

*Refer to the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

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
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a 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 subject or may require medical or surgical intervention.

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 (please refer to ICH E2D Guideline 2004).

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 (please refer to ICH E2D Guideline 2004).

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 Chief Medical Office and Patient Safety (CMO & PS) as per Section 9.2.2.

9.2.2 SAE reporting

Screen Failures & Run-In Failures

Note the following requirement for Screen Failures: SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis.

For subjects considered Run-In Failures, SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Run-In Failure must be reported to Novartis.

Treated Subjects

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the End of Study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below.

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 immediately, without undue delay, and under no circumstances later than 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 Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Chief Medical Office and Patient Safety (CMO& PS) Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (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 Table 15-1 Appendix 1 for complete definitions of liver events.

Follow-up of liver events

Every liver event defined in Table 15-1 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 Table 15-1 Appendix 1.

- Repeating liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) 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 on the unscheduled local laboratory 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 GGT. 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 retesting can decrease to once a week or less if abnormalities stabilize or the study drug has been discontinued and the subject is asymptomatic.
    Retesting 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 Appendix 1.
  - 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. Refer to the Site Operations Manual for additional details.

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.

All follow-up information, and the procedures performed must be recorded as appropriate in the CRF. Refer to the Site Operations Manual for additional details.

9.5 Reporting of study treatment 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 Chief Medical Office and Patient Safety (CMO& PS) department if the treatment error is associated with an SAE.

All instances of misuse or abuse must be documented in the adverse event (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 Chief Medical Office and Patient Safety (CMO& PS). 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 Guidance for capturing study treatment 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

Reproductive toxicity and teratogenicity data are not available for the investigational drug at this time, therefore no guidelines on therapeutic recommendations in case of pregnancy are available. This study enrolls women on highly effective birth control and who are considered not to be of childbearing potential, thus pregnancy is not an expected outcome for any female study participant. However, in the case that a pregnancy in a female study participant should occur, please follow the below reporting guidelines.

To ensure subject safety, each pregnancy occurring after signing the informed consent 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.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Chief Medical Office and Patient Safety (CMO&PS) Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

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

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.

9.7 Prospective suicidality assessment

Not applicable.

9.8 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 (email) 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 (email) 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 data capture requirements (i.e. eSource or eCRFs) 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 data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and 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.

Continuous remote monitoring of each site's data may be performed by Novartis or CRO working on behalf of Novartis. Additionally, a central analytics organization may analyze data and identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

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 data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion 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.

All 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 will review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct 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. The signed copy of the Data Query Form is kept at the investigator site.

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).

Randomization codes and data about all study drug(s) dispensed to the subject and all dosage changes will be tracked using an 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 relevant 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 after written agreement by Novartis management.

10.4 Data Monitoring Committee

Not required.

10.5 Adjudication Committee

Not required.

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 who received any study drug.

The PK analysis set will include all subjects with at least one available valid (i.e. not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations with relevant impact on PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data. Data collected after a change of the background therapy not

based on the CSE algorithm (see Section 3.1) will be excluded from the analysis set if assessed as having a potentially relevant impact on PD.

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, drug tests and any other relevant information will be listed by treatment group and subject. A summary of the steroid dose (prednisone) assigned at the start of the treatment phase and of the prior immunosuppressant therapy will be provided too.

11.3 Treatments

Data for study drug administration, rescue medication and concomitant therapies (including steroid dose) 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 CMK389 versus placebo on the clinical disease activity of sarcoidosis patients as measured by the change from baseline in the percent predicted FVC at week 16 in the PD population. This will be assessed regardless by the background steroid dose and assuming all patients remained on their treatment throughout the study.

11.4.1 Primary Variable(s)

The primary variable will be the change from baseline in percent predicted FVC after 16 weeks from the first dose of the study drug.

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 FVC by time interaction, prior sarcoidosis immunosuppressant therapy (stratification factor) and baseline prednisone dose. The correlation among the repeated measures collected on the same subject will be assessed via an unstructured covariance matrix. The stratification factor may be removed in case of strata with low sample sizes impacting on the convergence of the model.

Uninformative priors will be utilized to obtain the posterior estimates. Baseline is defined as Day 1.

The posterior probability that CMK389 is better than placebo in terms of change from baseline in percent predicted FVC at 16 weeks will be calculated. If it is at least 90%, it will be considered a sign of efficacy of CMK389 in this patient population.

The primary analysis will include all available data from patients in the PD analysis set with baseline and at least one post baseline assessment.

