STATISTICAL ANALYSIS PLAN

A double-blind, multi-center, two-part, randomized, placebo-controlled study of the safety, tolerability, and efficacy of 4 weeks of treatment with AP1189 in early rheumatoid arthritis (RA) patients with active joint disease

Protocol Code:	SynAct-CS002
Study sponsor:	SynAct Pharma ApS
Clinical Study Phase:	IIa
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1 INTRODUCTION

1.1 Background

The methods and presentation of data analyses proposed for this study are described in detail in this Statistical Analysis Plan (SAP), in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis.

This SAP is based on the analyses described in the protocol and the data actually obtained in the study. Any deviations from the methods in the protocol will be described and explained in section 3.12.

The preparation of this SAP was completed prior to unblinding of the study.

1.2 Confidentiality Statement

This SAP is a confidential document that belongs to the sponsor. It is not to be copied or distributed to other parties without written approval from the sponsor.

1.3 Compliance with Good Clinical Practice

This SAP is designed to ensure compliance with appropriate ICH guidelines, particularly E9 (Statistical Principles for Clinical Trials) and E3 (Structure and Content of Clinical Study Reports).

1.4 Work Policy (Standard Operating Procedures)

The following statistical Standard Operating Procedures (SOP) belonging to CroxxMed ApS will be followed during the conduct of the study:

- SOP for Statistical Protocol input, Analysis and Study Reporting
- SOP for Statistical Programming

1.5 Software and File Storage

The data will be processed within the SAS®/Windows environment. The statistical report will be written in Microsoft Office Word 2010.

Electronic documents will be protected with a study-specific password.

- Software: SAS®, version 9.4.

- Location: Original database at CroxxMed ApS, the study statistician will obtain copies. The study statistician will keep SAS programs during the conduct of the analysis.

1.6 Clean File

A Clean File meeting will be held just before closing the database for the final analysis. At this meeting, it will be decided which subjects will be included in the analysis(-es), and the database will be declared clean and accurate.

The randomization code can be broken after Clean File and entered/loaded into the database in accordance with the Clean File Protocol.

1.7 Backup and Recovery Procedures

A system backup will be run every night, and the data will be stored in secure settings at a hosted server at the Electronic Data Capture vendor's premises.

1.8 Archiving

Electronic documents will be stored at CroxxMed during the conduct of the study. The original SAP (with signatures) will be filed in the Trial Master File once the study is closed. The Trial Master File will be in paper form, and electronic documents will be stored as a backup for a short period of time after study closure.

2 STUDY OBJECTIVE(S) AND DESIGN

2.1 Objective(s) and Variables

2.1.1 Primary Safety Objective

- To compare the safety of AP1189 against placebo by evaluating AEs, SAEs, and laboratory abnormalities.

2.1.2 Primary Safety Variables

AEs, SAEs, and laboratory abnormalities.

See section 3.6 for details of the calculation of primary safety variables.

2.1.3 Primary Efficacy Objective

- Effect of AP1189 vs. placebo in subjects with severe active RA (CDAI > 22), undergoing up-titration with MTX, by showing a change in CDAI from severe (CDAI > 22) to moderate or lower (CDAI ≤ 22) after 4 weeks treatment compared to baseline.

2.1.4 Primary Efficacy Variables

The change in CDAI after 4 weeks of treatment compared to baseline will be evaluated by assessing the following, by treatment group:

- Mean change in CDAI from baseline to week 4
- Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline.

See section 3.6 for details of the calculation of primary efficacy variables.

2.1.5 Secondary Efficacy Objectives

To compare the effects of AP1189 against placebo by assessing:

- Proportion of subjects achieving a reduction of more than 10 (ten) swollen and/or tender joints at week 4 compared to baseline
- Proportion of subjects achieving a change in CDAI score at week 4 compared to baseline
    - Proportion of subjects with a 5-point decrease
    - Proportion of subjects with a 10-point decrease
    - Proportion of subjects with a 15-point decrease
- Proportion of subjects achieving a change in value to ≤ 3.2 as measured by DAS28 at week 4 compared to baseline

- Change in subject-reported HAQ-DI at week 4 compared to baseline
- Change in subject-reported fatigue using FACIT-Fatigue at week 4 compared to baseline
- Proportion of subjects achieving American College of Rheumatology (ACR) response assessed by ACR20, ACR50, and ACR70

2.1.6 Secondary Efficacy Variables

The secondary efficacy variables are described in 2.1.5 above, with the following addition:

- The number of swollen and/or tender joints are found by summarizing SJC and TJC.

