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)

Statistical Analysis Plan

Version Number and Date: FINAL 1.0, 07MAY2019

NCT03622658

STATISTICAL ANALYSIS PLAN

IZN-101

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)

AUTHOR: [redacted]

VERSION NUMBER AND DATE: FINAL 1.0, 07 MAY 2019

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V1.0 (Dated 29APR2019) for Protocol IZN-101.

	Name	Signature	Date
Author:	[redacted]		
Position:			
Company:	IQVIA		

Upon review of this document and the tables and listing shells template, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
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Company:	

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0	29Apr2018	[redacted]	Not Applicable – First Draft Version

LIST OF ABBREVIATIONS

AE	Adverse event
ASAS	Assessment of spondyloarthritis international Society
ASDAS-CRP	Ankylosing Spondylitis Disease Activity Score - C-reactive protein
ATC	Anatomical Therapeutic Chemical
BASDAI	Bath ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
COM	Completers analysis set
ECG	Electrocardiogram
eCRF	Electronic case report form
ENR	All enrolled analysis set
FAS	Full analysis set
FEV_1	Forced expiratory volume in the first second
FVC	Forced vital capacity
HR	Hearth rate
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical research council
PAP	Pulmonary alveolar proteinosis
PEF	Peak expiratory rate
PPAS	Pre-protocol analysis set
PT	Preferred term
RND	All randomised set
SAF	Safety analysis set
SD	Standard deviation
SOC	System organ class
SpO_2	Peripheral oxygen
TEAE	Treatment emergent adverse event
TNF	Tumour necrosis factor
ULQ	Upper limit of quantification
VAS	Visual Analogue scale
WHO	World health organization

TABLE OF CONTENTS

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol IZN-101. It describes the data to be summarized and analysed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on protocol version 3 (Amendment 2), dated 05Jul2018.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective is to assess the efficacy of namilumab 150 mg subcutaneous (sc), given on Weeks 0, 2, 6 and 10 in subjects with axial spondyloarthritis (axSpA)

2.2. SECONDARY OBJECTIVES

- 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
- To assess the safety and tolerability of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 in subjects with axSpA

2.3. EXPLORATORY OBJECTIVES

- To assess the efficacy of namilumab 150 mg sc, given on Weeks 0, 2, 6 and 10 on radiologic responses in subjects with axSpA
- 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 axSpA