A supplementary analysis may be conducted including also FVC values collected after a change of the background therapy not based on the CSD algorithm.

If data permits, additional subgroup analysis of the primary endpoint will be conducted for the following three subgroups: increased, no change and decreased prednisone dose at week 16 compared to baseline.

11.4.3 Handling of missing values/censoring/discontinuations

Estimates of the missing values will be derived by the model under the missing at random (MAR) assumption. Alternative assumptions may be explored to investigate the robustness of the results under plausible non-missing at random situations.

11.4.4 Summary statistics of safety

All information obtained on adverse events will be displayed by treatment group 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.

The number (and proportion) of subjects with AEs of Special Interest (Section 9.1) will be summarized by treatment.

11.4.5 Summary statistics of pharmacokinetics

Not applicable

11.4.6 Sensitivity analyses

The impact of the changes in steroid dose may be investigated performing two sensitivity analyses. In the first one all FVC data following an increase of the steroid dose will be set to missing and estimated via the model assuming MAR. In the second analysis a penalty will be applied to all the data following an increase of the steroid dose. Further details will be included in the statistical analysis plan (SAP).

11.5 Analysis of secondary variable(s)

11.5.1 Efficacy / Pharmacodynamics

Data from other secondary variables will be listed and summarized. Graphical representations over time will be presented. Models similar to the one described for the primary analyses will be carried-out to investigate treatment difference for the continuous variables collected at each visit of the treatment epoch. Pulmonary physiology scores will be analyzed via ANCOVA model for repeated measures, while the percentage of subjects that, at Week 16, deteriorate (defined as: relative reduction from baseline in FVC $\geq$ 10% or in FEV1 $\geq$ 10% or in DLCO $\geq$ 15% or relative of 6MWD $\geq$ 50 m) and the percentage of subjects who increased the steroid dose at least one time during the treatment epoch, will be analyzed using logistic regression. This analysis will be carried out if at least 20% of the subjects will show a deterioration/increase of the steroid dose.

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

- A maximum of 10 focal nodal uptake regions (mediastinal, hilar)

- A maximum of 10 focal regions of uptake in lung parenchyma
- A maximum of 10 extra-thoracic focal uptake regions on the whole body scan

[^{18}F]FDG-PET/CT mean uptake in the reference tissue:

- 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 lymph nodes after 16 weeks of treatment will be analyzed using ANCOVA with baseline SUVmax and baseline steroid doses as covariates, and treatment and prior sarcoidosis immunosuppressant therapy as factors.

The same analysis as for the percent change from baseline in SUVmax in the lymph nodes 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 correlation between changes from initial FDG-PET scan in SUVmax and changes from baseline in FVC, FEV1 and 6MWT distance will be assessed with graphical methods.

11.5.2 Safety

Vital signs

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

ECG evaluations

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

Clinical laboratory evaluations

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

11.5.3 Pharmacokinetics

CMK389 plasma concentration data will be listed by treatment, and visit/sampling time point. Descriptive summary statistics will be provided by visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

For pharmacokinetic parameter determination, please see Section 8.7.

The descriptive statistics (n, mean, CV%, standard deviation (SD), median, geometric mean, geometric CV%, minimum and maximum) will be presented by time of dosing (1st to 4th dose) for all PK parameters of CMK389 except Tmax, where only n, median, minimum and maximum will be presented

11.5.4 Pharmacokinetic / pharmacodynamic interactions

Not applicable.

11.5.5 Other assessments

Commercially Confidential Information

11.7 Sample size calculation

We assume around 15% drop out, which should provide FVC data at week 16 from 56 patients (approximately 28 in each arm), if approximately 66 patients are randomized.

Commercially Confidential Information

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 16 weeks of treatment. This was derived via simulations using the QTD software. With 28 patients per group providing data at week 16 and assuming a standard deviation of 9% (Judson et al 2014), there is approximately 80% power to meet the efficacy criterion (posterior probability that CMK389 is better than placebo >= 90%), if the true effect of CMK389 over placebo is 5%. Furthermore there is 10% 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

Commercially 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 by 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.

12.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed or overseen by Novartis Pharma Auditing and Compliance Quality Assurance (or CRO working on behalf of Novartis), a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

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 agree 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 and health authorities, where required, 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.

14 References

References are available upon request.

Baughman RP, Drent M, Kavuru M, et al (2006) Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med; 174: p. 795-802.

Baughman RP, Judson MA, Costabel U, et al (2013) Efficacy Of Treatment With Ustekinumab Or Golimumab In Patients With Chronic Skin Sarcoidosis. Am J Respir Crit Care Med; 187: p. A1066.

