Study Number: IZN-101

Study Title: A Phase 2a Proof of Concept, Randomised, Double-Blind, Placebo-Controlled Study to Evaluate the Safety/Tolerability and Efficacy of 4 Subcutaneous Injections of Namilumab (150mg) Given Over 10 weeks in Subjects with Moderate-To-Severely Active Axial Spondyloarthritis Including Those Previously Exposed to Anti-TNF Therapy (NAMASTE Study)

Clinical Study Protocol

Amendment 2, FINAL 05 July 2018

NCT03622658

TITLE PAGE

Protocol Title: A phase 2a proof of concept, randomised, double-blind, placebo-controlled study to evaluate the safety/tolerability and efficacy of 4 subcutaneous injections of namilumab (I 50 mg) given over 10 weeks in subjects with moderate-to-severely active axial spondyloaitlnitis including those previously exposed to anti-TNF therapy (NAMASTE study)

Protocol Number: IZN-101

Amendment Number: 2

Product: Namilumab

Short Title: Efficacy and safety of namilumab for moderate-to-severe axial spondyloaitlnitis

Study Phase: 2a

Sponsor Name: Izana Bioscience Limited

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Coordinating Investigator:
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Regulatory Agency Identifying Number(s):

IND number: Not applicable

EudraCT number: 2018-000176-15

Date of Protocol: Final, 05 Jul 2018

Sponsor Signatory:

I have read this protocol in its entirety and agree to conduct the study accordingly:

[redacted]

09 July 2018

Date

08 July 2018

Date

Coordinating Investigator:

I have read this protocol in its entirety and agree to conduct the study accordingly:

[redacted]

9[11]Jully2018

Date

Medical Monitor name and contact information can be found in Appendix 2.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1 Document History

Document	Date	Substantial	Region
Amendment 2	05 Jul 2018	No	Global
Amendment 1	04 May 2018	Yes	Global
Original Protocol	16 Feb 2018	-	-

Amendment 2 (05 Jul 2018)

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment:

The protocol was amended to include a review of the safety data by a Safety Review Team, revise the number of Investigators and study centres from 8 to 10, and to clarify or correct several inconsistencies and editorial errors.

Table 2 Description of Changes in Amendment

Section #	Description of Change	Brief Rationale
1.1	Number of Investigators and study centres updated from 8 to 10.	Revised for increase in number of participating Investigators and study centres.
1.1 , 9.6	Safety Review Team added to review safety data.	Revised per input from Ethics Committee.
1.2	Screening Period in Figure 1 revised from "Up to 28 weeks" to "Up to 28 days".	Corrected an error in the figure.
4.2.1, 5.1/Inclusion criterion #9, 6.5	Changed "and" to "or" for stable doses of MTX, sulfasalazine or leflunomide.	Revised for clarity and accuracy.
5.1 /Inclusion criteria #8, 9, and 10	Added references and links to Appendix 5.	Revised to include links to the list of excluded medications and treatments in the appendix.
5.2 /Exclusion criterion #4	Revised exclusion of intra-articular corticosteroids to during the Screening Period.	Revised for clarity and accuracy.
6.5	Revised permitted use of stable non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 to within 28 days prior to randomisation and during the study; revised permitted use of stable oral corticosteroids (≤ 10 mg) to 28 days prior to Baseline, not Screening.	Revised for consistency with Appendix 5.
8.1	Basis of subject's overall assessment of the severity of spinal pain revised to single question on VAS.	Revised to correct an error in number of questions.
8.2.4.2	Lateral chest x-ray deleted.	Removed to lessen the burden on subjects as in the experts' opinions this procedure is not required.
Appendix 5	Revised excluded oral corticosteroids to within 28 days prior to Baseline, not Screening.	Revised for consistency with inclusion/ exclusion criteria.
Appendix 8	Added new appendix for protocol amendment history.	Revised per protocol template to include previous amendments.
Throughout	Minor editorial and document formatting revisions.	Editorial updates and corrections.
Title Page, page headers and footers, Protocol Amendment Summary, Table 1, Table 2, Appendix 9	Updated amendment number, date, and changes made with current amendment.	Revised to include changes included with current amendment.

TABLE OF CONTENTS

TABLE OF TABLES

TABLE OF FIGURES

1.0 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A phase 2a proof of concept, randomised, double-blind, placebo-controlled study to evaluate the safety/tolerability and efficacy of 4 subcutaneous injections of namilumab (150 mg) given over 10 weeks in subjects with moderate-to-severely active axial spondyloarthritis including those previously exposed to anti-TNF (tumour necrosis factor) therapy. (NAMASTE study)

Short Title: Efficacy and safety of namilumab for moderate-to-severe axial spondyloarthritis

Rationale:

The purpose of this study is to assess the effect of namilumab, a granulocyte-macrophage colony-stimulating factor (GM-CSF) inhibitor, on the clinical response in subjects with axial spondyloarthritis (axSpA). Current treatment options, including non-steroidal anti-inflammatory drugs (NSAIDs), tumour necrosis factor inhibitors (TNFi) and interleukin (IL)-17 inhibitors, do not provide clinical response for many patients (see Section 2.2) and new treatment options are needed.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To assess the efficacy of namilumab 150 mg subcutaneous (sc), given on Weeks 0, 2, 6 and 10 in subjects with axSpA	• Proportion of subjects who achieve an ASAS20 clinical response at Week 12
Secondary	
• To assess the efficacy of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 on other clinical responses in subjects with axSpA	• Proportion of subjects who achieve ASAS40 and ASAS70 response at Week 12 • Proportion of subjects who achieve an ASAS20 clinical response at Week 6 • Proportion of subjects who achieve ASDAS-CRP response at Weeks 6 and 12

• To assess the safety and tolerability of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 in subjects with axial spondyloarthritis	• Adverse events (AEs)
	• Serious adverse events (SAEs)
	• Laboratory evaluations
	• Vital signs
	• Electrocardiograms (ECGs)
	• Physical examinations
	• Assessments of pulmonary function
	  o MRC breathlessness scale
	  o Chest x-ray
	  o Lung function tests
	  o Pulse oximetry
	• Immunogenicity
	• AEs of special interest:
	  o Pulmonary alveolar proteinosis (PAP)
	  o Neutropaenia
	  o Myeloid suppression

Exploratory	
• To assess the efficacy of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 on radiologic responses in subjects with axial spondyloarthritis • To assess the effect of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 on other clinical responses, biomarkers, immunophenotyping, and pain scores in subjects with axial spondyloarthritis	• Proportion of subjects who show a radiological response on MRI at 12 weeks • Proportion of subjects who achieve ASAS20 clinical response at Weeks 2 and 10 • Proportion of subjects who achieve ASDAS-CRP response at Weeks 2 and 10 • Joint count, tendon swelling, and enthesitis at Weeks 2, 6, 10, and 12 • Serum biomarkers including CRP, faecal biomarkers including calprotectin and microbiome • Pre- and post-treatment immunophenotyping with CyTOF and gene expression (RNA seq) of CD4, CD8, CD56 and CD14 cells • Neuropathic pain score (painDETECT™) at 6 and 12 weeks
AE=adverse event; ASAS20/40/70=Assessment in Ankylosing Spondylitis with 20%/40%/70% improvement; ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score C-reactive Protein; axSpA=axial spondyloarthritis; CyTOF=cytometry by time of flight; ECG=electrocardiogram; MRC=Medical Research Council; MRI=magnetic resonance imaging; PAP=pulmonary alveolar proteinosis; SAEs=serious adverse events.	

Overall Design:

This is a proof-of-concept, randomised, double-blind, placebo-controlled, multi-centre study designed to evaluate the safety/tolerability and efficacy of 4 subcutaneous (sc) injections of namilumab 150 mg given over 10 weeks as therapy in subjects with moderately-to-severely active axSpA, including those with a history of inadequate response to or intolerance to anti-TNF therapy. The study will allow enrolment of up to 50% of subjects with primary non-response to prior anti-TNF treatment.

The study will consist of a maximum 4-week Screening Period, followed by a 12-week double-blind treatment evaluation period, followed by a 16-week safety follow-up period, for a maximum study duration of approximately 32 weeks or 224 days per subject. Eligible subjects will be randomised on Day 1 of Week 0 and receive study treatment administered sc on Day 1 of Week 0, Week 2 (loading dose), Week 6 and Week 10. Subjects will return on Week 12 for an End of Treatment (EoT) visit during which efficacy and safety assessments will be performed. Subjects will have a follow-up visit 16 weeks after the EoT visit.

Number of Investigators and Study Centres:

Up to 10 Investigators and 10 study centres are expected to participate in this study.

Number of Subjects:

Approximately 70 subjects will be screened to achieve 42 subjects randomly assigned to study treatment (36 on active treatment and 6 on placebo) and 42 evaluable subjects for an estimated total of 36 evaluable subjects on the active treatment arm and 6 evaluable subjects in the placebo treatment arm.

Treatment Groups and Duration:

Test product, dose and mode of administration:

Namilumab 150 mg sc administered at Weeks 0, 2, 6 and 10.

Reference therapy, dose and mode of administration:

Matching placebo solution sc administered at Weeks 0, 2, 6 and 10.

Statistical Methods:

The primary endpoint will be ASAS20. Based on literature data, the prior for the placebo and namilumab groups will follow a beta distribution with mean of 0.3 and 0.6, respectively. Weighting for the priors will be equivalent to 20 and 5 subjects, respectively. Sample size is the smallest sample size so that $P\{\theta act > \theta pbo | Y(HA)\} > 0.927$ with probability 0.9, assuming true response rates of 0.3 and 0.6 for the control and namilumab arms, respectively. For a 6:1 randomisation, 42 patients need to be randomised.

Efficacy endpoints will be summarised by treatment group and visit. The posterior distribution of the primary endpoint will be computed using the conjugate priors, and the mean, standard deviation, and 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of the posterior distribution will be presented.

Safety data will be analysed using the Safety Analysis Set. Adverse events will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA). Incidence rates of treatment-emergent AEs (TEAEs) will be presented by treatment group. Laboratory, ECG, and vital signs will be summarised by treatment group and scheduled visit.

Safety Review Team:

A Safety Review Team consisting of the Coordinating Investigator, the Sponsor's Medical Expert/Chief Medical Officer, and an independent Safety Physician will review ongoing safety data on a monthly basis. The data review will be conducted for randomised subjects and will include a review of vital signs, laboratory assessments, ECGs, AEs (including AEs of special interest and SAEs), physical examinations, and assessments of pulmonary functions. The Safety Review Team will provide consolidated feedback of the Team's findings to the study team. Additional details of the Safety Review will be provided separately.