See section 3.6 for details of calculation of secondary efficacy variables.

2.1.7 Tertiary Efficacy Objectives

Effect of AP1189 compared to placebo at week 4 compared to baseline on inflammatory and collagen destructive biomarkers. The biomarkers include:

- CXCL13
- IL-1β
- IL-6
- IL-10
- TNF-α

2.1.8 Arthroscopy sub-Study

Effect of AP1189 compared to placebo on joint structures and inflammation as assessed by synovial biopsy at baseline and after 4 weeks treatment (only for Part 2 at selected sites, if applicable).

2.1.9 Exploratory Objective

NA

2.2 Study Type and Design

Study Phase: IIa

Study Design: Double-blind, multi-center, two-part, randomized, placebo-controlled study with 4 weeks of treatment with AP1189 in early rheumatoid arthritis (RA)

Study Flow Chart: Study flow chart is shown in the study protocol, Table 3, section 20 Schedule of Visits.

3 STATISTICAL ANALYSIS CONSIDERATIONS

3.1 Types of Analysis

All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) will be summarized by treatment and time point. Continuous variables will be summarized using n, mean, standard deviation, median, minimum, and maximum values. For categorical (nominal) variables, the number

of patients per category, and percent of the total number of patients will be presented.

Descriptive statistics (continuous and categorical variables summarized as above) will be used for an exploratory description of exposure. Plasma concentrations will be used to measure exposure.

All efficacy endpoints will be evaluated by treatment group using descriptive statistics (continuous and categorical variables summarized as above). Confidence intervals will be presented where appropriate.

3.2 Analysis Data Sets

The sets of subjects to be analyzed are defined as follows:

- The **safety analysis set** consists of all subjects who received the study medication at least once, analyzed by received treatment.
- The **pharmacokinetic (PK) analysis set** consists of all subjects who completed the study and did not have any protocol deviation or events implying a bias for the PK evaluation.
- The **efficacy analysis set** consists of all randomized subjects who received the study medication at least once, analyzed by randomized treatment (intention to treat). A second analysis of the primary efficacy endpoint, for robustness, will be performed for all randomized subjects who complete the study without any major protocol violations (per protocol).

All safety and tolerability analyses will be conducted on the safety data set, all PK analyses will be conducted on the pharmacokinetic data set, and all efficacy analyses will be conducted on the efficacy data set.

3.3 Measurement Times, Missing Data, and Outliers

Measurement Times
The first date registered (screening visit) is to be used to define Baseline visit (Week 0 visit, within 14 days from screening). Week 1 visit is defined to be 7 days (±1 day) after Baseline, Week 2 visit 14 days (±1 day) after Baseline, Week 3 visit 21 days (±1 day) after Baseline, Week 4 visit 28 days (±1 day) after Baseline, final visit 7 (±2) days after the last investigational medicinal product has been taken, and visit 8 (end of study follow-up call) 4 weeks (±3 days) after the last investigational medicinal product has been taken, as described in protocol section 20.1. Any dates outside these visit windows are noted by the Data Manager during data validation as protocol deviations.

Missing Data
Subjects with missing data will be included where possible, e.g. in the description of the patient population. Wherever the analysis requires data on a variable, subjects with missing data on that variable will be excluded from the analysis (e.g. when calculating changes from baseline). Missing items will not be imputed in any way, however plasma concentration values below the level of quantification will be set to LoQ/2 for the pharmacokinetic analysis.

Outliers
No procedure for dealing with outliers was foreseen in the trial protocol and therefore one analysis with the actual values and at least one other analysis eliminating or reducing the outlier effect will be performed and differences between their results will be discussed.

3.4 Prognostic Variables

NA

3.5 Subgroup Analyses

A sub-study taking place in Bulgaria and Moldova was added to the clinical study protocol. The sub-study was added to investigate if the effect of AP1189 in newly diagnosed subjects with severe RA who are to start up-titration with methotrexate is comparable in these two countries compared to the main study. In addition to analyzing the main study and the sub-study separately, all data will be pooled to investigate the overall effect in all participating countries.

3.6 Data Transformation and Derived Variables

Demographic analysis

Age at inclusion (years) will be calculated from date of birth and screening date.