Benson JM, Sachs CW, Treacy G, et al (2011) Therapeutic targeting of the IL-12/23 pathways: generation and characterization of ustekinumab. Nat Biotechnol; 29 p. 615-24.

Bestall JC, Paul EA, Garrod R, et al (1999) Usefulness of the Medical Research Council (MRC) dyspnea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax; 54: p. 581-586.

Braun JJ, Kessler R, Constantinesco A, et al (2008) 18F-FDG PET/CT in sarcoidosis management: review and report of 20 cases. Eur J Nucl Med Mol Imaging; 35: p. 1537-1543.

Brudin LH, Valind S-O, Rhodes CG, et al (1994) Fluorine-18 deoxyglucose uptake in sarcoidosis measured with positron emission tomography. Eur J Nucl Med; 21: p. 297-305.

Chau A, Markley JC, Juang J, Tsen LC (2016). Cytokines in the perinatal period – Part I. Int J Obstet Anesth. 2016a May;26:39-47.

Chen ES, Moller DR (2011) Sarcoidosis - scientific progress and clinical challenges. Nat Rev Rheumatol; 7: p. 457-67.

Culver BH, Graham BL, Coates AL, et al (2017) Recommendations for a Standardized Pulmonary Function Report: An Official American Thoracic Society Technical Statement. Am J Respir Crit Care Med 196: 1463–1472.

Dastoori M, Fedele S, Leao JC, et al (2013) Sarcoidosis - a clinically orientated review. J Oral Pathol Med; 42: p. 281-9.

El-Kabarity RH and Naguib AH (2011). Serum levels of IL-18, IL-12 and TH-1/TH-2 ratio in patients with pre-eclampsia Egypt J Immunol; 18(1):1-8.

Fisch R, Jones I, Jones J, et al (2014) Bayesian Design of Proof-of-Concept Trials. Therapeutic Innovation & Regulatory Science; 49(1): p. 155-162.

Graham BL, Brusasco V, Burgos F, et al (2017) 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur. Respir. J; 49: p. 1-31.

Gupta D, Agarwal R, Aggarwal AN, et al (2012) Sarcoidosis and tuberculosis: the same disease with different manifestations or similar manifestations of different disorders. Curr Opin Pulm Med; 18: p. 506-16.

Hwang AY, Smith SM, Grums JG, et al (2017) "Adrenal Gland Disorders." Pharmacotherapy: A Pathophysiologic Approach, 10e Eds. New York, NY: McGraw-Hill. http://accesspharmacy.mhmedical.com.ezproxymcp.flo.org/content.aspx?bookid=1861&sectionid=134128262. Accessed March 7, 2019.

Holland AE, Spruit MA, Troosters T, et al (2014) An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur. Respir. J; 44: p. 1428-46.

Hoshino K, Tsutsui H, Kawai T, et al (1999) Cutting edge: generation of IL-18 receptor deficient mice: evidence for IL-1 receptor-related protein as an essential IL-18 binding receptor. J Immunol; 162: p.5041-4.

ICH E2D Guideline (2004) Clinical Safety Data Management: Definitions and Standards for expedited reporting.

ICRP (1991) Radiological Protection in Biomedical Research ICRP Publication 62. Ann ICRP; 22 (No. 3); p. 1-18.

ICRP (2008) Radiation dose to patients from radiopharmaceuticals. Addendum to ICRP publication 53. ICRP Publication 106. Approved by the Commission in Oct 2007 p. 1-197.

Iannuzzi MC, Rybicki BA, Teirstein AS (2007) Sarcoidosis. N Engl J Med; 357: p. 2153-65.

Imperiale A, Riehm S, Braun J-J (2013) Interest of [18F]FDG PET/CT for treatment efficacy assessment in aggressive phenotype of sarcoidosis with special emphasis on sinonasal involvement. Q J Nucl Med Mol Imaging; 57: p. 177-186.

Judson MA, Baughman RP, Costabel U, et al (2013) Safety And Efficacy Of Treatment With Ustekinumab Or Golimumab In Patients With Chronic Sarcoidosis. Am J Respir Crit Care Med; 187: p. A1065.

Judson MA, Baughman RP, Costabel U, et al (2014) Safety and efficacy of ustekinumab or golimumab in patients with chronic sarcoidosis. Eur Respir J. 2014 Nov;44(5): p. 1296-307.

Keijsers RGM, Verzijlbergen JF, van Diepen DM, et al (2008) 18F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. Sarcoidosis Vasc Diffuse Lung Dis; 25: p. 143-150.