3. STUDY DESIGN

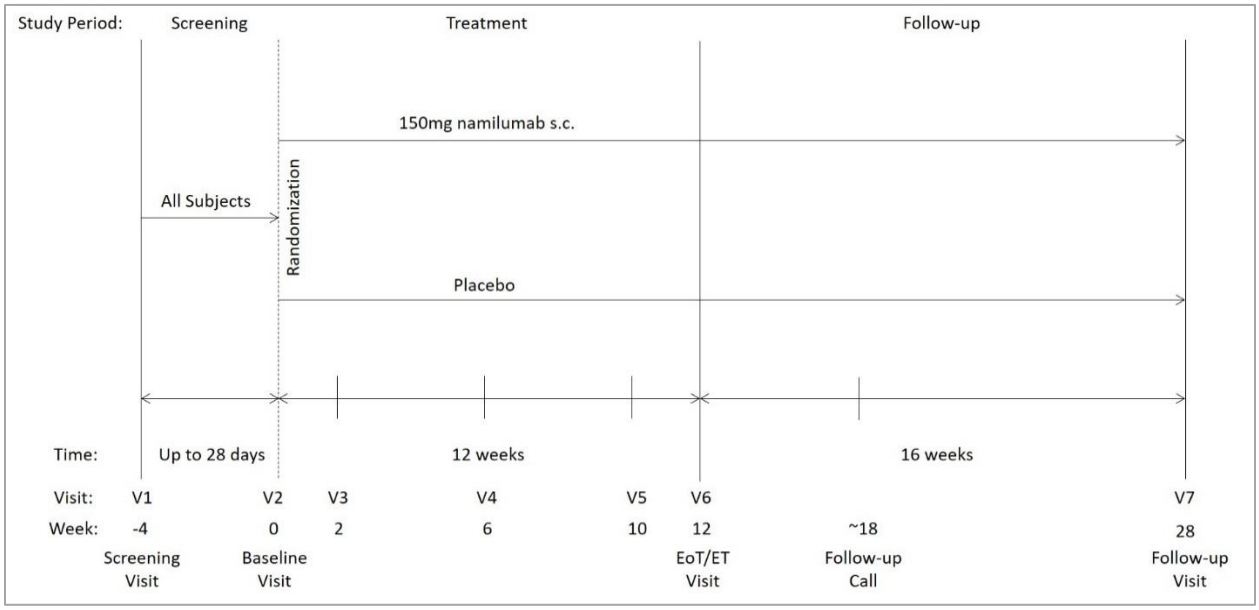
3.1. GENERAL DESCRIPTION

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 moderate-to-severely active axSpA, including those with a history of inadequate response to or intolerance of 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.

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. Randomisation will be stratified by prior use of anti-TNF agents.

Treatment Groups and Duration:
Test product, dose and mode of administration:
Namilumab 150 mg sc administered at Day 1 of Weeks 0, 2, 6 and 10.
Reference therapy, dose and mode of administration:
Matching placebo solution sc administered at Day 1 of Weeks 0, 2, 6 and 10.

Table A: Study Schema



3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 1.3 of the protocol.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

Full analysis set modified

- The full analysis set (FAS) was defined in the protocol as "All subjects randomly assigned to study treatment and who take at least 1 dose of study treatment and have specific post-baseline assessments available". This has been updated in Section 5.3 of this SAP to be "The full analysis set (FAS) will contain all subjects in the all randomised set (RND) who received at least one dose of study medication".
- The reason for this change is that all subjects with missing data at week 12 for efficacy will be considered as non-responders (as per protocol definition) thus they will all be included in the FAS if randomised and treated.
- Date of agreement of change is 12April2019

Per-protocol analysis set modified

- The per protocol analysis set was defined in the protocol as "All subjects in the Full Analysis Set that have week 10 efficacy data." This has been updated in Section 5.3 of this SAP to be "The per-protocol analysis set (PPAS) will contain all subjects in the COM who did not experience any protocol deviations that might affect the efficacy results."
- The reasons for this change are that there was a typographical error in the definition (week 10 instead of week 12) and that the goal of the per-protocol analysis is also to investigate the effect of the compound under investigation in patients who did not violate the protocol.
- Date of agreement of change 12April2019

Interim analysis for strategic purposes

- An interim analysis for strategic purposes is added to obtain preliminary results once all randomized subjects have completed the week 12 assessments.
- Date of agreement of change 12April2019

Primary endpoint definition amendment

- The definition has been amended to: "A subject with an improvement from baseline of at least 20% and an absolute improvement of at least 10 units on a 0-100 VAS in at least 3 of the following four domains collected on the eCRF and no worsening in the fourth domain."
- The amendment is due to an improper definition in the protocol.
- Date of agreement of change 12April2019

ASAS70 analysis removed

- ASAS70 endpoint has been removed as it is not a validated measure
- Date of agreement of change 12April2019

4. PLANNED ANALYSES

Interim analysis.
Final analysis.

4.1. DATA MONITORING COMMITTEE (DMC)

There will be no DMC for this study. A blinded team will review the safety data on a monthly basis.

4.2. INTERIM ANALYSIS

One interim analysis will be performed once all subjects randomized have completed their 12 week assessments. The aim of this analysis is to obtain preliminary results on the primary and secondary efficacy endpoints to be used for strategic and business purposes only. An unblinded team will run the analysis on the primary and secondary efficacy endpoints and the results will be shared with a limited number of people that will be described in a dedicated charter.

4.3. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock, Sponsor Authorization of Analysis Sets and Unblinding of Treatment.

5. ANALYSIS SETS

Agreement and authorization of subjects included/excluded from each analysis set will be conducted prior to the unblinding of the study.