1.2 Study Schema

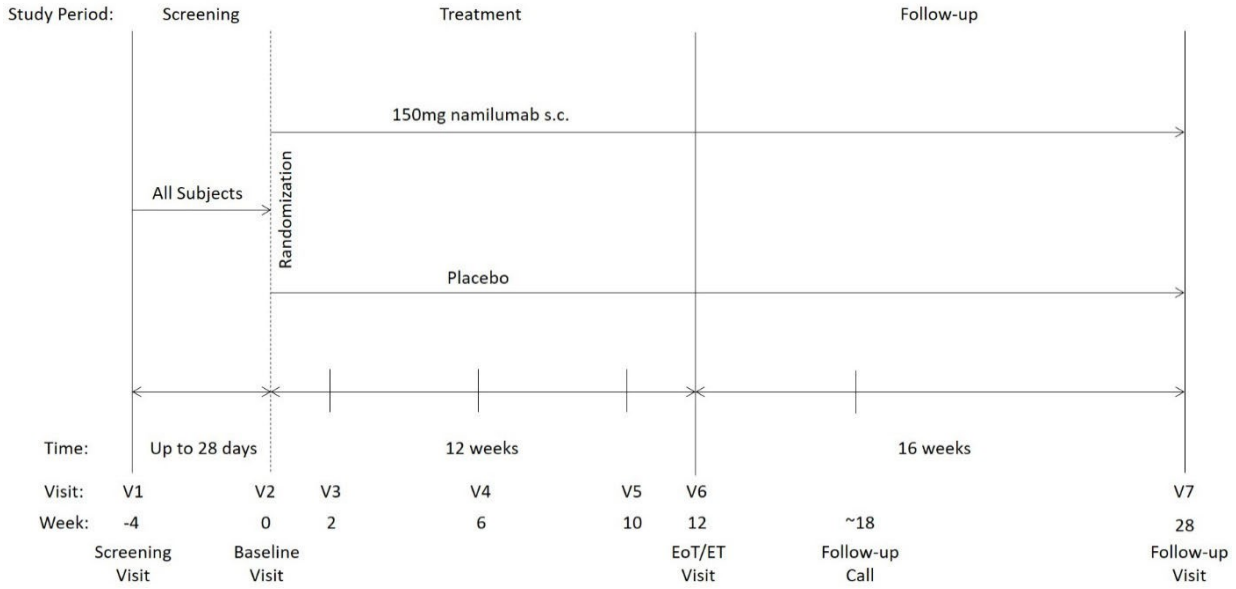

Figure 1 Study Schema

1.3 Schedule of Activities

Table 3 Schedule of Activities

Procedure	Screening[1] (Up to 28 Days before Day 1)	Treatment Period[2]				EoT/ ET Visit	FU Phone Contact[3]	Follow-up
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**		**7**
Study Week	**-4 to -1**	**0**	**2**	**6**	**10**	**12**		**28**
Study Day/Window	**-28 to -8**	**1**	**15/±2**	**43/±2**	**71/±2**	**85/±2**		**197/±4**
Screening								
Informed consent	X							
Inclusion and exclusion criteria	X	X						
Demography	X							
Medical history	X							
Past and current medical conditions	X							
Safety Assessments								
Full physical examination	X					X		X
Height	X							
Weight	X					X		
Vital signs[4]	X	X	X	X	X	X		X
12-lead ECG	X			X	X	X		X
Clinical laboratory assessments (haematology, chemistry including CRP and ESR, urinalysis)	X	X	X[5]	X	X[5]	X		X[5]
Serum pregnancy test[6] (WOCBP only)	X							
Urine pregnancy test[6] (WOCBP only)		X	X	X	X	X		X
HIV testing	X							
Serology (Hep B and C)	X							
QuantiFERON-TB (or equivalent test)	X							
Lung function tests[7]		X				X		
Pulse oximetry	X	X	X	X	X	X		X
MRC breathlessness scale	X	X	X	X	X	X		X
Chest x-ray[8]	X					X		X
Adverse events	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X

Procedure	Screening[1] (Up to 28 Days before Day 1)	Treatment Period[2]				EoT/ ET Visit	FU Phone Contact[3]	Follow-up
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**		**7**
Study Week	**-4 to -1**	**0**	**2**	**6**	**10**	**12**		**28**
Study Day/Window	**-28 to -8**	**1**	**15/±2**	**43/±2**	**71/±2**	**85/±2**		**197/±4**
Efficacy Assessments								
Subject's Global Assessment of Disease Status		X	X	X	X	X		
Subject's assessment of spinal pain	X	X	X	X	X	X		
BASFI		X	X	X	X	X		
BASDAI	X	X	X	X	X	X		
MRI	X[9]					X[10]		
ASDAS-CRP assessment		X	X	X	X	X		
Neuropathic pain score (painDETECT™)		X		X		X		
Joint count, tendon swelling, and enthesitis		X	X	X	X	X		
PK/PD Assessments[11]								
Blood sample saved for Total GM-CSF (namilumab/GM-CSF complexes), namilumab serum concentration, immunogenicity[12] and immunology[13]		X	X			X		X
Saliva sample for DNA (optional)		X						
Blood sample for biomarkers and immunophenotyping		X	X			X		X
Blood sample for HLA-B27[14]	X							
Stool sample for calprotectin		X	X			X		X
Stool sample for microbiome analysis		X	X			X		X
IMP administration								
Randomisation		X						
Subcutaneous dosing of IMP		X	X	X	X			

AE=adverse event; ANA=anti-nuclear antibody; ASDAS=Assessment of SpondyloArthritis Disease Activity Score; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; CRP=C-reactive protein; ECG=electrocardiogram; EoT=End of Treatment; ESR=erythrocyte sedimentation rate; ET=Early Termination; FU=Follow-up; GM-CSF=granulocyte-macrophage colony-stimulating factor; Hep=hepatitis; HIV=human immunodeficiency virus; IMP=investigational medicinal product; MRC=Medical Research Council; MRI=magnetic resonance imaging; PAP=pulmonary alveolar proteinosis; PD=pharmacodynamic; PK=pharmacokinetic; WOCBP=women of childbearing potential.

1. Screening may be a maximum 4 weeks prior to baseline for some subjects (where stabilisation/wash-out of concomitant medication is needed) and only 1 week prior to baseline for subjects that already meet all inclusion/exclusion criteria).
2. Subjects who discontinue the study prior to the EoT visit should attend the EoT/ET visit and follow the schedule for the FU period.
3. One FU telephone contact will be performed between study completion and end of study visit approximately 6 weeks after last dosing; AE and concomitant medication will be collected.
4. In the treatment period, both pre-dosing and post-dosing (approximately 30 minutes post-dosing) vital sign assessments are to be performed.
5. Blood draw for evaluation of CRP and ESR only.
6. Pregnancy testing at Screening will be in serum; pregnancy testing at other visits will be in urine; a positive urine test will be confirmed with a serum pregnancy test.
7. Lung function tests includes: FEV_1, FVC and PEF.
8. Chest x-ray within 3 months of Screening to assess for PAP.
9. The pre-dosing MRI can be performed within 6 months before Screening.
10. Although the post-dosing EoT MRI is scheduled to occur at the week 12 visit, the MRI may be performed between weeks 12 and 16 if possible for study centres with logistical issues that prevent performing the MRI at the week 12 visit. The EoT MRI is optional; however, the study centres are requested to perform the EoT MRI on all subjects to the extent possible.
11. PK/PD sampling must be taken pre-dose (t=0).
12. Stored sample for immunogenicity assessment for evaluation of anti-namilumab antibodies.
13. Immunology assessment for evaluation of ANA (anti-dsDNA if ANA is positive).
14. HLA-B27 testing will only be performed in subjects whose HLA-B27 status is unknown.

2.0 INTRODUCTION

Namilumab (AMG203 or MT203) is a human immunoglobulin G1 (IgG1) monoclonal anti-granulocyte-macrophage colony stimulating factor (GM-CSF) antibody, with a molecular weight of approximately 146 kDa, which potently and specifically neutralises human and macaque GM-CSF.

2.1 Study Rationale

The purpose of this study is to assess the effect of namilumab, a GM-CSF inhibitor, on the clinical response in subjects with axial spondyloarthritis (axSpA). Current treatment options including non-steroidal anti-inflammatory drugs (NSAIDs), tumour necrosis factor inhibitors (TNFi) and interleukin (IL)-17 inhibitors do not provide clinical response for many patients (see Section 2.2) and new treatment options are needed.

GM-CSF is thought to be a key activator of the innate arm of the immune system and as such is involved in the chronic stages of inflammatory and autoimmune diseases. GM-CSF acts as a pro-inflammatory cytokine and is aberrantly overproduced in a multitude of inflammatory and autoimmune human diseases, including rheumatoid arthritis (RA), psoriasis and axSpA. The central role of GM-CSF in the immune response and evidence of its involvement in human inflammatory and autoimmune diseases is a major rationale for the development of an anti–GM-CSF antibody as novel therapy for the treatment of these diseases, including axSpA.

2.2 Background

Spondyloarthropathy (SpA) refers to a group of rheumatic disorders that share common clinical features, extra-articular manifestations and a genetic association with the type 1 major histocompatibility complex HLA-B27. SpA comprises two subgroups based on primary localisation of symptoms: axSpA, which includes non-radiographic axSpA (nr-axSpA), radiographic axSpA and ankylosing spondylitis (AS), and peripheral SpA (phSpA), which includes psoriatic arthritis, reactive arthritis, enteropathic arthritis and undifferentiated SpA (Scotti 2017).

AxSpA is characterised by a broad clinical spectrum of disease manifestations, including inflammatory back pain, peripheral arthritis, dactylitis, uveitis, psoriasis, inflammatory bowel disease and aortic insufficiency (Strand 2017). Additional symptoms such as fatigue, sleep problems, depression and sexual dysfunction can profoundly affect health-related quality of life and limit work, leisure and daily activities (Strand 2017). The prevalence of axSpA is approximately 1% of the general population (Raine 2014).

Current pharmacological treatment options for patients with axSpA include local glucocorticoid injections, NSAIDs, TNFi and IL-17A inhibitors (Toussirot 2017). However, results from

clinical trials show that only 50 to 65% of subjects with axSpA who were treated with TNFi for 24 weeks and 58 to 64% of subjects with AS who were treated with IL-17A inhibitors for 16 weeks exhibit a low level clinical response (ASAS20) (Davis 2005; Inman 2008; Landewe 2014; van der Heijde 2005; van der Heijde 2006; Baeten 2015). In clinical practice, up to 45% of subjects with axSpA treated for 2 years with TNFi discontinue this treatment. Thus, there is a need for new therapies to expand the treatment options in this chronic progressive disease.

Namilumab has been investigated by Takeda Pharmaceuticals (Takeda) as a treatment option for RA. Non-clinical studies have shown that namilumab has demonstrated potent and specific neutralising bioactivity of cynomolgus monkey and human GM-CSF.

Safety Pharmacology: No namilumab-related acute effects on the respiratory, cardiovascular, and central nervous system were detected in cynomolgus monkeys in safety pharmacology investigations included in the 4-week toxicity study and an initial 26-week repeat-dose toxicity study with namilumab. Mild and transient elevations in C-reactive protein (CRP) as well as aspartate transaminase (AST) and alanine transaminase (ALT) were observed in some test animals. In an initial 26-week repeat-dose toxicity study, minimal-to-moderate foamy alveolar macrophage accumulation occasionally accompanied by inflammation and the presence of extracellular debris in the alveolar space of the lung were noted at higher doses of 10 mg/kg/2-weeks or more. In a supplemental toxicity study of namilumab up to 3 mg/kg/2-weeks, foamy alveolar macrophage accumulation was observed across all dose groups as well as the control group, but no inflammation or extracellular debris was observed, and the findings were considered to be incidental and/or spontaneous in nature and not adverse.

Clinical Studies: Seven clinical studies have been completed with namilumab: 2 studies in healthy subjects; a study in Japanese and Caucasian healthy subjects; 4 studies in subjects with mild-to-moderate RA on treatment with methotrexate (MTX); and 1 study in subjects with moderate-to-severe psoriasis. The half-life ($t_{1/2}$) of namilumab was 25 days following intravenous (i.v.) administration and 21 days following subcutaneous (sc) administration. The safety profile of namilumab showed the treatment was generally safe and well-tolerated. One serious adverse event (SAE) was reported in a healthy subject: this consisted of a 6 second, self-limited episode of wide complex tachycardia after infusion of 3 mg/kg namilumab, which was recorded as a suspected unexpected serious adverse reaction (SUSAR) (serious due to a medically important event, unexpected and related as assessed by the Investigator), but was not considered life-threatening or medically serious. No other related SAEs were reported. Non-related SAEs included cardiac events, breast cancer and non-small cell lung cancer. No allergic reactions were reported.

A detailed description of the chemistry, pharmacology, efficacy and safety of namilumab is provided in the current Investigator's Brochure.

2.3 Benefit/Risk Assessment

Namilumab has not yet been administered to patients with axSpA, and therefore no benefit has yet been shown.

Namilumab has been administered to healthy volunteers, subjects with psoriasis and subjects with RA. However, due to limited clinical experience with namilumab, all subjects should be closely monitored for any potential occurrence of serious events, such as severe hypersensitivity or lung disorders, cardiac events and hepatic toxicity. When necessary, namilumab administration should be discontinued and appropriate medical interventions initiated. In addition, appropriate prophylactic measures should also be considered in subjects thought to be at higher risk for these events.