Efficacy analysis

The HAQ-DI scale will be scored in accordance with Bruce and Fries, The Health Assessment Questionnaire (HAQ), *Clinical and Experimental Rheumatology*, 2005. Maska et al. summarize the scoring procedure as below (see https://onlinelibrary.wiley.com/doi/full/10.1002/acr.20620):
"1) identify the highest subcategory score from each of the 8 categories. Adjust for use of aids/help by increasing the category score from 0 or 1 to a 2 if use of aids/help for that category (utilize table of companion aids/help for HAQ categories). If the category score is already a 2 or 3, no adjustment is made; 2) sum the category scores; and 3) divide the final sum by the number of categories answered to obtain the final HAQ score rounded to the nearest value evenly divisible by 0.125. Requires a minimum of 6 categories answered; if less, do not score."

The FACIT-Fatigue total subscale will be scored in accordance with http://www.ser.es/wp-content/uploads/2015/03/FACIT-F_INDICE.pdf.

Change from baseline to week 4 (value at week 4 minus value at baseline) will be calculated for the following variables:

- CDAI
- DAS28
- HAQ-DI total score
- FACIT-Fatigue total subscale score
- number of swollen and/or tender joints (summarizing SJC and TJC)
- CXCL13
- IL-1β
- IL-6
- IL-10
- IL-6/IL-10 ratio
- TNF-α

In addition, percent change from baseline to week 4 (change from baseline as defined above divided by the baseline value) will be calculated for the following variables:

- CXCL13
- IL-1β
- IL-6
- IL-10
- IL-6/IL-10 ratio
- TNF-α

Indicators noting the following will be constructed, based on the above defined change in CDAI score from baseline to week 4:

- a 5-point decrease
- a 10-point decrease
- a 15-point decrease
- a 20-point decrease
- a 30-point decrease

Indicators noting a change in CDAI score will be constructed as follows:

- from severe (CDAI > 22) to moderate or lower (CDAI ≤ 22) at week 4 compared to baseline
- from severe (CDAI > 22) to low or remission (CDAI ≤ 10) at week 4 compared to baseline
- from severe (CDAI > 22) to remission (CDAI ≤ 2.8) at week 4 compared to baseline

Indicators noting a change in DAS28 will be constructed as follows:

- from > 3.2 to ≤ 3.2 at week 4 compared to baseline
- An indicator noting a change in DAS28 from high (DAS28 > 5.1) to moderate or lower (DAS28 ≤ 5.1) at week 4 compared to baseline

For the calculation of ACR response rates, indicators noting the following will be constructed:

- ≥20% improvement (reduction) in swollen and tender joint counts (SJC and TJC summarized) at week 4 compared to baseline
- ≥50% improvement (reduction) in swollen and tender joint counts (SJC and TJC summarized) at week 4 compared to baseline
- ≥70% improvement (reduction) in swollen and tender joint counts (SJC and TJC summarized) at week 4 compared to baseline
- ≥20% improvement (reduction) in Patient's Global Assessment of Disease Activity (dataset VAS) at week 4 compared to baseline
- ≥50% improvement (reduction) in Patient's Global Assessment of Disease Activity at week 4 compared to baseline

- ≥70% improvement (reduction) in Patient's Global Assessment of Disease Activity at week 4 compared to baseline
- ≥20% improvement (reduction) in Physician's Global Assessment of Disease Activity (dataset VAS) at week 4 compared to baseline
- ≥50% improvement (reduction) in Physician's Global Assessment of Disease Activity at week 4 compared to baseline
- ≥70% improvement (reduction) in Physician's Global Assessment of Disease Activity at week 4 compared to baseline
- ≥20% improvement (reduction) in Patient's Assessment of Pain at week 4 compared to baseline
- ≥50% improvement (reduction) in Patient's Assessment of Pain at week 4 compared to baseline
- ≥70% improvement (reduction) in Patient's Assessment of Pain at week 4 compared to baseline
- ≥20% improvement (increase) in Health Assessment Questionnaire (HAQ-DI) total score at week 4 compared to baseline
- ≥50% improvement (increase) in Health Assessment Questionnaire (HAQ-DI) total score at week 4 compared to baseline
- ≥70% improvement (increase) in Health Assessment Questionnaire (HAQ-DI) total score at week 4 compared to baseline
- ≥20% improvement (reduction) in C-Reactive Protein (CRP) at week 4 compared to baseline
- ≥50% improvement (reduction) in C-Reactive Protein (CRP) at week 4 compared to baseline
- ≥70% improvement (reduction) in C-Reactive Protein (CRP) at week 4 compared to baseline