5.1. ALL ENROLLED ANALYSIS SET [ENR]

The all enrolled (ENR) set will contain all subjects who signed informed consent for this study.

5.2. ALL RANDOMISED ANALYSIS SET [RND]

The all randomised (RND) set will contain all subjects in the ENR set who were randomised to study medication.
For analyses and displays based on RND, subjects will be classified according to randomised

treatment.

5.3. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain all subjects in the RND set who received at least one dose of study medication.
The intent-to-treat principle is preserved, despite the exclusion of subjects randomised who did not take the study medication, because the decision of whether or not to begin the treatment could not be influenced by knowledge of the assigned treatment, i.e. the study medication is blinded.
For analyses and displays based on FAS, subjects will be classified according to randomised treatment.

5.4. COMPLETERS ANALYSIS SET (S) [COM]

The completers analysis set (COM) will contain all subjects in the FAS that have week 12 efficacy data and subjects will be classified according to the randomised treatment.

5.5. PER PROTOCOL ANALYSIS SET [PPAS]

The per-protocol analysis set (PPAS) will contain all subjects in the COM who did not experience any protocol deviations that might affect the efficacy results. Protocol deviations for exclusion will be defined and detailed in a separate document to be agreed and signed by IQVIA and the Sponsor before database lock.

5.6. SAFETY ANALYSIS SET [SAF]

The safety analysis set (SAF) will contain all subjects in the RND set who receive at least one dose of study medication and subjects will be classified according to treatment received.
If there is any doubt whether a subject was treated or not, they will be assumed as treated for the purposes of analysis and classified according to the randomised treatment.

6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show the start/ stop day of assessments and events and will appear in every listing where an assessment date or event date appears.
Reference start date is defined as the day of the first dose of study medication, (Day 1 is the day of the first dose of study medication).

- If the date of the assessment or event is on or after the reference date:

Study Day = (date of event – reference date) + 1.

- If the date of the assessment or event is prior to the reference date:

Study Day = (date of event – reference date).

In the situation where the assessment or event date is partial or missing, the date will appear as partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in 17, if defined, otherwise they will appear as missing.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the reference start date (including unscheduled assessments). In the case where the last non-missing measurement and the reference start date coincide, that measurement will be considered pre-baseline, but Adverse Events (AEs) and medications commencing on the reference start date will be considered post-baseline.

6.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by visit summaries but will contribute to the

best/ worst case value where required (e.g. shift table).
In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries.

Early termination data will be mapped to the next available visit number for by-visit summaries.
Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

No visit windowing will be performed for this study.

6.5. STATISTICAL TESTS

The default significance level will be 5%; confidence intervals will be 95% and all tests will be two-sided, unless otherwise specified in the description of the analyses.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

6.7. SOFTWARE VERSION

All analyses, summaries and listings will be performed using SAS® software (version 9.4 or higher).

7. STATISTICAL CONSIDERATIONS

7.1. DESCRIPTIVE STATISTICS

If not otherwise specified, categorical variables will be summarized by counts and percentages and continuous variables by mean, standard deviation (SD), median, min and max.

7.2. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustment for covariates will be used in the primary analysis.

7.3. MULTICENTRE STUDIES

This study will be conducted by multiple investigators at multiple centres in UK. Randomisation to treatment arms is not stratified by centre.

7.4. MISSING DATA

Missing safety data will not be imputed unless otherwise specified.
Missing efficacy data will be handled as described in Section 14.1.2, 14.2.2 and 14.3.2 of this analysis plan.

7.5. MULTIPLE COMPARISONS/ MULTIPLICITY

Primary and secondary endpoints will be analysed hierarchically, thus no multiplicity correction will be applied.