The possibility of a severe allergic reaction, including anaphylaxis, which can manifest as life-threatening bronchospasm or hypotension, should always be considered. A physician should be available on-site and supplies of epinephrine, antihistamine and corticosteroid readily accessible when a subject is being administered the investigational medicinal product (IMP). A subject who has such an allergic reaction should not receive additional IMP injections.

Special attention should be given to respiratory symptoms arising during namilumab treatment, due to the theoretical risk of pulmonary alveolar proteinosis (PAP). If the symptoms are mild and a likely cause of the symptoms can be established, the subject can remain in the study and the condition treated at the discretion of the Investigator. Should the symptoms be severe, or no likely cause can be established, the subject should be referred to a pulmonologist for further evaluation that may include chest computer tomography scanning and broncho-alveolar lavage including cytology.

In case of unforeseen (e.g., dental) surgery between Screening and End of Study, subjects should receive adequate antibiotic prophylaxis.

Clinical evidence indicates that immunisation in subjects with immune-mediated inflammatory diseases does not increase clinical or laboratory parameters of disease activity (Gluck 2008). Live vaccines are contraindicated because of the potential risk of immune-suppression associated with any immunomodulators, but non-live (killed) vaccines can be used (Rahier 2010). Vaccination status is best checked and updated before the start of any immunomodulatory therapy with agents such as MTX or namilumab.

In view of the potential for interference with response to an investigational drug, restrictions on vaccine use are in place for clinical studies involving namilumab. At present the effect of namilumab on vaccine response is not known.

Live (live-attenuated) vaccines are not permitted within 2 weeks prior to randomisation or during the study treatment and safety follow-up periods.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of namilumab may be found in the Investigator's Brochure.

3.0 OBJECTIVES AND ENDPOINTS

Table 4 Study Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of namilumab 150 mg subcutaneous (sc), given on Weeks 0, 2, 6 and 10 in subjects with axSpA	• Proportion of subjects who achieve an ASAS20 clinical response at Week 12
Secondary	
• To assess the efficacy of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 on other clinical responses in subjects with axSpA	• Proportion of subjects who achieve ASAS40 and ASAS70 response at Week 12 • Proportion of subjects who achieve an ASAS20 clinical response at Week 6 • Proportion of subjects who achieve ASDAS-CRP response at Weeks 6 and 12
• To assess the safety and tolerability of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 in subjects with axial spondyloarthritis	• AEs • SAEs • Laboratory evaluations • Vital signs • Electrocardiograms (ECGs) • Physical examinations • Assessments of pulmonary function o MRC breathlessness scale o Chest x-ray o Lung function tests o Pulse oximetry • Immunogenicity • AEs of special interest: o Pulmonary alveolar proteinosis (PAP) o Neutropaenia o Myeloid suppression

Objectives	Endpoints
Exploratory	
• To assess the efficacy of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 on radiologic responses in subjects with axial spondyloarthritis • To assess the effect of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 on other clinical responses, biomarkers, immunophenotyping, and pain scores in subjects with axial spondyloarthritis	• Proportion of subjects who show a radiological response on MRI at 12 weeks • Proportion of subjects who achieve ASAS20 clinical response at Weeks 2 and 10 • Proportion of subjects who achieve ASDAS-CRP response at Weeks 2 and 10 • Joint count, tendon swelling, and enthesitis at Weeks 2, 6, 10, and 12 • Serum biomarkers including CRP, faecal biomarkers including calprotectin and microbiome • Pre- and post-treatment immunophenotyping with CyTOF and gene expression (RNA seq) of CD4, CD8, CD56 and CD14 cells • Neuropathic pain score (painDETECT™) at Week 6 and 12

AE=adverse event; ASAS20/40/70=Assessment in Ankylosing Spondylitis with 20%/40%/70% improvement; ASDAS-CRP=Ankylosing Spondylitis Disease Activity Score C-reactive Protein; axSpA=axial spondyloarthritis; CyTOF=cytometry by time of flight; ECG=electrocardiogram; MRC=Medical Research Council; MRI=magnetic resonance imaging; PAP=pulmonary alveolar proteinosis; SAEs=serious adverse events.

4.0 STUDY DESIGN

4.1 Overall Design

This is a proof-of-concept, randomised, double-blind, placebo-controlled, multi-centre study designed to evaluate the safety/tolerability and efficacy of 4 sc injections of namilumab 150 mg given over 10 weeks as therapy in subjects with moderately-to-severely active axSpA, including those with a history of inadequate response to or intolerance to anti-tumour necrosis factor (TNF) therapy. The study will allow enrolment of up to 50% of subjects with primary non-response to prior anti-TNF treatment.

The study will consist of a maximum 4-week Screening period, followed by a 12-week double-blind treatment evaluation period, followed by a 16-week safety follow-up period, for a maximum study duration of approximately 32 weeks or 224 days per subject. Eligible subjects will be randomised on Day 1 of Week 0 and receive study treatment administered sc on Day 1 of Week 0, Week 2 (loading dose), Week 6 and Week 10. Subjects will return on Week 12 for an End of Treatment (EoT) visit during which efficacy and safety assessments will be performed. Subjects will have a follow-up visit 16 weeks after the EoT visit.

4.2 Scientific Rationale for Study Design

This study is designed as a phase 2a proof-of-concept study evaluation of namilumab in the treatment of subjects with axSpA. Subjects who have inadequately responded to or experienced intolerance to previous treatment with an anti-TNF agent may be included but will be limited to 50% of the total study population; this sub-population may respond significantly to namilumab, providing a sensitive basis for dose selection/optimisation in advance of further (phase 3) clinical development. The overall study population is also considered likely to benefit from the novel mechanism of namilumab, which may provide a new treatment option for subjects intolerant to or failing previous therapies.

The choice of 150 mg/mL namilumab for this investigation was based on the dose demonstrating maximal efficacy in clinical studies of rheumatoid arthritis and still within the margins of safety.

4.2.1 Subject Population Studied (Defined by Demography, Disease and/or Treatment Characteristics)

In order to ensure that the study data will be relevant to the future use of this agent in clinical practice, the design is representative of clinical practice in terms of both the selected study populations and concomitant medications (stable doses of NSAIDs, MTX, sulfasalazine or leflunomide).

4.2.2 Justification for Design and Sample Size

A parallel-arm, randomised, double-blind, placebo-controlled study design is a conventional and well-established design to assess proof-of-concept effects of new biologics in axSpA. This study design follows the Committee for Proprietary Medicinal Products (CPMP)/European Medicines Agency (EMA) Draft Guideline (12 October 2017): "*EMA Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis*" (EMA/CPMP/EWP/4891/03 Rev. 1).

Sample size justification is provided in Section 9.2.

4.2.3 Justification of Control Group

The choice and rationale of a control group is in accordance with the CPMP/EMA Guideline (December 2003). Section 5.1 of the guideline recommends use of placebo controls for a limited duration of 3 to 6 months. The use of NSAIDs with gastric protection and low-dose corticosteroids, all in stable doses, is allowed to ensure a minimum background treatment remains in place.

Acknowledging the general need to ensure use of a minimum period for treatment comparison with placebo in clinical studies, the planned investigation will be conducted over 12 weeks. Throughout this period discomfort for placebo-treated subjects will be minimised by the concomitant use of standard of care therapy: this approach will include stable dose pain-relief medication together which may include MTX.

4.2.4 Justification for Route, Dose Regimen, Treatment Period, with Reference to Previous Exposure, PK/PD Profile and Non-clinical Safety

This will be the first time that namilumab is to be administered subcutaneously to subjects with moderate-to-severe axSpA. Non-clinical studies have not revealed any risks associated with multiple dosing and clinical studies in healthy volunteers and subjects with RA and psoriasis have shown namilumab to be safe and well tolerated (see Investigator's Brochure). The current administration schedule is designed based on the simulation of pharmacokinetic (PK) results of the first-in-man study. With the selected schedule, the steady state serum concentration is expected to be reached by the second injection. The half-life of namilumab as determined from the first-in-man study data is 25 days and thus supports maintenance dosing with a 4-week interval.

The time to onset of action of namilumab in patients with axSpA is not established; however, it is expected to be in a range within 12 weeks from first administration. Therefore, some clinical effect is expected after 12 weeks in this study.

4.2.5 Justification for Primary Endpoints

The primary endpoint, Assessment in Ankylosing Spondylitis with 20% improvement (ASAS20) clinical response at 12 weeks, and the secondary endpoints, ASAS40, ASAS70, Ankylosing Spondylitis Disease Activity Score C-reactive Protein (ASDAS-CRP) response, and improvement of CRP, are consistent with the revised EMA Draft guidance (12 October 2017) for studies in axSpA.

4.3 Justification for Dose

The namilumab drug product is a single-dose liquid solution for sc injection containing 20 mg/mL, 50 mg/mL, 80 mg/mL or 150 mg/mL namilumab active ingredient. From the NEXUS study performed in subjects with moderate-to-severe RA, it was concluded that 150 mg was the most effective dose of namilumab in subjects with RA, as well as being associated with a manageable safety profile. In addition, the chronic toxicology study in cynomolgus monkeys demonstrated that the 150 mg dose in humans lies within a favourable therapeutic window of equivalent doses in monkeys (see Section 1.1.5 in the Investigator's Brochure). Therefore, the dose of 150 mg/mL was chosen for the current study in subjects with axSpA.

Treatment-related treatment-emergent AEs (TEAEs) associated with namilumab 150 mg were single cases of infection, oropharyngeal pain/dental caries, headache, decreases in neutrophil counts/neutropenia, elevated liver function tests and decreased forced expiratory volume (FEV)/force vital capacity (FVC) (see Table 6.b in the Investigator's Brochure). Based on haematology and clinical chemistry variables, there were no clinically significant or serious cases of neutropenia or abnormal liver function and there were no cases of confirmed PAP. No deaths or treatment-related SAEs were reported in subjects receiving namilumab 150 mg. These results suggest that the 150 mg dose chosen for the current study is safe and well tolerated.

4.4 End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last subject in the study.

5.0 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Subjects are eligible to be included in the study only if all of the following criteria apply:

1. Age ≥18 and ≤75 years of age.
2. Diagnosis of axSpA by an appropriately qualified physician and classified using ASAS criteria ≥3 months prior to Baseline; symptoms must have started before age 45.
3. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥4 and spinal pain score ≥40, at screening and Baseline.
4. MRI evidence of active axSpA ≤6 (ideally ≤3) months prior to randomisation using ASAS criteria.
5. A negative tuberculosis (TB) screening assessment.
6. A female subject of childbearing potential who is sexually active with a non-sterilised male partner agrees to routinely use adequate contraception from signing of the informed consent throughout the duration of the study until the end of the safety follow up (18 weeks after last dose) (see Appendix 7).
7. A male subject who is non-sterilised and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of the informed consent throughout the duration of the study until the end of the safety follow up (18 weeks after last dose) (see Appendix 7).
8. Stable NSAID use for 28 days prior to study entry (see Appendix 5).
9. Stable use of MTX (≤25 mg/week), sulfasalazine (≤3 g/day) or leflunomide (≤20 mg/day) for 28 days prior to study entry (see Appendix 5).
10. Stable oral corticosteroid dose ≤10 mg for 28 days prior to study entry (see Appendix 5).
11. Capable of giving signed informed consent as described in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

In addition, the following inclusion criteria will apply for some subjects:

12. Inadequately responded to or experienced intolerance to previous treatment with an anti-TNF agent (limited to 50% of the total study population).
    Note: Criteria for inadequate response to or experienced intolerance to previous treatment with an anti-TNF agent are defined as:

- Signs and symptoms of persistently active disease despite a history of at least one12-week regimen of one of the following agents:
    - Infliximab: 5 mg/kg i.v.
    - Etanercept: 50 mg weekly
    - Adalimumab: 40 mg fortnightly
    - Golimumab: 50 mg monthly
    - Certolizumab pegol: 400 mg SC initially and at Weeks 2 and 4, followed by 200 mg every 2 weeks or 400 mg every 4 weeks

OR

- Recurrence of symptoms during scheduled maintenance dosing following prior clinical benefit (discontinuation despite clinical benefit does not qualify).