The ACR response rates ACR20, ACR50, and ACR70 are defined as follows (using the indicators above):
≥20%, ≥50% and ≥70% improvement at week 4 compared to baseline, respectively, in:

- Swollen and tender joint counts (SJC and TJC summarized), and 3 of the following 5 assessments:
    - Patient's Global Assessment of Disease Activity
    - Physician's Global Assessment of Disease Activity
    - Patient's Assessment of Pain
    - Health Assessment Questionnaire (HAQ-DI)
    - C-Reactive Protein (CRP)

The Patient Global Assessment of Disease Activity RA, the Investigator Global Assessment of Disease Activity RA, and the CDAI score will be presented in absolute values and values relative to placebo by dividing the mean, median, min, and max values for each active treatment group by the corresponding value for the placebo group.

An indicator noting whether a subject received rescue treatment (joint injections with corticosteroid) during the 4-week treatment period (Baseline visit to Visit 6) will be constructed. The team will go

through the concomitant medication listings to define which subjects received rescue treatment before analyses.

Pharmacokinetic analysis

Plasma concentration values below the level of quantification will be set to LoQ/2 for the analysis.

Safety analysis

The QT interval on the ECGs is corrected from Bazett, Hodges or ECAPS to Fridericia. The laboratory values from the different sites may be reported in different units, which will be corrected to:

Variable	Unit to be used in analyses/report	Conversion formula(s)	Comments
Corrected QT Interval (QTc)	QTc Fridericia	$QTcF = QT/(RR^{1/3})$ [1]	The reported QT and RR intervals will be used to calculate QTcF.
HbA1c	mmol/mol		mmol/L used at sites in Moldova and Bulgaria
White blood cell	10E9/L		g/dl used at some sites
Neutrophils	10E9/L		g/dl used at some sites
Lymphocytes	10E9/L		g/dl used at some sites
Monocytes	10E9/L		g/dl used at some sites
Eosinophils	10E9/L		g/dl used at some sites
Basophils	10E9/L		g/dl used at some sites
Hemoglobin	mmol /L		g/dl used at some sites
Red blood cells (RBC)	10E12/L		g/dl used at some sites
Thrombocytes	10E9/L		g/dl used at some sites
Alanine transaminase (ALT)	U/L	(µkat/L) *60 = U/L[2]	µkat/L used at some sites
Aspartate transaminase (AST)	U/L	(µkat/L) *60 = U/L[2]	µkat/L used at some sites
γ−glutamyltransferase (GGT)	U/L	(µkat/L) *60 = U/L[2]	µkat/L used at some sites
Bilirubin (total)	µmol/L		
Bilirubin (conjugated)	µmol/L		µkat/L used at some sites
Alkaline phosphatase (ALP)	U/L	(µkat/L) *60 = U/L[2]	µkat/L used at some sites
Glucose (non-fasting)	mmol/L		
TSH	10E3/L	(U/L) /1000 = mIU/L mIE/L	
Total T3	nmol/L		

Free T3	pmol/L		Sweden and Denmark measure Total T3, while Norway measures Free T3.
Free T4	pmol/L		Some sites measure Total T4
Potassium	mmol/L		
Sodium	mmol/L		
Chloride	mmol/L		Site 04 measures chloride in whole blood, the other sites in plasma
Calcium	mmol/L		
Albumin	g/L		
Creatinine	µmol/L		
C-Reactive Protein (CRP)	mg/L		
Urea	mmol/L		

[1] https://www.clinigate.com/clinicalc/corrected-qt-interval-qtc.php
[2] http://unitslab.com/node/55

Conversion formulas available from relevant medical sources will be used and documented in the Statistical Report.

All the clinical sites are using their local laboratory to measure safety parameters, which means that different reference intervals will apply.

Additional units might be collected and will be converted according to standard practice.

Lab values reported as a non-numerical value (e.g., '<1') will be converted to an appropriate numerical value for numerical analyses (e.g., calculation of mean values). The team will decide the numerical value to be used before analyses. Lab values below the level of quantification will be set to LoQ/2 for the analyses.

Urine culture results will be entered as free text. The text entries will be combined into categories for summaries, where the categories will be decided by the team before analyses.

3.7 Interim Analysis

An interim analysis has been performed, evaluating the first (minimum) 24 subjects from Part 1 of the trial in order to assess the safety and efficacy of the investigational product before proceeding to Part 2. Version 1 of this analysis plan was used for the interim analysis.