7.6. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as stated in the exploratory analysis sections. It should be noted that the study was not designed to detect treatment differences with high statistical power within subgroups.
The following subgroups will be assessed and described within the exploratory analysis sections:

- Prior use of anti-TNF treatment
  - Yes
  - No
- Duration of disease

- <2 years
- ≥2 years

- Gender:
  - Female
  - Male

8. OUTPUT PRESENTATIONS

A separate template shows conventions for presentation of data in outputs.
The templates provided describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent will be accounted for in this study.
Subject disposition, screen failures and withdrawals, and reasons for exclusion from each analysis sets will be presented for the ENR set. Protocol deviations, including inclusion and exclusion criteria will be presented for the RND set.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented, by randomised group and overall, for the FAS.
The following demographic and other baseline characteristics will be reported for this study and collected on the eCRF:

- Age (years) - calculated relative to date of consent
- Duration of the disease
- Sex
- Race
- Ethnicity
- Baseline Weight (kg)
- Height (cm)

- BMI (kg/m^2)
- Prior use of anti-TNF treatment (stratification factor)

11. MEDICAL HISTORY

Medical History information will be presented for the FAS.

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) V. 21.0
    - Medical History conditions are defined as those collected in the medical history eCRF page.
    - Presented by SOC (System Organ Class) and PT (Preferred Term).

12. MEDICATIONS

Medications will be presented for the SAF and coded using WHO Drug Dictionary Version Dictionary B3 format version March 2018.
See 17 for handling of partial dates for medications, in the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication.
- 'Concomitant' medications are medications which:
    - started prior to, on or after the first dose of study medication and started no later than 14 days following last dose of study medication,
    - AND ended on or after the date of first dose of study medication or were ongoing at the end of the study.
- 'Post' medications are medications which started more than 14 days following the last dose of study medication.
- Incidence of prior, concomitant and post medications will be presented by ATC Level 4 code and Preferred Term (PT).

13. STUDY MEDICATION EXPOSURE

Exposure to study medication, expressed as number of subjects who received their 1st, 2nd, 3rd and 4th injections, and duration of exposure, will be presented for the SAF.
The date of first study medication administration will be taken from the eCRF "Subcutaneous dosing of IMP" form. The date of last study medication will be taken from the eCRF "End of Treatment" form.
Interruptions, compliance, and dose changes will not be taken into account for duration of exposure.

13.1. DERIVATIONS

Duration of exposure (days) = date of last study medication injection – date of first study medication injection+ 1.

14. EFFICACY ENDPOINTS

All efficacy data will be listed for all randomised subjects.

14.1. PRIMARY EFFICACY ENDPOINT

14.1.1. PRIMARY EFFICACY ENDPOINT AND DERIVATION

- Proportion of subjects who achieve an ASAS20 clinical response at Week 12

ASAS20 responder is defined as follow:

A subject with an improvement from baseline of at least 20% and an absolute improvement of at least 10 units on a 0-100 VAS in at least 3 of the following four domains collected on the eCRF and no worsening in the fourth domain (defined as a 20% increase from baseline and an absolute increase of 10 units):

- Subject's Global Assessment of Disease Status,
- Subject's Assessment of Spinal Pain,

- Function (overall BASFI score),
- Inflammation, (average of the last 2 questions of BASDAI: intensity of morning stiffness, duration of morning stiffness)

The data used to calculate ASAS20 are collected in the eCRF at Baseline and Week 12.

14.1.2. Missing Data Methods for Primary Efficacy endpoint

Subject with missing primary endpoint data (either at Baseline or Week 12) will be treated as non-responders.

14.1.3. Primary Analysis of Primary Efficacy endpoint

The primary objective of this study is to test the hypothesis that there is no difference in the ASAS20 responders proportion between the namilumab and the placebo group.

H_0: $\pi_{nam} = \pi_{pbo}$, where π represents the ASAS20 responder rate.

The primary endpoint ASAS20 will be assessed using a Bayesian analysis on the FAS. 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 $\nu = 5$. The parameterization used here is beta(α, β) where rate = α/ν and $\nu=\alpha + \beta$, and the density of beta(α, β) is proportional to $x^{\alpha}(1-x)^{\beta}$. Posterior distributions will be calculated using simulation (100000 random draws). The parameter distributions (estimated rates and rates difference) 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 and presented. Values of $\eta > 0.927$ will provide strong evidence that namilumab exhibits therapeutic benefit relative to placebo control.