OR

- History of intolerance of at least one TNF antagonist (including, but not limited to infusion-related reaction, demyelination, congestive heart failure and infection).

5.2 Exclusion Criteria

Subjects are excluded from the study if any of the following criteria apply:

1. A current diagnosis of axSpA with a BASDAI >4 but no evidence of inflammation on MRI.
2. Discontinued biologic therapy such as adalimumab, etanercept, infliximab, golimumab and certolizumab pegol <8 weeks prior to Baseline.
3. Previous or current use of oral corticosteroid and meets one of the following criteria:
    - Is receiving prednisone or prednisone equivalent >10 mg/day at Baseline;
    - Has discontinued use of corticosteroid within 28 days of Baseline;
    - Has not been on stable doses of corticosteroid for at least 28 days prior to Baseline; or
    - Has been taking both oral budesonide and prednisone (or equivalent) simultaneously.
4. Received intra-articular corticosteroids during the Screening Period or i.v. corticosteroids within 14 days prior to Screening or during the Screening Period.
5. Received anti-IL-17A or anti IL12/23 therapy.
6. Received cyclosporine, tacrolimus or mycophenolate mofetil within 28 days prior to Baseline.
7. Previously received stem cell transplantation.
8. Infection(s) requiring treatment with i.v. anti-infectives within 28 days prior to the Baseline Visit or oral anti-infectives within 14 days prior to the Baseline Visit.
9. Screening laboratory and other analyses show any of the following abnormal results:

- Bilirubin > upper limit of normal (ULN) and serum AST or ALT > 1.5 × ULN;
- Estimated glomerular filtration rate <40 mL/min/1.73 m^2;
- Total white blood cell (WBC) count <3,000/µL;
- Absolute neutrophil count (ANC) <1,000/µL;
- Platelet count <100,000/µL;
- Absolute lymphocyte count <750/µL;
- Haemoglobin <9 g/dL.

10. Any active or recurrent viral infection that based on the Investigator's clinical assessment makes the subject an unsuitable candidate for the study, including recurrent/disseminated herpes zoster or known history of human immunodeficiency virus (HIV).
11. Hepatitis B (hepatitis B virus surface antigen [HBsAg] positive [+] or detected sensitivity on the hepatitis B virus [HBV] DNA polymerase chain reaction [PCR] qualitative test for hepatitis B core antibodies [HBc Ab]/hepatitis B surface antibody [HBsAb] positive subjects) or hepatitis C (hepatitis C virus [HCV] RNA detectable in any subject with anti-hepatitis C virus antibody [HCV Ab]).
12. Any active or chronic recurring infections or untreated latent TB.
13. History of moderate-to-severe congestive heart failure (New York Heart Association [NYHA] class III or IV), risk factors for coronary syndrome, hypertension, angina and myocardial infarction, cerebrovascular accident and any other condition within 6 months, which in the opinion of the Investigator, would put the subject at risk by participation in the study.
14. Receipt of any live vaccine within 2 weeks prior to randomisation, or will require live vaccination during study participation including up to 1 month after the last dose of study drug.
15. Evidence of current or prior dysplasia or history of malignancy (including of the gastrointestinal tract) other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma or localised carcinoma in situ of the cervix or adenomatous polyp that has been completely resected.
16. Has had any uncontrolled and/or clinically significant (per Investigator's judgement) illness, hospitalisation, or has had any surgical procedure requiring general anaesthesia within 30 days prior to Screening, or has any planned surgical procedure within 6 months after randomisation.
17. Known current or previous interstitial lung disease.
18. Positive pregnancy test at Screening (serum) or Baseline (urine).
19. Female subjects who are breastfeeding or considering becoming pregnant during the study.
20. Considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
21. Received any investigational agent or procedure within 30 days or 5 half-lives prior to Baseline, whichever is longer.

22. History of clinically significant drug or alcohol (> 40 units per week) use in the last 12 months.
23. Related to or a dependent of the site staff, or a member of the site staff.

5.3 Lifestyle Considerations

No restrictions with regard to lifestyle are required.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomly assigned to study treatment/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after discussion with the Medical Advisor/Sponsor Medical Representative. Rescreened subjects should not be assigned the same subject number as for the initial screening.

Safety assessments that are measured and do not meet the inclusion/exclusion criteria may be repeated once without the subject being considered a screen failure.

Subjects who are rescreened more than 2 weeks after their first screen will have all assessments repeated.

6.0 STUDY TREATMENT

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo or medical device(s) intended to be administered to a subject according to the study protocol.

6.1 Study Treatment(s) Administered

Table 5 Study Treatment Details

Study Treatment Name:	Namilumab	Placebo
Dosage Formulation:	Solution for injection	Solution for injection
Unit Dose Strength(s)/Dosage Level(s):	[redacted]	[redacted]
Route of Administration:	Subcutaneous	Subcutaneous
Dosing Instructions:	[redacted]	[redacted]
Packaging and Labelling:	Supplies of namilumab will be labelled according to local regulations.	Supplies of placebo will be labelled according to local regulations

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Preparation

All IMPs are provided in sterile, single-use glass vials. [redacted]. Each carton and vial will be labelled with a unique medication identification (MED ID) number and will be dispensed via an interactive web response system (IWRS).

6.2.2 Handling

All study medications will be administered by the Investigator or designee.

The subject will visit the clinic for dosing of [redacted] of blinded study medication by a single subcutaneous injection on Days 1, 15, 43 and 71.

6.2.3 Storage

The Investigator or designee must confirm that appropriate temperature conditions have been maintained for all clinical trial material received and that any discrepancies are reported and resolved before use.

The clinical trial material must be stored according to the manufacturer's stipulation, as specified on the label.

During shipping, vials will be protected from light and maintained between [redacted] Each shipment will include a packing slip listing the contents of the shipment, and any applicable forms.

All clinical trial material must be kept in an appropriate, limited-access, secure location until used or returned to the sponsor or designee. All study medication must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every day.

The Investigator or designee must confirm that appropriate temperature conditions have been maintained for all clinical trial material received and that any discrepancies are reported and resolved before use.

The Investigator is responsible for ensuring that deliveries of clinical trial material from the sponsor are correctly received, recorded, and handled, and stored safely and properly in accordance with the Code of Federal Regulations (CFR) or national and local regulations, and used in accordance with this protocol.

The Sponsor must be notified immediately of any temperature excursions, shipping and handling or storage discrepancies.

Drug supplies will be counted and reconciled at the site before being returned to Takeda or designee or being destroyed.

6.3 Measures to Minimise Bias: Randomisation and Blinding

6.3.1 Investigational Drug Assignment and Dispensing Procedures

Study medication will be provided in a blinded fashion and dispensed in accordance with randomisation code. Randomisation will be performed by IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each study site. Study treatment will be dispensed at the study visits as summarised in the Schedule of Activities (SoA). Returned study treatment must not be re-dispensed to subjects.

The Investigator or Investigator's designee will access the IWRS at Screening to obtain the subject study number. The Investigator or the Investigator's designee will utilise the IWRS to randomise the subject into the study. During this contact, the Investigator or designee will provide the necessary subject-identifying information, including the subject number assigned at screening. The MED ID number of the study medication to be dispensed will then be provided by the IWRS. If the MED ID number is lost or damaged, the site can request a replacement from the IWRS. (Refer to the IWRS manual provided separately). The MED ID number will be entered onto the electronic case report form (eCRF). At all drug-dispensing visits, the Investigator or designee will again contact the IWRS to request additional investigational drug for a subject.

6.3.2 Randomisation Code Creation and Storage

The randomisation schedule will be created by the Sponsor or designee and stored in a secure area, accessible only to authorised personnel. Block sizes will be specified in the randomisation specifications. Randomisation will be stratified by prior use of anti-TNF agents.

6.3.3 Investigational Drug Blind Maintenance

Products are not visually identical, however, to protect the blind, a clear yellow label will be applied to the cover of the syringe prior to the drug product being drawn from the vial. Vials and cartons will be supplied with a blinded label, randomisation will be unblinded and dispensation will be completed by an unblinded pharmacist.

The IMP blind will be maintained using the IWRS, which can be accessed and broken by the Investigator or designee in an emergency for unblinding of study medication assignments to ensure the safety of the subject.

6.3.4 Unblinding Procedure

The IMP blind shall not be broken by the Investigator unless information concerning the investigational drug is necessary for the medical treatment of the subject. In the event of a medical emergency, if possible (but not required), the medical monitor should be contacted before the IMP blind is broken to discuss the need for unblinding and if unblinding is required.

For unblinding a subject, the IMP blind can be obtained and broken by the Investigator at any time, by accessing the IWRS.

The Sponsor must be notified as soon as possible if the IMP blind is broken. The date, time and reason for the blind being broken must be recorded in the eCRF.

If any site personnel are unblinded to a subject's treatment, investigational drug must be stopped immediately and the subject must be withdrawn from the study. The Investigator or other site personnel should not reveal the specific treatment assignment of the unblinded subject to the medical monitor or other contract research organisation (CRO) or Sponsor staff. The subject should continue to the EoT/Early Termination (ET) Visit.

6.3.5 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the Sponsor or designee, or before being destroyed at the site (if approved by the Sponsor for destruction at the site).

The Investigator or designee must ensure that the clinical trial material is used in accordance with the approved protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of the clinical trial material, the Investigator must maintain records of all

Sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the Sponsor or designee.

Upon receipt of the clinical trial material, the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and that the medication is received within the labelled storage conditions in good condition. If there are any discrepancies between the packing list versus the actual product received, the Sponsor must be contacted to resolve the issue. The packing list should be filed in the Investigator's essential document file.

The Investigator must maintain 100% accountability for all clinical trial material received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Frequently verifying that actual inventory matches IWRS inventory.
- Verifying that the IWRS is completed for the MED ID used to prepare each dose.
- Verifying that all containers used are documented accurately in the IWRS.
- Verifying that required IWRS fields are completed accurately.

If any dispensing errors or discrepancies are discovered, the Sponsor must be notified immediately.

The current inventory of all clinical trial material at sites will be tracked through the IWRS.

The IWRS will include all required information as a separate entry for each subject to whom clinical trial material is dispensed.

The Investigator will be notified of any expiry date extension for clinical trial material during the study conduct. On expiry date notification from the Sponsor or designee, the site must complete all instructions outlined in the notification including segregation of expired clinical trial material for return to the Sponsor or its designee for destruction.

In the event of expiry date extension of supplies already at the study site, supplies may be relabelled with the new expiry date. In such cases, the Sponsor or its designee will prepare additional labels and all necessary documentation for completion of the procedure.

6.4 Study Treatment Compliance

The prescribed dosage, timing and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

All study medications will be administered by the Investigator or designee. Subject noncompliance is therefore not applicable.

If a subject misses a dose, the dose should be administered as close as possible to the missed scheduled dose, but there should be at least 2 weeks between doses. If a period of 2 weeks between doses is not possible, then the missed scheduled dose should not be administered and the subject dosing should resume with the next scheduled dosing.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrolment (within 28 days before the time of enrolment) or receives during the study must be recorded on the eCRF along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The use of stable doses of NSAIDs/COX-2 is permitted within 28 days prior to randomisation and during the study; the use of stable doses of MTX, sulfasalazine or leflunamide is permitted from 28 days prior to Screening and during the study.

The use of stable oral corticosteroids (≤10 mg) is permitted from 28 days prior to Baseline and during the study.

A list of excluded medications/therapy is provided in Appendix 5.

6.6 Dose Modification

No dose modifications are permitted in this study.

6.7 Treatment after the End of the Study

The Sponsor will not provide any additional care to subjects after they leave the study because such care should not differ from what is normally expected for subjects with axSpA.

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Treatment

Subjects may be discontinued from study treatment for the following reasons:

1. Pre-treatment event or treatment-emergent AE. The subject has experienced a pre-treatment event or a treatment-emergent AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the pre-treatment event or AE.

    - Liver Function Test Abnormalities
    - Study medication must be discontinued immediately with appropriate clinical follow-up (including repeat laboratory tests) until the subject's laboratory profile has returned to normal/baseline status, if the following circumstances occur at any time during study medication treatment:

        - ALT or AST >8 × ULN, or
        - ALT or AST >5 × ULN and persists for more than 2 weeks, or
        - ALT or AST >3 × ULN in conjunction with elevated total bilirubin >2 × ULN or international normalised ratio (INR) >1.5, without any anti-coagulant treatment, or
        - ALT or AST >3 × ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%).