All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) and efficacy data for the primary efficacy endpoint were summarized by treatment and time point for the subjects included in Part 1 of the study, i.e., the following tables (see Appendix 4 for details) were presented (any MedDRA coding of AEs will not be performed for the interim):

- Table 11.4.1.3 (CDAI score)

- Table 11.4.1.4 (CDAI score, change from baseline to week 4)
- Table 11.4.1.5 (CDAI score, change from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline)
- Table 12.2.1.1 to Table 12.5.5.1 (all safety tables).

Listings showing the following data were also presented:

- Patient disposition (including end of study information), i.e., the following listings (see Appendix 4 for details):
  - Listing 6.4.1 (Visit Registration)
  - Listing 6.4.2 (Informed Consent, Randomization, Subject Summary)
  - Listing 6.4.3 (Alcohol Consumption)
  - Listing 16.2.8.1 TB and Serology Tests)
  - Listing 6.4.10 (Inclusion Exclusion Criteria)
- Demographics and baseline characteristics, i.e. the following listings (see Appendix 4 for details):
  - Listing 16.2.4.1 (Demographics)
  - Listing 6.4.5 (Vital Signs)
  - Listing 16.2.4.3 (Age)
- Safety profiles (laboratory values, adverse events, related adverse events, serious adverse events (SAE), adverse events leading to withdrawal), i.e., the following listings (see Appendix 4 for details):
  - Listing 16.2.8.2 (Blood Biochemistry)
  - Listing 16.2.8.3 (Blood Haematology)
  - Listing 16.2.7.1 (Adverse Event Q).
- Efficacy data for the primary study endpoint
  - Listing 16.2.6.3 (CDAI)
  - Listing 16.2.6.7 (Changes from baseline in CDAI)

An independent external statistician conducted the interim analysis. The external statistician is included in the Data Monitoring Committee (DMC) established by the sponsor. The DMC reviewed the unblinded data from the interim analysis and recommended one of the three study designs for Part 2 to the Steering Committee. The criteria for choice of design are described in the Data Monitoring Committee Charter (Appendix 3). All recommendations are documented and signed by the DMC members, and they provided a summary of the safety and tolerability data obtained in Part 1 and their design recommendation for Part 2.
The independent external statistician will ensure that the interim analysis is a completely confidential process. Sponsor, investigators, and other study personnel will be kept blind. The Steering Committee's final decision on design choices for Part 2 of the study was communicated to all investigators and study personnel as soon as the decision was made.

At the end of the study, any discrepancies between the final and the interim data, which could significantly impact the analysis, should be documented.

3.8 Handling Study Centre Effects

Study centers will be presented separately in summaries of the primary endpoints in the final analysis, reported by country and individual sites. In addition to absolute values for each treatment group, values relative to the effect in the placebo group will be presented.

3.9 Multiplicity Issues

No multiplicity issues are present in this study.

3.10 Handling Withdrawals and Protocol Deviations

All protocol deviations that occur during the study will be considered for their severity/impact and taken into consideration when subjects are assigned to analysis data sets, see section 3.2. Details of subject assignment to the analysis data sets will be listed.

3.11 Concomitant Medication

Any recorded concomitant medications (including prescription, non-prescription, and herbal medications) will be listed by subject number, including the generic or trade name, strength, frequency of dosing, and the reason for its use.

3.12 Documentation and Other Considerations

Protocol Section *12.2 Primary efficacy Objective* states "Effect of AP1189 vs. placebo in subjects with severe active RA (CDAI > 22), undergoing up-titration with MTX, by showing a change in CDAI from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks treatment compared to baseline." The cut-off values for the CDAI score correspond to severe (CDAI>22) or moderate **or lower** (CDAI ≤ 22), which is the wording used in this analysis plan.

Protocol Section *12.3 Secondary efficacy Objectives* states that the "Proportion of subjects achieving American College of Rheumatology (ACR) response assessed by ACR20, ACR50, and ACR70" will be assessed. These responses will be assessed at week 4 compared with baseline (no time point was specified in the protocol).

Protocol Section *12.4 Tertiary Efficacy Objectives* states that the "Effect of AP1189 compared to placebo at week 4 compared to baseline on inflammatory and collagen destructive biomarkers" will be assessed. The comparison to baseline will be made by calculating the change for these biomarkers (CXCL13, IL-1β, IL-6, IL-10, and TNF-α) at week 4 compared with baseline (the calculation of a change from baseline was not specified in the protocol). In addition, the ratio IL-6/IL-10 will be evaluated in the same way.