14.1.4. Sensitivity Analysis of Primary Efficacy Variable(s)

- Sensitivity to missing data assumptions
  - A sensitivity analysis imputing missing placebo subjects as Responders instead of Non-Responders will be performed.
- Sensitivity to adjustment for covariates

- A sensitivity analysis including the stratification as covariate will be performed.

- Sensitivity to analysis set
  - The primary analysis will be repeated for the COM and PPAS analysis set.

14.2. SECONDARY EFFICACY

The secondary efficacy analyses will be performed for FAS and PPAS.

14.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

14.2.1.1. Proportion of subjects who achieve an ASAS40 clinical response at Week 12

ASAS40 responder is defined as follow:

A subject with an improvement from baseline of at least 40% and an absolute improvement of at least 20 units on a 0-100 VAS scale in at least 3 of the following four domains derived on the eCRF and no worsening at all in the fourth domain:

- Subject's Global Assessment of Disease Status,
- Subject's Assessment of Spinal Pain,
- Function (overall BASFI score),
- Inflammation, (average of the last 2 questions of BASDAI: intensity of morning stiffness, duration of morning stiffness)

The data used to calculate ASAS40 are collected in the eCRF at Baseline and Visit 6 (week 12).

14.2.1.2. Proportion of subjects who achieve an ASAS20 clinical response at Week 6

ASAS20 responder is defined as described in the primary efficacy endpoint Section 14.1.1

14.2.1.3. Proportion of subjects who achieve ASDAS-CRP response at Weeks 6 and 12

ASDAS-CRP scores is derived in the eCRF (according to the formula defined in Section 8.1 of

the protocol).
The disease activity states are defined as follows:

ASDAS-CRP score	Activity states
<1.3	Inactive disease
≥ 1.3 and <2.1	Moderate disease activity
≥ 2.1 and ≤3.5	High disease activity
>3.5	Very high disease activity

14.2.2. Missing Data Methods for Secondary Efficacy Variable(s)

Subjects with missing primary endpoint data (either at Baseline or Week 12) will be treated as non-responders.

14.2.3. Analysis of Secondary Efficacy endpoints

14.2.3.1. Analysis of Secondary endpoints 1, 2 and 3

The secondary endpoints will be analysed by means of the Fisher exact test (to account for the small size of the placebo sample). The null hypothesis is that there is no difference in the response rate between the two treatments.

14.3. Exploratory Efficacy

14.3.1. Exploratory Efficacy Variables & Derivations

14.3.1.1. Analysis of the primary and secondary endpoint components at Week 2, 6, 10 and 12

Subject's Global Assessment of Disease Status
Descriptive statistics of the subject's global assessment of disease status (as collected in the eCRF) for each time point (including baseline) and the change from baseline will be presented.

Subject's Assessment of Spinal Pain,
Descriptive statistics of the subject's assessment of spinal pain (as collected in the eCRF) for each time point (including baseline) and the change from baseline will be presented.

Function (BASFI)
Descriptive statistics of each BASFI item (as collected in the eCRF) and the overall BASFI score (as derived in the eCRF) for each time point (including baseline) and the change from baseline will be presented.

Bath ankylosing spondylitis disease activity index (BASDAI)
Descriptive statistics of each BASDAI item (as collected in the eCRF), and the BASDAI score (as derived in the eCRF) for each time point (including baseline) and the change from baseline will be presented.

14.3.1.2. Proportion of subjects who show a radiological response on MRI at 12 weeks

The radiological response is collected in an external data transfer and will be summarized descriptively in the Clinical Study Report.

14.3.1.3. Proportion of subjects who achieve ASAS20 clinical response at Weeks 2 and 10

The ASAS20 will be derived as defined for the primary endpoint in Section 14.1.1.

14.3.1.4. Proportion of subjects who achieve ASDAS-CRP response at Weeks 2 and 10

The ASDAS-CRP response will be derived as defined in the secondary endpoint Section 14.2.1.3.