2. If a diagnosis of PAP is confirmed during the course of this study (see Section 8.2.4), the subject should be withdrawn and treatment initiated as applicable.
3. Major protocol deviation. The discovery post-randomisation that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
4. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
5. Pregnancy. The subject is found to be pregnant.

Subjects who discontinue study treatment will not be replaced.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.2 Subject Discontinuation/Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioural, compliance or administrative reasons.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the study centre study records.

See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3 Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study centre.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The study centre must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

Protocol waivers or exemptions are not allowed.

Clinically significant safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 250 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

The following clinical assessments will be performed according to the SoA.

ASAS20 Clinical Response

An improvement of at least 20% and an absolute improvement of at least 10 units on a 0-100 scale in at least 2 of the following domains: Subject's Global Assessment of Disease Status, Subject's Assessment of Spinal Pain, Function (BASFI), and Inflammation (last 2 questions of BASDAI) (Sieper 2009). ASAS40 and ASAS70 are defined as above with improvements of at least 40% and 70%, respectively.

Subject's Global Assessment of Disease Status

The subject's overall assessment of current disease status (e.g., during the past week and the past 48 hours) on a 100 mm horizontal visual analogue scale (VAS). The left-hand extreme of the line is symptom-free and no AS symptoms and the right-hand extreme is maximum AS disease severity.

Subject's Assessment of Spinal Pain

The subject's overall assessment of the severity of spinal pain is based on a single question on a 100 mm horizontal VAS. The left-hand extreme of the line is "no pain" (symptom-free) and the right-hand extreme is "most severe pain" (maximum pain).

BASDAI

The BASDAI is a subject-administered assessment of 6 parameters specific to AS. The following parameters are assessed on a 100 mm horizontal VAS: fatigue, spinal pain, peripheral arthritis, enthesitis, intensity of morning stiffness and duration of morning stiffness.

For questions 1-5, the left-hand extreme of the line is "none" (symptom-free) and the right-hand extreme is "very severe" (maximum severity). Whereas for question 6, a time-axis is used. The left-hand extreme of the line is "0 hours" and the right-hand extreme is "2 or more hours".

The BASDAI score is: [Q1 + Q2 + Q3 + Q4 + (Q5 + Q6)/2]/5

BASFI

The BASFI is an assessment of function in an AS subject. The subject provides their own assessment of 10 questions on a 100 mm horizontal VAS. The BASFI score is the mean of these values.

ASDAS-CRP

The ASDAS-CRP is a composite index to assess disease activity in AS (Lukas 2009). It combines 5 disease activity variables with only partial overlap, resulting in one single score with better validity, enhanced discriminative capacity and improved sensitivity to change as compared to single-item variables (Lukas 2009; van der Heijde 2009).

The ASDAS-CRP will be calculated according to the following formula:

0.12 x back pain + 0.06 x duration of morning stiffness + 0.11 x patient global assessment + 0.07 x peripheral pain/swelling + 0.58 x ln (CRP +1)

Values below the CRP threshold will be computed as half of the value of the threshold.

For disease activity states, the following defined cut-offs will be used: ASDAS <1.3 to define "inactive disease", 1.3 ≤ ASDAS <2.1 to define "moderate disease activity", 2.1 ≤ ASDAS ≤3.5 to define "high disease activity", and ASDAS >3.5 to define "very high disease activity". A change of ≥1.1 units represents "clinically important improvement", and a change of ≥2.0 units represents major improvement.

Magnetic Resonance Imaging

An MRI of the axial skeleton will be taken at the times indicated in the SoA. The MRI will be obtained using 1.0, 1.5 or 3.0 Tesla scanners and phase array coils. Sagittal images of the upper (including C2 to T10) and lower (including T8 to S1) spine will be taken. The field of view is 34 to 38 cm. The following sequences may be used: T1 weighted turbo spin echo with a slice thickness of 3 mm and STIR (a sequence with intrinsic fat saturation) with a slice thickness of 3 mm.

MRI scans will be evaluated using Spondyloarthritis Research Consortium of Canada (SPARCC) MRI index for scoring inflammation of the spine.

Details of site training, MRI acquisition and central reading methods are detailed in the procedure manual for MRI examinations and the Imaging Review Charter (provided separately). MRI scans will be sent to the Central Imaging Laboratory. Specific shipping and transmitting instructions are provided in the procedure manual for MRI examination.

Immunophenotyping and Biomarker Evaluation

Pre- and post-treatment immunophenotyping with FACS, CyTOF and cell subset specific gene expression analysis (RNA seq and qPCR) of CD4, CD8, CD56 and CD14 cells will be performed. Blood, serum and urine will be analysed for protein and other biomarkers including genetic markers. Stool samples will be taken for microbiome analysis.

Neuropathic Pain Score

The painDETECT™ score (Freynhagen 2006) will be administered on Weeks 0, 6, 12 and 28. Absolute score and proportion fulfilling criteria for neuropathic pain on painDETECT™ score will be enumerated.

Joint Count, Tendon Swelling and Enthesitis

A swollen and tender joint count (68 joints) and the Leeds Enthesitis score (Healy 2008) will be performed on Weeks 0, 2, 6, 10 and 12.

8.2 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

Safety assessments will be performed throughout the study from signing of the consent form by the monitoring of AEs, physical examinations, vital signs, laboratory results (haematology, serum biochemistry and urinalysis), lung function tests and electrocardiograms (ECG).

In addition, exploratory monitoring for signs of PAP will be conducted throughout the study using a breathlessness questionnaire (Medical Research Council [MRC] Breathlessness Scale),

chest x-ray, lung function testing and pulse oximetry; see Section 8.2.4 for further information on this aspect of safety assessment.

8.2.1 Physical Examinations

A general physical examination (including height and weight, cardiovascular, respiratory, gastrointestinal and neurological systems) should be performed and recorded as "normal" or "abnormal" with specified abnormalities at the times indicated in the SoA.

8.2.2 Vital Signs

Vital signs (pulse rate, systolic and diastolic blood pressure and temperature) will be taken at the times indicated in the SoA. The blood pressures should be taken after the subject has been seated for at least 5 minutes. Additional readings may be taken at the discretion of the Investigator in the event of an adverse reaction.

8.2.3 Electrocardiograms

A single 12-lead ECG will be obtained as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT and QTc intervals.

8.2.4 Target-specific Safety Evaluation: Pulmonary Alveolar Proteinosis

8.2.4.1 Medical Research Council (MRC) Breathlessness Scale

The MRC Breathlessness Scale will be used to assess any dyspnoea in the subjects taking part in the study. The scale consists of 5 levels of perceived breathlessness based on different physical activity: its categories range from 1-5 as shown in Table 6 (Stenton 2008).

Table 6 MRC Breathlessness Scale

Grade	Degree of Breathlessness Related to Activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yards or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

The MRC breathlessness scale will be used at the time points specified in the SoA and any clinically significant changes may trigger the withdrawal of the subject and adequate follow-up, at the Investigator's discretion.

8.2.4.2 Chest X-ray

A baseline posterior-anterior (PA) chest x-ray taken no later than 3 months prior to the visit, with no clinically significant abnormalities consistent with PAP, should be available at screening. If no such x-ray is available, then subjects will be required to undergo this procedure at Baseline and assessment made before any study medication is administered to the subject at this clinic visit. Further x-rays will also be required during clinic visits at Weeks 12 and 28, respectively (as shown in SoA).

8.2.4.3 Lung Function Testing

Spirometry for pulmonary function testing will be performed at the time points specified in the SoA. All measurements will be performed pre-dose and will be recorded with a handheld device and be transferred into the eCRF. Values will be corrected to BTPS (body temperature and pressure, saturated) conditions.

The following parameters will be recorded and be transferred into the eCRF:

FEV_1: Forced Expiratory Volume in the first second

FVC: Forced Vital Capacity (expiratory)

PEF: Peak Expiratory Flow Rate

The Investigator should ensure that the measurement is adequately done and that no coughing, inadequate technique or other incidents obscure the result.

8.2.4.4 Pulse Oximetry

Pulse oximetry will be measured using standardised devices, at the time points specified in the SoA.

The result on the saturation of peripheral oxygen (SpO_2) will be recorded and transferred into the eCRF.

8.2.5 Pulmonary Alveolar Proteinosis

If a subject develops any signs or symptoms consistent with PAP during the course of this study, adequate measures to diagnose the condition should immediately be initiated and if confirmed, the subject should be withdrawn and treatment initiated as applicable. Judgement on symptoms relating to PAP will be the responsibility of the Investigator. All PAP assessments will be documented in the eCRF.

Subjects should be referred to a pulmonologist for:

1) 12% deterioration in FEV_1 and/or FVC

   or

2) deterioration by >5% decrease in oxygen saturation (SpO_2),

   or

3) an increase in MRC Breathlessness Scale score of 2 from baseline.

Diagnosis tools for PAP include but are not limited to, repeated chest x-ray, high resolution computerised tomography (CT)-scanning, and bronchoalveolar lavage (see Appendix 6 for guidance on management of respiratory signs and symptoms). Data from any such assessments will be captured in the eCRF.

Any incident which requires an investigation for PAP should be recorded as an AE named "suspected pulmonary alveolar proteinosis" and followed until a final outcome is determined. This includes a final determination of signs and symptoms attributed to PAP and every effort should be made to elucidate both the actual cause as well as the causality relation to namilumab.

8.2.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study medication. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the Sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study medication (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations must be recorded in the eCRF.

8.2.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory or physical examination abnormalities noted at the Screening examination. The condition (i.e., diagnosis) should be described.

8.2.8 Clinical Safety Laboratory Assessments

See Appendix 3 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The Investigator must review the laboratory report, document this review and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal

laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 18 weeks after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the aetiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 3, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3 Adverse Events

The definitions of an AE or SAE can be found in Appendix 4.

Adverse events will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorised representative).

The Investigator and any designees are responsible for detecting, documenting and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or study procedures, or that caused the subject to discontinue the study treatment (see Section 7.0).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All SAEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix 4. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be reasonably

related to the study treatment or study participation, the Investigator must promptly notify the Sponsor.

The method of recording, evaluating and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 4.

8.3.2 Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilisation, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 4.

8.3.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) and Investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female subjects and, if indicated, female partners of male subjects, will be collected after the start of study treatment until term or outcome.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Adverse Events of Special Interest

Adverse events of special interest include:

- PAP
- Neutropaenia
- Myeloid suppression

Prolonged systemic neutralisation of GM-CSF bears a theoretical risk of inducing PAP. This is based on the fact that people with an idiopathic PAP reveal polyclonal antibodies recognising human GM-CSF with high avidity and specificity. PAP is a rare disease and the condition has a variable clinical course, from spontaneous resolution to respiratory failure, and approximately 31% of people with autoimmune PAP are asymptomatic (Suzuki 2010). Patients with idiopathic PAP gradually develop symptoms because surfactant protein in the lung alveoli is insufficiently cleared by GM-CSF-starved macrophages. Symptoms, such as dyspnoea, become clinically evident late, when surfactant accumulation in the alveoli has reached a level so that oxygen uptake is impaired (Burmester 2012). The risk of developing PAP after single or short-term repeated administration of namilumab is considered very low. PAP is a slowly developing disorder and clinical symptoms are not expected to develop until after years of disrupted GM-CSF signalling. In hereditary PAP caused by mutation in the GM-CSF receptor, between 1.5 to 9 years could elapse before symptoms develop, but also among homozygote carriers of the mutation asymptomatic cases are described, indicating that disrupted GM-CSF signalling is not the only factor needed for developing PAP (Fredriksson 1978). An important observation is that characteristic changes on x-ray develop in advance of severe symptoms. The issue has been addressed in the namilumab toxicology program, with no signs of PAP to date. Clinical data on GM-CSF inhibition are also without signals. In the mavrilimumab phase 2 study, 149 RA subjects were exposed to 4 different dose levels of mavrilimumab administered every 2 weeks for 12 weeks and no one developed PAP (Burmester 2012). In PRIORA, 3 repeated injections of 150 mg namilumab 2 weeks apart did not induce PAP in the first 12 dosed subjects who have been evaluated for AEs and of which at least 8 received namilumab.