Protocol Section *23.6 Pharmacokinetic Analyses* states that "Descriptive statistics will be used for an exploratory description of exposure in relation to effect." However, only one sample is taken at each visit (for some visits), with variability in the time from last dosing to sampling. Thus, the relationship between exposure and effect is not possible to evaluate, and exposure will therefore be described without relation to effect..

No other changes to analyses specified in the protocol have been identified at the time of writing this SAP.

4 Evaluation of Enrolment, Disposition, Exclusions, Evaluable Subjects

Variables are listed below (CRF annotation presented in parenthesis), along with a short description of how they will be presented.

For a list of proposed tables, see Appendix 4.

Variable (CRF annotation)	**How to be presented**
Visit or Follow-up call performed (VRYN)	# patients by visit (included in patient disposition table)
Date of visit (VRDT)	Listing only
Informed consent (INFC)	Listing only
Date of subject signature (INFCDT)	Listing only
Date of investigator signature (INFCIDT)	Listing only
Alcohol consumption (SUNCF, SUAC, SUENDDT)	Listing only
QuantiFERON-in-Tube test taken (TBYN)	Listing only
QuantiFERON-in-Tube test Date (TBDT)	Listing only
QuantiFERON-in-Tube test Result (TBRES)	Listing only
All inclusion/exclusion criteria met (IEYN, INCL1, INCL1, INCL3), INCL4, INCL5, INCL6, INCL7, INCL8, INCL9, INCL10, INCL11, INCL12, INCL13, EXCL1, EXCL2, EXCL3, EXCL4, EXCL5, EXCL6, EXCL7, EXCL8, EXCL9, EXCL101, EXCL10, EXCL11, EXCL12, EXCL13, EXCL14, EXCL15, EXCL17, EXCL18, EXCL19, EXCL20)	# patients not meeting any criteria, by visit (performed both at screening and inclusion), included in patient disposition table
Patient eligibility (ELIGYN)	# patients and % /category (2 categories: Yes/No), included in patient disposition table
Randomization date (RNDT)	Listing only
Randomization number (RN)	Listing only
IMP dispensed, Date, and Kit number (IMPDISYN, IMPDISDT, IMPDISNO)	Listing only
Patient diary handed out (DIARYHO)	Listing only
IMP from the previous week returned, Number of bottles used, Number of bottles unused, Number of bottles missing (IMPRETYN, IMPRETDT, IMPUSE, IMPUNUSE, IMPMISS)	Listing only

IMP diary: Date, time, Medication taken (DIA1DT, DIA1TM, DIA1MED, DIA1REAS, DIA2DT, DIA2TM, DIA2MED, DIA2REAS, DIA3DT, DIA3TM, DIA3MED, DIA3REAS, … , DIA30DT, DIA30TM, DIA30MED, DIA30REAS)	Listing only
Completed study (DSSTAT)	# patients and % /category (2 categories: Yes/No), included in patient disposition table
Date of completion/Screen failure/Early withdrawal (DSDAT)	Listing only
Primary reason for not completing (DSDE1COD, DSSPEC)	# patients and % /category (6 categories: Screen Failure/Adverse Event/ Subject choice/Investigator choice/Non-compliance with study protocol/Other, plus any reason for 'other'), included in patient disposition table
Due to AE No. (DSAENO)	Listing only

5 Evaluation of Demographics and Other Baseline Characteristics

Demographic/Baseline variable summaries will be provided for all subjects in the safety analysis set, by treatment as well as for all subjects in total, by time point for variables measured more than once.

Variables are listed below (CRF annotation presented in parenthesis), along with a short description of how they will be presented.

For a list of proposed tables, see Appendix 4.

5.1 Demographic variables

Variable (CRF annotation)	**How to be presented**
Date of birth (BRTHDT)	Listing only (and used to define age)
Age at inclusion (derived, see Section 3.6)	n, mean, sd, median, min, max, # patients and % /age group (4 age groups: <18/ 18-64/65-84/>85/Total)
Gender (SEX)	# patients and % /category (3 categories: Female/Male/Unknown)

Ethnicity (ETHNIC)	# patients and % /category (2 categories: Hispanic or Latino/Not Hispanic or Latino)
Race (RACE, RACEOTH)	# patients and % /category (6 categories: American Indian or Alaska Native/Asian/Black or African American/Native Hawaiian or Pacific Islander/White/Other, plus any specification of 'other')
Height (HEIGHT)	n, mean, sd, median, min, max
Weight (WEIGHT) at screening	n, mean, sd, median, min, max

6 EFFICACY ANALYSIS

6.1 Description of Efficacy Variables

Efficacy variable summaries will be provided for all subjects in the efficacy analysis set, by treatment and by rescue treatment received within the 4-week treatment period as well as for all subjects in total, by time point for variables measured more than once.