14.3.1.5. Joint count, tendon swelling, and enthesitis at Weeks 2, 6, 10, and 12

The change from baseline to the time point of interest for the following variables, derived in the eCRF, will be summarized:

- Total number of swollen joints
- Total number of tender/painful joints
- Leeds Enthesis Scores

14.3.1.6. Serum biomarkers including CRP, faecal biomarkers including calprotectin and microbiome

The change from baseline will be summarised descriptively for the following biomarkers:
From eCRF: C-reactive protein (CRP) (quantitative variable)
From central lab: Erythrocyte sedimentation rate

HLA-B27 will only be available at screening, therefore results will be listed only. Analysis of faecal calprotectin and microbiome analysis data will not be included in the clinical study report and will therefore be described in a separate analysis plan.

14.3.1.7. Pre- and post-treatment immunophenotyping with CyTOF and gene expression of CD4, CD8, CD56 and CD14 cells

Analysis of these parameters will not be included in the clinical study report and will therefore be described in a separate analysis plan.

14.3.1.8. Neuropathic pain score (painDETECT™) at Week 6 and 12

Change from baseline in painDETECT™ score derived in the eCRF will be summarized descriptively.

14.3.2. Missing Data Methods for Exploratory Efficacy Variable(s)

No imputation for missing data will be used for the exploratory endpoints with the exception of the endpoints related to ASAS and ASDAS-CRP responder that will follow the same rule used for the primary and secondary analysis (i.e. subject with missing data at the timepoint of interest will be considered as non-responder).

14.3.3. Inference on Exploratory Efficacy Variables

The exploratory efficacy endpoints will only be analysed descriptively, and no hypothesis testing will be performed.

15. SAFETY OUTCOMES

All tables for safety outcomes will be based on the SAF.
All listings will be based on the RND analysis set.
There will be no statistical comparisons between the treatment groups for safety data.

15.1. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 21.0.
Treatment emergent adverse events (TEAEs) are defined as AEs that started on or after the first dose of study medication and prior to the last date of study medication + 125 days (inclusive).

See 17 for handling of partial dates for AEs. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case; i.e. treatment emergent.
An overall summary of number of subjects within each of the categories described in the sub-section below, will be provided as specified in the templates.
Listings will include TEAEs and Non-TEAEs.

15.1.1. ALL TEAES

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity and relationship to study medication.
Multiple occurrences for the same subject of an AE classified with the same SOC/PT will be counted only once in the summaries.

15.1.1.1. Severity

Severity is classed as mild/ moderate/ severe (increasing severity). TEAEs starting after the first dose of study medication with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/ PT, the AE with the worst case severity will be used in the corresponding severity summaries.

15.1.1.2. Relationship to Study Medication

Relationship, as indicated by the Investigator, is classed as "unrelated", "unlikely to be related", "possibly related", "probably related" (increasing severity of relationship). TEAEs with a missing relationship to study medication will be regarded as "probably related" to study medication. If a subject reports the same AE more than once within that SOC/ PT, the AE with the worst case relationship to study medication will be used in the corresponding relationship summaries. In addition to the summary of the four categories, a summary presenting the two categories "possibly related" and "probably related" grouped as "related" and the other two as "not related" to study medication will be produced.

15.1.2. TEAEs Leading to Discontinuation of Study Medication

TEAEs leading to permanent discontinuation of study medication will be identified by using the action taken with study medication classed as "drug withdrawal" and listed.

15.1.3. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events page of the eCRF. A summary of serious TEAEs by SOC and PT will be prepared.
A listing with the additional information collected in the eCRF for SAE will be prepared.

15.1.4. Adverse Events Leading to Death

TEAEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events page of the eCRF. A listing of Adverse Events leading to death will be prepared.

15.1.5. Adverse Events of Special Interest

The following TEAEs of special interest (for which there is a specific tick box in the eCRF) will be summarized separately (but included in all other summaries):

- Pulmonary alveolar proteinosis (PAP)
- Neutropaenia
- Myeloid suppression

15.2. DEATHS

If any subjects die during the study the information will be presented in a data listing.
A subject is considered died if the outcome of an AE or of a SAE is death or if the Reason for study discontinuation is death.