8.4 Treatment of Overdose

An overdose is defined as a known deliberate or accidental administration of investigational drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities until namilumab can no longer be detected systemically (at least 125 days).
3. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

According to the already available results of a PK study no specific antidote is available for namilumab. In case of overdose, it is recommended that the appropriate supportive medical care is provided. In case of allergic reaction, withdrawal of study medication is advised. For treatment of allergic reactions, current guidelines for treatment (e.g., with corticosteroids) should be applied.

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Optional saliva samples will be taken on Day 1 from consenting subjects for genotypic analysis.

8.8 Biomarkers

Collection of samples for biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all subjects in this study as specified in the SoA:

- Blood for immunophenotyping and gene expression analysis
- Serum/plasma for CRP and other protein and non-protein biomarkers
- Stool for faecal calprotectin and microbiome analysis

Samples will be tested for exploratory objectives to evaluate the effect of namilumab on biomarkers at 12 weeks.

Samples may be stored for a maximum of 10 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of biomarker responses to namilumab.

8.8.1 Immunogenicity Assessments

Antibodies to namilumab will be evaluated in serum samples collected from all subjects according to the SoA. Additionally, serum samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to namilumab and the titre of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to namilumab and/or further characterise the immunogenicity of namilumab.

The detection and characterisation of antibodies to namilumab will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to study treatment will also be evaluated for namilumab serum concentration to enable interpretation of the antibody data. Antibodies may be further characterised and/or evaluated for their ability to neutralise the activity of the study treatment(s). Samples may be stored for a maximum of 5 years (or according to local regulations) following the last subject's last visit for the study at a facility selected by the Sponsor to enable further analysis of immune responses to namilumab.

8.9 Medical Resource Utilisation and Health Economics

Medical Resource Utilisation and Health Economics parameters are not evaluated in this study.

9.0 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The hypothesis to be tested is H_0: $\pi_{nam} = \pi_{pbo}$, where π represents the ASAS20 rate. The hypothesis will be evaluated using a Bayesian analysis.

Prior clinical data in AS were used as the basis for prior distributions. Criteria for inclusion of studies were that the studies involved a similar biological agent, and were double-blind and placebo-controlled. Week 12 was the target visit and was used in the calculations for the priors, but for secukinumab Week 16 was used since Week 12 data were not reported outside of the figures.

Data for control groups are shown in Figure 2 and Table 7. The estimated sample-size weighted mean ASAS20 was 0.34. The secukinumab studies allowed for prior DMART and anti-TNF agents, which yielded a lower ASAS20 than the other studies.

Data for the active groups are shown in Figure 3 and Table 8. The estimated sample-size weighted mean ASAS20 was 0.6. As can be seen, a fair amount of variability is shown in the results with a secukinumab (75 mg) group with a low ASAS20 of 0.41, and tofacitinib (5 mg twice daily [BID]) with an ASAS20 of 0.81. The remaining studies exhibit ASAS20 tightly clustered around 0.6.

Based on these results, the prior for the control will be targeted to ASAS20 of 0.3, and the active ASAS20 to 0.6.

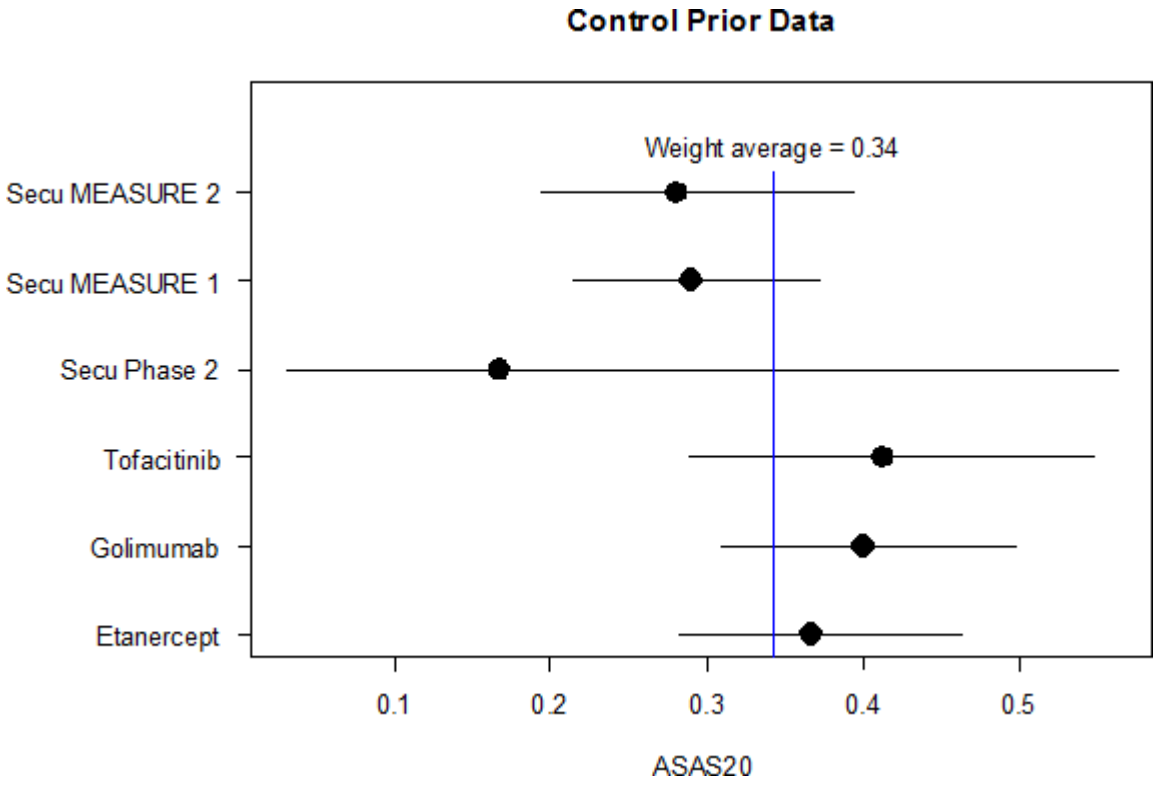

Figure 2 Estimated ASAS20 and 95% Confidence Intervals for Placebo Treatment Group Data

Secu = secukinumab.

Table 7 Reported ASAS20 Results for Placebo Treatment Group for Reference Studies

Compound	Reference	Week	N	ASAS20
Etanercept	Maksymowych (2015)	12	106	0.37
Golimumab	Sieper (2012, 2016) ACR	12	100	0.40
Tofacitinib	van der Heijde (2017)	12	51	0.41
Secukinumab (phase 2)	NCT00809159	12	6	0.17
Secukinumab	Baeten 2015; MEASURE 1	16	122	0.29
Secukinumab	Baeten 2015; MEASURE 2	16	74	0.28
Pooled			459	0.34

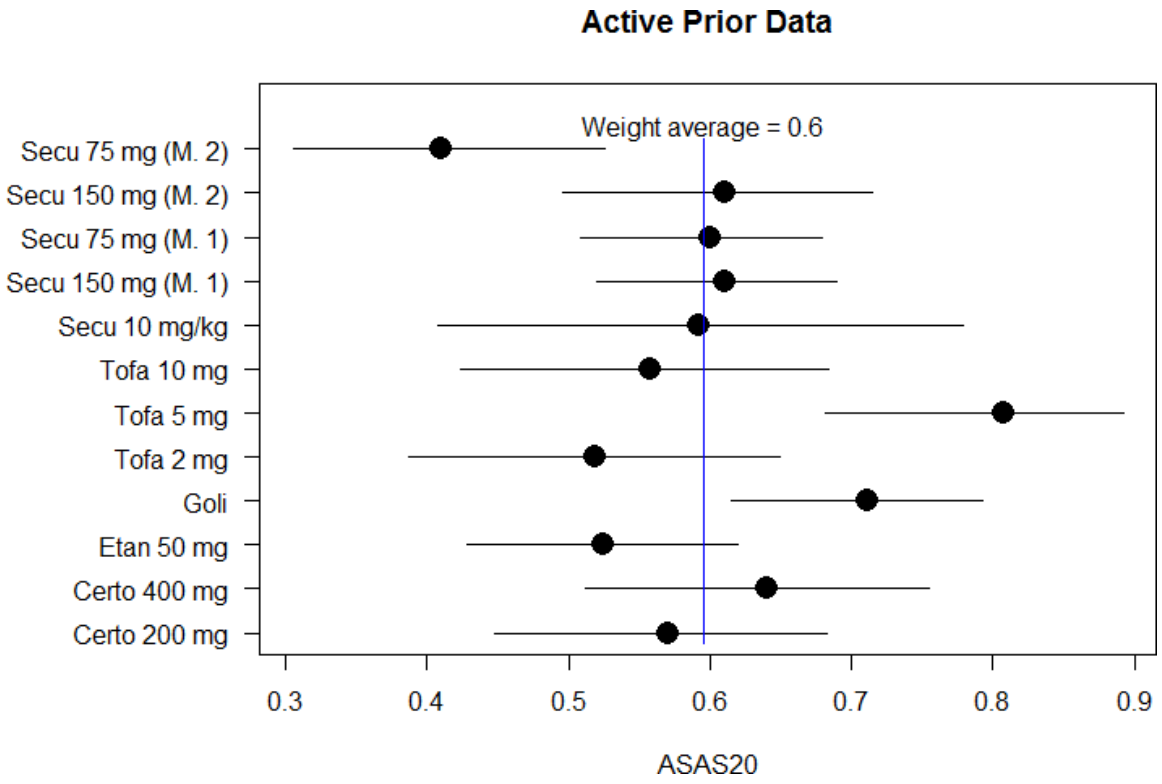

Figure 3 Estimated ASAS20 and 95% Confidence Intervals for Active Treatment Group Data

Secu = secukinumab (M.1 = MEASURE 1 study, M.2 = MEASURE 2 study); Tofa = tofacitinib; Goli = golimumab; Etan = etanercept; Certo = Certolizumab pegol.

Table 8 Reported ASAS20 Results for Active Treatment Group for Reference Studies

Compound	Reference	Dose	Week	N	Value
Certolizumab pegol	Label	200 mg Q2weeks	12	65	0.57
Certolizumab pegol	Label	400 mg Q2weeks	12	56	0.64
Etanercept	Maksymowych (2015)	50 mg Q1week	12	101	0.52
Golimumab	Sieper (2012, 2016) ACR	Gol Q4weeks	12	97	0.71
Tofacitinib	van der Heijde (2017)	2 mg BID	12	52	0.52
Tofacitinib	van der Heijde (2017)	5 mg BID	12	52	0.81
Tofacitinib	van der Heijde (2017)	10 mg BID	12	52	0.56
Secukinumab	NCT00809159	10 mg/kg	12	23	0.59
Secukinumab	Baeten 2015; MEASURE 1	150 mg	16	125	0.61
Secukinumab	Baeten 2015; MEASURE 1	75 mg	16	124	0.60
Secukinumab	Baeten 2015; MEASURE 2	150 mg	16	72	0.61
Secukinumab	Baeten 2015; MEASURE 2	75 mg	16	73	0.41
Pooled				892	0.60

9.2 Sample Size Determination

The placebo prior = beta(p=0.3, n=20), and the prior for active is beta(p=0.6, n=5). The sample sizes are the smallest n such that the median $Q(P\{\theta_{act} > \theta_{pbo}| Y(H_A)\}, 1 - \gamma) > Q(P\{\theta_{act} > \theta_{pbo}| Y(H_0)\}, \gamma)$, where $Q(f, \gamma)$ represents the γ quantile from the distribution f, and $Y(H_A)$ represents data generated under the alternative hypothesis, and $Y(H_0)$ represents data generated under the null hypothesis. Sample sizes are shown in Table 9. The recommended sample size is 42 (6 on placebo, 36 on active). A plot of the distribution of $P\{\theta_{act} > \theta_{pbo}| Y\}$ with both hypotheses overlapping as a function of the total sample size is shown in Figure 4.