Variables are listed below (CRF annotation presented in parenthesis), along with a short description of how they will be presented. Numeric codes are defined in the annotated CRF.

For a list of proposed tables, see Appendix 4.

6.1.1 Description of primary efficacy variables

Variable (CRF annotation)	**How to be presented**
Patient Global Assessment of Disease Activity RA, cm (PGADA, dataset CDAI)	n, mean (95% CI), sd, median, min, max, by visit
Patient Global Assessment of Disease Activity RA, cm, relative to placebo (derived, see Section 3.6)	Mean, median, min, max, by visit, country, and site
Investigator Global Assessment of Disease Activity RA, cm (IGADA, dataset CDAI)	n, mean (95% CI), sd, median, min, max, by visit
Investigator Global Assessment of Disease Activity RA, cm, relative to placebo (derived, see Section 3.6)	mean, median, min, max, by visit, country, and site
CDAI score calculated (CDAI)	n, mean (95% CI), sd, median, min, max, by visit

CDAI score calculated, relative to placebo (derived, see Section 3.6)	Mean, median, min, max, by visit, country, and site
CDAI change from baseline to week 4 (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max, by visit
Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate or lower (CDAI ≤ 22) at week 4 compared to baseline (derived, see Section 3.6)	# patients and % /category (2 categories: Yes/No)

6.1.2 Description of secondary efficacy variables

Variable (CRF annotation)	**How to be presented**
Joint Tenderness and Swelling assessment performed (JTSYN)	# patients and % /category, by visit (2 categories: Yes/no)
Joint Tenderness and Swelling Date (JTSDT)	Listing only
Temporomandibular joint tenderness and swelling (TJ1L, TJ1R, SJ1L, SJ1R, JOINT1N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Sternoclavicular joint tenderness and swelling (TJ2L, TJ2R, SJ2L, SJ2R, JOINT2N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Acromioclavicular joint tenderness and swelling (TJ3L, TJ3R, SJ3L, SJ3R, JOINT3N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Shoulder tenderness and swelling (TJ4L, TJ4R, SJ4L, SJ4R, JOINT4N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Elbow tenderness and swelling (TJ5L, TJ5R, SJ5L, SJ5R, JOINT5N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Wrist tenderness and swelling (TJ6L, TJ6R, SJ6L, SJ6R, JOINT6N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metacarpophalangeal joint I tenderness and swelling (TJ7L, TJ7R, SJ7L, SJ7R, JOINT7N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metacarpophalangeal joint II tenderness and swelling (TJ8L, TJ8R, SJ8L, SJ8R, JOINT8N)	# patients and % /category, by visit (3 categories: present/absent/not done)

Metacarpophalangeal joint III tenderness and swelling (TJ9L, TJ9R, SJ9L, SJ9R, JOINT9N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metacarpophalangeal joint IV tenderness and swelling (TJ10L, TJ10R, SJ10L, SJ10R, JOINT10N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metacarpophalangeal joint V tenderness and swelling (TJ11L, TJ11R, SJ11L, SJ11R, JOINT11N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Thumb interphalangeal joint tenderness and swelling (TJ12L, TJ12R, SJ12L, SJ12R, JOINT12N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal interphalangeal joint II tenderness and swelling (TJ13L, TJ13R, SJ13L, SJ13R, JOINT13N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal interphalangeal joint III tenderness and swelling (TJ14L, TJ14R, SJ14L, SJ14R, JOINT14N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal interphalangeal joint IV tenderness and swelling (TJ15L, TJ15R, SJ15L, SJ15R, JOINT15N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal interphalangeal joint V tenderness and swelling (TJ16L, TJ16R, SJ16L, SJ16R, JOINT16N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Distal interphalangeal joint II tenderness and swelling (TJ17L, TJ17R, SJ17L, SJ17R, JOINT17N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Distal interphalangeal joint III tenderness and swelling (TJ18L, TJ18R, SJ18L, SJ18R, JOINT18N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Distal interphalangeal joint IV tenderness and swelling (TJ19L, TJ19R, SJ19L, SJ19R, JOINT19N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Distal interphalangeal joint V tenderness and swelling (TJ20L, TJ20R, SJ20L, SJ20R, JOINT20N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Knee tenderness and swelling (TJ21L, TJ21R, SJ21L, SJ21R, JOINT21N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Hip tenderness and swelling (TJ22L, TJ22R, SJ22L, SJ22R, JOINT22N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Ankle tenderness and swelling (TJ23L, TJ23R, SJ23L, SJ23R, JOINT23N)	# patients and % /category, by visit (3 categories: present/absent/not done)