Laskarin G, Strbo N, Bogovic Crncic T, et al (2005) Physiological role of IL-15 and IL-18 at the maternal-fetal interface. Chem Immunol Allergy 89:10-25.

Mahler DA, Wells CK (1988) Evaluation of clinical methods for rating dyspnea. Chest; 93 p. 580-586.

Miller MR, Hankinson J, Brusasco V, et al (2005) Standardisation of spirometry. Eur. Respir. J. 26: p. 319-38.

Milman N, Graudal N, Loft A, et al (2012) Effect of the TNF-a inhibitor adalimumab in patients with recalcitrant sarcoidosis: a prospective observational study using FDG-PET. Clin Respir J; 6: p. 238-247.

Netea MG, Joosten LAB, Lewis E, et al (2006) Deficiency of interleukin-18 in mice leads to hyperphagia, obesity and insulin resistance. Nat Med; 12: p.650-656.

Newman LS (2000) Immunologic mechanisms in granulomatous lung disease. Immunopharmacology; 48: p. 329-31.

Okamura H, Tsutsi H, Komatsu T, et al (1995) Cloning of a new cytokine that induces IFN-gamma production by T cells. Nature; 378: p. 88-91.

Commercially Confidential Information

Romagnani S (2006) Regulation of the T cell response. Clin Exp Allergy; 36: p. 1357-66.

Sampson HA, Munoz-Furlong A, Campbell RL, et al (2006) Second symposium on the definition and management of anaphylaxis: Summary Report- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium. J Allergy Clin Immunol 2006;117(2):391-97.

Sobic-Saranovic DP, Grozdic IT, Videnovic-Ivanov J, et al (2013) Responsiveness of FDG PET/CT to treatment of patients with active chronic sarcoidosis. Clin Nucl Med; 38: p. 516-521.

Takeda K, Tsutsui H, Yoshimoto T, et al (1998) Defective NK Cell Activity and Th1 Response in IL-18–Deficient Mice. Immunity; 8: 383-90.

Tokmadzić VS, Tsuji Y, Bogović T, et al (2002) IL-18 is present at the maternal-fetal interface and enhances cytotoxic activity of decidual lymphocytes. Am J Reprod Immunol. 48:191-200.

Utz JP, Limper AH, Kalra S, et al (2003) Etanercept for the treatment of stage II and III progressive pulmonary sarcoidosis. Chest; 124: p. 177-85.

Vorselaars ADM, Crommelin HA, Deneer VHM, et al (2015) Effectiveness of infliximab in refractory FDG PET-positive sarcoidosis. Eur Respir J; 46: p. 175-185.

Wilson R, Moor J, Jenkins C, Miller H, et al (2004). Abnormal first trimester serum interleukin 18 levels are associated with a poor outcome in women with a history of recurrent miscarriage. Am J Reprod Immunol; 51(2):156-9.

Yoshimoto T, Takeda K, Tanaka T, et al (1998) IL-12 up-regulates IL-18 receptor expression on T cells, Th1 cells, and B cells: synergism with IL-18 for IFN-gamma production. J Immunol; 161: p. 3400-7.

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 ALT or AST elevation with coagulopathy ALT or AST elevation accompanied by symptoms Isolated ALT or AST elevation > 8 × ULN Jaundice	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Complete CRFs per liver event guidance*
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
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*

*Liver event guidance for CRF completion is available in the Site Operations Manual

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

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ³ 50 % + **OR if <18 years old, eGFR ≤ 35 mL/min/1.73 m²**	• 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 patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	Assess & document • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] Corresponds to KDIGO criteria for Acute Kidney Injury

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 recommended to make slide specimen available for evaluation by the RSG to potentially identify project-wide patterns of nephrotoxicity.)

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

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or 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 diseases or causes, e.g., dehydration due to delirium, tumor lysis

Table 16-2 Renal Event Follow Up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in CRF • Urine dipstick and sediment microscopy evidence of DIN: crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output 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 Monitor patient regularly (frequency at investigator's discretion) until - • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) 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. • Analysis of urine markers in samples collected over the course of the DIN event

17 Appendix 3: Relative Potencies of Glucocorticoids

Table 17-1 Steroid Equivalents

Glucocorticoid	Equivalent Potency (mg)[+]
Cortisone	25
Hydrocortisone	20
Prednisone	5
Prednisolone	5
Triamcinolone	4
Methylprednisolone	4
Betamethasone	0.6
Dexamethasone	0.75

[+] Modified from (Hwang et al 2017).