Table 9 Sample Sizes for 6:1 Randomisation, Based on the Parameter γ

γ	N Placebo	N Active	N Total
0.80	2	12	14
0.85	4	24	28
0.90	6	36	42

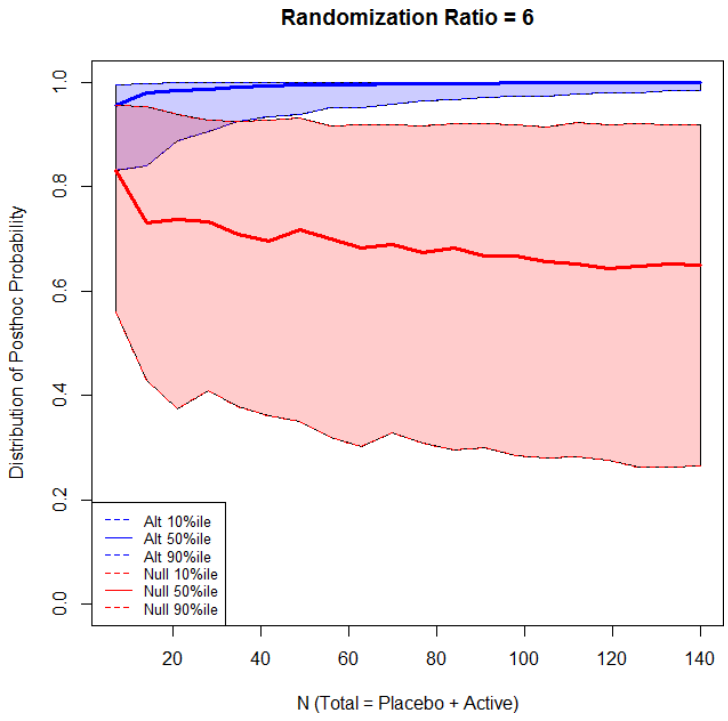

Figure 4 Distribution of Posterior Probability $P(\theta_{act} > \theta_{pbo})$ as a Function of Total Sample Size, Under Both Hypotheses

Shaded areas represent the middle 80% of the distribution (between the 10th and 90th percentiles).

9.3 Populations for Analyses

For purposes of analysis, the analysis sets in Table 10 are defined. For efficacy analyses, the Full Analysis Set (FAS) will be the primary analysis set, and the Per Protocol (PP) Analysis Set will be secondary. For safety analyses, the Safety Analysis Set will be the primary analysis set.

Table 10 Analysis Sets

Analysis Set	Description
Entered Analysis Set	All subjects who sign the ICF.
Randomly Assigned to Study Treatment Analysis Set	All subjects in the Entered Analysis Set who are assigned to study treatment.
Full Analysis Set	All subjects randomly assigned to study treatment and who take at least 1 dose of study treatment and have specific post-baseline assessments available.
Per Protocol	All subjects in the Full Analysis Set that have week 10 efficacy data.
Completer Analysis Set	All subjects in the Full Analysis Set who complete the study.
Safety Analysis Set	All subjects randomly assigned to study treatment and who take at least 1 dose of study treatment. Subjects will be analysed according to the treatment they actually received.

9.4 Statistical Analyses

The Statistical Analysis Plan (SAP) will be developed and finalised before database lock and will describe the subject analysis sets to be included in the analyses, and procedures for accounting for missing, unused and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

All analyses, summaries and listings will be performed using SAS® software (version 9.2 or higher), or R (version 3.2 or higher).

The following descriptive statistics will be used as applicable to summarise the study data unless otherwise specified:

- Continuous variables: sample size (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).
- Categorical variables: frequencies and percentages.

Individual subject data will be presented in listings.

9.4.1 Efficacy Analyses

Table 11 Efficacy Analyses

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint ASAS20 will be assessed using a Bayesian analysis. The control arm will have a beta prior with parameters rate = 0.3 and $\nu = 20$, and the namilumab arm will have a beta prior with rate 0.6 and $\nu = 5$. Posterior distributions will be calculated, and parameter distributions shown. The mean, standard deviation, and 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of the posterior distribution will be presented. The posterior distribution will also be presented graphically. Given the observed data, the posterior probability $\eta \equiv P(\pi_{nam} > \pi_{pbo})$ will be calculated (Raineri 2014) and presented. Values of $\eta > 0.927$ will provide strong evidence that namilumab exhibits therapeutic benefit relative to placebo control. Missing data will be treated as non-responders for this analysis. For assessment of robustness of the analysis, the analysis will be performed on Completer Analysis Set.
Secondary	Summary statistics of ASAS20, ASAS40 and other efficacy endpoints will be summarised by visit and treatment group. Summary statistics will be provided on both the Full and PP Analysis Sets.
Exploratory	Statistics used to summarise these endpoints will be described in the SAP.

9.4.1.1 Handling of Missing Data

Non-responder imputation will be used for missing data in the FAS. Missing data will be excluded from analysis in the PP Analysis Set.

Missing data will not be imputed in the Safety Analysis Set.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

TEAEs are defined as AEs that first occurred or worsened in severity after the first administration of study treatment and prior to 125 days after the last administration of study treatment.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each study treatment, numbers of TEAEs and incidence rates will be tabulated by preferred term and system organ class.

TEAEs by maximum severity, TEAEs by relationship to study treatment, SAEs, TEAEs leading to death and TEAEs leading to discontinuation of study treatment will be tabulated for each treatment group. Commonly occurring TEAEs, i.e., those that occur in 5% or more of the subjects in either treatment group, will be summarised using descriptive statistics.

All laboratory test results, vital signs measurements, ECG results, weight and body mass index (BMI) will be summarised for each treatment group using descriptive statistics at each scheduled visit for raw numbers and change from baseline. The incidence of treatment-emergent abnormal laboratory, vital sign and ECG values will also be summarised using descriptive statistics.

visit for raw numbers and change from baseline. The incidence of treatment-emergent abnormal laboratory, vital sign and ECG values will also be summarised using descriptive statistics.

9.4.3 Other Analyses

Biomarker exploratory analyses will be described in the SAP.

9.4.4 Missing Data

Data from subjects who withdraw from the study, including AEs and any follow-up, will be included in the analyses of primary and secondary outcomes.

Missing data (including those due to early discontinuations) will be imputed by a non-responder imputation (NRI). The NRI will be the primary imputation method for handling the missing data.

As a sensitivity analysis, the analysis will also be performed on completers only.

9.5 Interim Analyses

No interim analysis for efficacy is planned.

9.6 Safety Review Team

A Safety Review Team consisting of the Coordinating Investigator, the Sponsor's Medical Expert/Chief Medical Officer, and an independent Safety Physician will review ongoing safety data on a monthly basis. The data review will be conducted for randomised subjects and will include a review of vital signs, laboratory assessments, ECGs, AEs (including AEs of special interest and SAEs), physical examinations, and assessments of pulmonary functions. The Safety Review Team will provide consolidated feedback of the Team's findings to the study team. Additional details of the Safety Review will be provided separately.

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11.0 APPENDICES

Appendix 1 Abbreviations

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AS	Ankylosing spondylitis
ASAS(20,40,70)	Assessment in Ankylosing Spondylitis with 20%/40%/70% improvement
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score C-reactive Protein
AST	Aspartate aminotransferase
axSpA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BID	twice daily
BMI	body mass index
BTPS	body temperature and pressure, saturated
CONSORT	Consolidated Standards of Reporting Trials
CPMP	Committee for Proprietary Medicinal Products
CRO	contract research organisation
CRP	C-reactive protein
CT	computerised tomography
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EoT	End-of-Treatment
ET	Early Termination
FAS	Full Analysis Set
FU	Follow-up
GM-CSF	granulocyte-macrophage colony-stimulating factor
HBV	hepatitis B virus
HCV	hepatitis C virus
Hep	hepatitis
HIV	human immunodeficiency virus

Abbreviation	Definition
ICF	informed consent
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IL(-17)	interleukin-17
IMP	investigational medicinal product
INR	international normalised ratio
IRB	Institutional Review Board
i.v.	intravenous
IWRS	interactive web response system
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MED ID	medication identification
min	minimum
MRC	Medical Research Council
MRI	magnetic resonance imaging
MTX	methotrexate
nr-axSpA	non-radiographic axSpA
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drugs
PA	posterior, anterior
PAP	pulmonary alveolar proteinosis
PCR	polymerase chain reaction
PD	pharmacodynamic
phSpA	peripheral spondyloarthritis
PK	pharmacokinetic
PP	Per Protocol
RA	Rheumatoid arthritis
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical Analysis Plan
sc	subcutaneous
SD	Standard deviation

Abbreviation	Definition
SoA	Schedule of Activities
SpA	spondyloarthropathy
SpO2	saturation of peripheral oxygen
SUSAR	suspected unexpected serious adverse reactions
TB	tuberculosis
TEAE	treatment-emergent adverse event
TNF	tumour necrosis factor
TNFi	tumour necrosis factor inhibitor
ULN	upper limit of normal
VAS	visual analogue scale
WBC	white blood cell
WOCBP	women of childbearing potential

Appendix 2 Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure and other relevant documents (e.g., adve1tisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC and regulato1y authority approval, when applicable, before implementation of changes made to the study design, except for changes necessa1y to eliminate an immediate hazard to subjects.

The Investigator will be responsible for the following:

- Providing written Sllllllillaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies and procedures established by the IRB/IEC.
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Providing oversight of the conduct of the study at the study centre and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative (Appendix 9). The study will not sta1t at any study centre at which the Investigator has not signed the protocol.

Financial Disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial info1mation as requested to allow the Sponsor to submit complete and accurate financial ce1tification or disclosure statements to the appropriate regulato1y authorities. Investigators are responsible for providing info1mation on financial interests during the course of the study and for 1 year after completion of the study.

Insurance

Sponsor will provide insurance in accordance with local guidelines and requirements as a minimum for the subjects in this study. The terms of the insurance will be kept in the study files.

Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorised designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

Data Protection

Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Administrative Structure

Table 12 Study Administrative Structure

Function	Responsible Organisation
Study Operations Management	CRO
Medical Monitoring	CRO
Study Master File	CRO
Randomisation Code	CRO
Data Management	CRO
Clinical Supply Management	3rd party
Quality Assurance Auditing	CRO
Biostatistics	CRO
Medical Writing	CRO
Laboratory Assessments	3rd party (local laboratories at sites)
Electrocardiogram Collection, Review, and Analysis	At site
Pharmacokinetic Sample Testing	3rd party
CRA	CRO
Pharmacovigilance	CRO

Medical Monitor

Dissemination of Clinical Study Data

The results of the study should be reported within 1 year from the end of the clinical study. Irrespective of the outcome, the Sponsor will submit to the European Union (EU) database a summary of the results of the clinical study within 1 year from the end of the clinical study. It shall be accompanied by a summary written in a manner that is understandable to laypersons.

Data Quality Assurance

All subject data relating to the study will be recorded on eCRFs unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorised study centre personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Source Documents

The Investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study centre's subjects. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's study centre.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Study Centre Closure

The Sponsor or designee reserves the right to close the study centre or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study centres will be closed upon study completion. A study centre is considered closed when all required documents and study supplies have been collected and a study centre closure visit has been performed.

The Investigator may initiate study centre closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study centre by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of subjects by the Investigator.
- Discontinuation of further study treatment development.