15.3. LABORATORY EVALUATIONS

Results from the local laboratory will be included in the reporting of this study for Haematology, Blood Chemistry, Serum Lipids, Urinalysis (Microscopic Examination will only be listed as performed on subset of subjects where blood or protein is abnormal), Immunogenicity and Other Screening Tests.
A list of laboratory parameters to be included in the outputs is included in Appendix 3 of the protocol.
Presentations will use SI Units.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

The following summaries will be provided for laboratory data:

- Actual and change from baseline by visit (for quantitative measurements)
- Incidence of abnormal values according to normal range criteria
- Shift from baseline according to normal range criteria (for quantitative measurements and categorical measurements)

15.3.1. LABORATORY REFERENCE RANGES AND ABNORMAL CRITERIA

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).

- High: Above the upper limit of the laboratory reference range.

15.4. ECG EVALUATIONS

The following ECG parameters (as collected in the eCRF) will be summarized:

- HR (bpm)
- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTc Interval (msec)
- Overall assessment of ECG (Investigator's judgement):
  - Normal
  - Abnormal, Not Clinically Significant
  - Abnormal, Clinically Significant

The following summaries will be provided for ECG data:

- Actual and change from baseline by visit (for quantitative measurements)
- Shift from baseline according to Investigator's judgement

15.5. VITAL SIGNS

The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (^{0}C)
- Weight (Kg)

The following summaries will be provided for Vital Signs data:

- Actual change from baseline and change from pre-dose to post-dose by visit

15.6. PHYSICAL EXAMINATION

Physical examination results will only be listed.

15.7. OTHER SAFETY ASSESSMENTS

15.7.1. PULMONARY ALVEOLAR PROTEINOSIS

15.7.1.1. Medical Research Council (MRC) Breathlessness Scale

Shift from baseline in MRC scale (collected in the eCRF) will be summarized as a qualitative variable.

15.7.1.2. Chest X-ray

Chest X-ray results (normal, abnormal) will be provided by local (Screening) or central reader and only be listed.

15.7.1.3. Lung Function Testing

The actual value and the change from baseline to each time point will be summarized for forced expiratory volume in the first second (FEV_1), forced vital capacity (expiratory) (FVC) and peak expiratory flow rate (PEF) (collected in the eCRF).

15.7.1.4. Pulse Oximetry

The change from baseline in saturation of peripheral oxygen (SpO_2) (collected in the eCRF) will be summarized.

15.7.1. SAFETY PARAMETERS THAT WILL ONLY BE LISTED

Details of SAE
Details of Adverse events of special interests
IP overdose report
Pregnancy reports
Genetic results (HLA-B27)

16. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Comments

These domains and/or variables will not be summarized or presented but will be available in the clinical study database.

17. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

START DATE	STOP DATE	ACTION
Known	Known	If start date < study med start date, then not TEAE If start date >= study med start date up to 125 after study med stop date, then TEAE
	Partial	If start date < study med start date, then not TEAE If start date >= study med start date up to 125 after study med stop date, then TEAE
	Missing	If start date < study med start date, then not TEAE If start date >= study med start date up to 125 after study med stop date, then TEAE
Partial, but known components show that it cannot be on or after study med start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study med start date	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date up to 125 after study med stop date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day

START DATE	STOP DATE	ACTION
		of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE
Missing	Known	If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, then not TEAE If stop date >= study med start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment, assign as concomitant If stop date >= study med start date and start date > end of treatment, assign as post study

START DATE	STOP DATE	ACTION
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment +14 days, assign as concomitant If stop date >= study med start date and start date > end of treatment + 14 days, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date <= end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment + 14 days, assign as concomitant If stop date >= study med start date and start date > end of treatment + 14 days, assign as post treatment

START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date and start date <= end of treatment + 14 days, assign as concomitant If stop date >= study med start date and start date > end of treatment + 14 days, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date <= end of treatment +14 days, assign as concomitant If start date > end of treatment + 14 days, assign as post treatment
Missing	Known	If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study med start date, assign as prior If stop date >= study med start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
[redacted]	Document Approval	29 May 2019 11:11:29 UTC