Publication Policy

The data generated by this study are confidential information of the Sponsor. The Sponsor will make the results of the study publicly available. The publication policy with respect to the Investigator and study centre will be set forth in the Clinical Trial Agreement.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual study centre data. In this case, a Coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix 3 Clinical Laboratory Tests

The tests detailed in Table 13 will be performed by the local laboratory at each Investigator site.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 13 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Haematology	Platelet Count	RBC Indices: Mean corpuscular volume (MCV) Mean corpuscular haemoglobin (MCH) Mean corpuscular haemoglobin concentration (MCHC) %Reticulocytes	White Blood Cell Count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
	Red Blood Cell (RBC) Count			
	Haemoglobin			
	Haematocrit			
Clinical Chemistry[a]	Blood Urea Nitrogen	Potassium	Aspartate Aminotransferase (AST)/Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total and direct bilirubin
	Creatinine	Sodium	Alanine Aminotransferase (ALT)/Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose	Calcium	Alkaline phosphatase	albumin
		Chloride	Phosphorous	
Serum Lipids	Total cholesterol	Triglycerides	HDL	LDL
Biomarkers	Faecal calprotectin	C-reactive protein (CRP)	HLA-B27	Erythrocyte sedimentation rate
	Stool sample for microbiome analysis			
Immunophenotyping				
Immunogenicity	Anti-namilumab antibodies			

Laboratory Assessments	Parameters
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum or urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[b] • Serology: Hepatitis B (hepatitis B virus surface antigen [HBsAg] positive [+] or detected sensitivity on the hepatitis B virus [HBV] DNA polymerase chain reaction [PCR] qualitative test for hepatitis B core antibodies [HBc Ab]/hepatitis B surface antibody [HBsAb] positive subjects) or hepatitis C (hepatitis C virus [HCV] RNA detectable in any subject with anti-hepatitis C virus antibody [HCV Ab]). • ANA (anti-dsDNA titres if ANA is positive) • QuantiFERON-TB test (or equivalent test) The results of each test must be entered into the (e)CRF.

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 7.1. All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalised ratio (INR) >1.5, if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

Appendix 4 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (haematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgement of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalisation for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a) Results in death
b) Is life-threatening The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c) Requires inpatient hospitalisation or prolongation of existing hospitalisation In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalisation" occurred or was necessary, the AE should be considered serious. Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d) Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e) Is a congenital anomaly/birth defect
f) Other situations: • Medical or scientific judgement should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF. Each event must be recorded separately.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the CRO in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the CRO. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the CRO.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterised as unrelated, unlikely to be related, possibly related, probably related or unknown (unable to judge).
  - "Probably related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
  - "Possibly related" suggests that the association of the AE with the study treatment is unknown; however, the AE is not reasonably supported by other conditions.
  - "Unlikely to be related" suggests that only a remote connection exists between the study treatment and the AE. Other conditions, including chronic illness, progression or expression of the disease state or reaction to concomitant therapy, appear to explain the reported AE.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
  - All efforts should be made to classify the AE according to the above categories. The category "unknown" (unable to judge) may be used only if the causality is not assessable, e.g., because of insufficient evidence, conflicting evidence, conflicting data or poor documentation.
- The Investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE

and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the CRO. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the CRO.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognised follow-up period, the Investigator will provide the CRO with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the Medical Monitor via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Medical Monitor will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the study centre will use the paper SAE data collection tool (see next section).
- The study centre will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given study centre, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a study centre receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the study centre can report this information on a paper SAE form (see next section) or to the CRO Safety Team by telephone/fax or email.
- Contacts for SAE reporting can be found in the safety paper forms for the sites.

SAE Reporting to the Medical Monitor via Paper CRF

- The secondary (backup) mechanism for reporting an SAE to the Medical Monitor will be via a paper CRF.
- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE paper form and the safety management plan.

Appendix 5 Excluded Medications/Therapy

Excluded medications/therapy is listed below. The use of an excluded medication/therapy is a protocol violation and must be recorded in the eCRF.

Excluded Medications and Treatments:

Any treatment antagonising GM-CSF or its receptor	At any time prior to the Screening visit, during the study, or for 14 weeks after the last dose of study medication
Not stable doses of methotrexate, sulfasalazine, leflunomide	Change in dosage within 28 days prior to the Screening visit and/or not planned to be continued at a stable dose with the same formulation until at least the end of Week 12
Hydroxychloroquine >400 mg/day or Chloroquine > 250mg/day	Within 4 weeks prior to the Screening visit and at any time during the study
Not stable doses of Hydroxychloroquine ≤400 mg/day or Chloroquine ≤250 mg/day	Within 28 days prior to the Screening visit and/or not planned to be continued at a stable dose with the same formulation until at least the end of Week 24
Any immunomodulatory biological agents or kinase inhibitor (either experimental or approved) except for previous treatment with TNF inhibitors.	At any time prior to the Screening visit and at any time during the study
Any adjustment in agents to treat dyslipidaemia	New treatment or dose-adjustment to on-going medication for dyslipidaemia, such as (but not limited to) statins, within 6 weeks prior to randomisation, i.e., a dose that is not stable for at least 6 weeks prior to randomisation
Infliximab, etanercept, adalimumab, golimumab or certolizumab pegol	Within 8 weeks prior to Baseline visit and at any time during the study
Anti-IL-17A or IL12/23 therapy	At any time prior to the Screening visit and at any time during the study
Stem cell transplantation	At any time prior to the Screening visit and at any time during the study
Cyclosporine, tacrolimus, or mycophenolate mofetil	Within 28 days prior to Baseline
Treatment with oral corticosteroids exceeding 10 mg/day prednisolone or equivalent, or has been taking both oral budesonide and prednisone (or equivalent) simultaneously	Within 28 days prior to the Baseline visit and at any time during the study
Not stable doses of oral corticosteroids ≤10 mg/day prednisolone or equivalent	Change in dosage within 28 days prior to the Screening visit and/or not planned to be continued at a stable dose with the same formulation until at least the end of Week 12
Any treatment with intravenous corticosteroids	Within 14 days prior to Screening or during the Screening period and at any time during the study
Intra-articular corticosteroids	Prohibited any time during screening and up to Week 12. A maximum of one injection given in a small joint (DIP or MCP) and clearly documented in the eCRF is allowed.

Changes in NSAID/COX-2 dose levels	Within 28 days prior to randomisation, and/or not planned to be continued at a stable dose with the same formulation until at least the end of Week 12 (with appropriate gastric protection). Except for safety related reasons, where dose reduction may be done.
Changes in the doses of opioid-containing medications	Within 4 weeks prior to randomisation and at any time during the study. Except for safety related reasons where reduction may be done.
Immunisation with a live or live-attenuated vaccine	Within 2 weeks prior to randomisation and at any time during the study and for 1 month following last study drug administration
Any investigational agent	Within 30 days or 5 half-lives prior to Baseline

Appendix 6 Management of Respiratory Signs and Symptoms in Relation to PAP Disease Background

A caveat of systemically neutralising GM-CSF could be a hypothetical potential for inducing pulmonary alveolar proteinosis (PAP). PAP is a rare disease characterised by intra-alveolar accumulation of surfactant components and cellular debris with minimal interstitial inflammation or fibrosis. In a proportion of patients with idiopathic PAP, autoantibodies against GM-CSF have been detected. It seems plausible that the autoantibodies reduce GM-CSF activity, resulting in alveolar macrophage dysfunction and surfactant accumulation.

Idiopathic PAP is a slowly developing disease. Clinical presentation may include dyspnoea, cough or shortness of breath. Changes may be visible on x-ray or computer tomography before clinically evident.

Management of Respiratory Signs and Symptoms in the Study

Subjects will be closely monitored regarding respiratory tract abnormalities in this clinical study. Pulse oximetry and breathlessness questionnaire will be performed at almost every visit and lung function will be measured as described in the protocol. Subjects should be referred to a pulmonologist according to the below instructions.

Events that can be handled by the primary investigator, and noted as AEs:

- Common cold
- URI
- Sinusitis

Events where referral to a pulmonologist is required

- Any of the above showing atypical clinical picture.
- 12% deterioration in FEV_1 and/or FVC, or
- Deterioration by >5% decrease in oxygen saturation (SpO2), or
- An increase in MRC Breathlessness Scale score of 2 from baseline.
- Shortness of breath and productive cough not showing typical pneumonia picture on x-ray.

Pulmonologist activities at the suspicion of PAP

The pulmonologist will investigate the condition stepwise.

- Reversibility of decrease in FEV_1 would point to the suspicion at asthma.
- No reversibility may point at COPD, but a need to rule out PAP may be needed.
- Investigation to rule out/ confirm PAP may include 6 min walk test, pulse oximetry during effort according to ATS guidelines. If a plausible explanation to the condition is not established, PAP may be suspected. CT scan and DLCO may be the first step in evaluating this condition, possibly followed by BAL and trans-bronchial biopsy.
- If a patient is diagnosed with asthma, COPD or pneumonia during the trial he or she can stay on the trial under thorough monitoring.

Appendix 7 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, nonsterilised** male subjects who are sexually active with a female partner of childbearing potential* must be advised not to donate sperm during this period.

From signing of informed consent, throughout the duration of the study, and for 18 weeks after last dose of study medication, female subjects of childbearing potential* who are sexually active with a nonsterilised male partner** must use adequate contraception. In addition, they must be advised not to donate ova during this period.

*Females NOT of childbearing potential are defined as those who have been surgically sterilised (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (e.g., defined as at least 1 year since last regular menses with an FSH >40 IU/L or at least 5 years since last regular menses, confirmed before any study medication is implemented).

**Sterilised males should be at least 1 year postvasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova and sperm during the course of the study.

During the Screening period of the study, a human serum chorionic gonadotropin pregnancy test will be performed only for women of childbearing potential. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the study procedures (SoA).

During the course of the study, regular urine human chorionic gonadotropin (hCG) pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures (SoA). In addition to a negative serum hCG pregnancy test at Screening, subjects also must have a negative urine hCG pregnancy test prior to receiving any dose of study medication.

Appendix 8 Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 (04 May 2018)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Overall Rationale for the Amendment 1:

The protocol was amended to address findings from a review by the Medicines and Healthcare Products Regulatory Agency (MHRA), which included clarifying several safety assessment time periods, revising an exclusion criterion based on abnormal liver transaminases, clarifying the process for the investigator to unblind study treatment in the event of a medical emergency, clarifying documentation of pulmonary alveolar proteinosis assessments, revising pregnancy contraception for consistency with Clinical Trial Facilitation Group (CTFG) guidance, and clarifying several inconsistencies.

Table 14 Description of Changes in Amendment 1

Section #	Description of Change	Brief Rationale
1.3/Table 1/Footnote 4	Time period for post-dosing vital signs added.	Time period for post-dosing vital signs clarified per request from MHRA.
1.3/Table 1/Footnote 8	Changed chest x-ray timing from 6 months to 3 months.	Revised for consistency with body of protocol.
5.2/Exclusion criterion #9	Exclusion based on abnormal liver transaminases revised.	Criterion revised to exclude subjects with elevated transaminases who also have elevated bilirubin.
6.2.1, 6.3.1, 6.3.3, 6.3.4, 6.3.5	Text revised to include interactive web response system (IWRS) for maintaining treatment blind that will allow investigators to unblind a subject's investigational medicinal product identity at any time in the event of a medical emergency.	Process for unblinding of subject's investigational medicinal product by investigator in the event of a medical emergency clarified.
8.2.5	Documentation of pulmonary alveolar proteinosis assessments revised.	Documentation of pulmonary alveolar proteinosis assessments revised and clarified to include all assessments.
Appendix 6	Events where referral to a pulmonologist is required were updated.	Revisions were made for consistency with Section 8.2.5 of the protocol body.
Appendix 7	Barrier methods for pregnancy contraception deleted and acceptable contraception revised.	Methods of pregnancy contraception revised to be consistent with CTFG recommendations.
Throughout	Minor editorial and document formatting revisions	Editorial updates and corrections.

Appendix 9 Signature of Investigator

PROTOCOL TITLE: A phase 2a proof of concept, randomised, double-blind, placebo-controlled study to evaluate the safety/tolerability and efficacy of 4 subcutaneous injections of namilumab (150 mg) given over 10 weeks in subjects with moderate-to-severely active axial spondyloarthritis including those previously exposed to anti-TNF therapy. (NAMASTE study)

PROTOCOL NO: IZN-101

VERSION: Amendment 2

This protocol is a confidential communication of Izana Bioscience Ltd. I confirm that I have read this protocol, I understand it and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE this signature page. PRINT your name, title, and the name of the study centre in which the study will be conducted. Return the signed copy to the CRO.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Centre: _____

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