Tarsus tenderness and swelling (TJ24L, TJ24R, SJ24L, SJ24R, JOINT24N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metatarsophalangeal joint I tenderness and swelling (TJ25L, TJ25R, SJ25L, SJ25R, JOINT25N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metatarsophalangeal joint II tenderness and swelling (TJ26L, TJ26R, SJ26L, SJ26R, JOINT26N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metatarsophalangeal joint III tenderness and swelling (TJ27L, TJ27R, SJ27L, SJ27R, JOINT27N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metatarsophalangeal joint IV tenderness and swelling (TJ28L, TJ28R, SJ28L, SJ28R, JOINT28N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Metatarsophalangeal joint V tenderness and swelling (TJ29L, TJ29R, SJ29L, SJ29R, JOINT29N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Great toe interphalangeal joint tenderness and swelling (TJ30L, TJ30R, SJ30L, SJ30R, JOINT30N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal and distal interphalangeal joints II tenderness and swelling (TJ31L, TJ31R, SJ31L, SJ31R, JOINT31N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal and distal interphalangeal joints III tenderness and swelling (TJ32L, TJ32R, SJ32L, SJ32R, JOINT32N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal and distal interphalangeal joints IV tenderness and swelling (TJ33L, TJ33R, SJ33L, SJ33R, JOINT33N)	# patients and % /category, by visit (3 categories: present/absent/not done)
Proximal and distal interphalangeal joints V tenderness and swelling (TJ34L, TJ34R, SJ34L, SJ34R, JOINT34N)	# patients and % /category, by visit (3 categories: present/absent/not done)
TJC sum (TJCSUM, duplicates in datasets JTS and CDAI)	n, mean (95% CI), sd, median, min, max, by visit
Re-entered TJC (28) (TJCENTRY)	Listing only (used for CDAI calculation)
SJC sum (SJCSUM, duplicates in datasets JTS and CDAI)	n, mean (95% CI), sd, median, min, max, by visit
Re-entered SJC (28) (SJCENTRY)	Listing only (used for CDAI calculation)

Total number of tender or swollen joints (SJC and TJC summarized)	n, mean (95% CI), sd, median, min, max, by visit
Proportion of subjects achieving a reduction of more than 10 (ten) swollen and/or tender joints (SJC and TJC, summarized) at week 4 compared to baseline (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving reduction)
Proportion of subjects achieving a 5-point decrease in CDAI score after 4 weeks of treatment compared to baseline (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving decrease)
Proportion of subjects achieving a 10-point decrease in CDAI score after 4 weeks of treatment compared to baseline (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving decrease)
Proportion of subjects achieving a 15-point decrease in CDAI score after 4 weeks of treatment compared to baseline (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving decrease)
DAS28 calculated (DAS28YN)	# patients and % /category, by visit (2 categories: Yes/no)
DAS28 score (DAS28)	n, mean (95% CI), sd, median, min, max, by visit
DAS28 change from baseline to week 4 (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max, by visit
Proportion of subjects achieving a change in DAS28 from DAS28 > 3.2 to DAS28 ≤ 3.2 at week 4 compared to baseline (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving change)
HAQ-DI questionnaire completed (HAQDIYN)	# patients and % /category, by visit (2 categories: Yes/no)
HAQ-DI questionnaire Date (HAQDIDT)	Listing only
HAQ-DI responses (HAQDI1, HAQDI2, HAQDI3, HAQDI4, HAQDI5, HAQDI6, HAQDI7, HAQDI8, HAQDI9, HAQAID1, HAQAID2, HAQAID3, HAQAID4, HAQAID5, HAQAID6, HAQAID7, HAQAID8, HAQAID9, HAQHELP1, HAQHELP2, HAQHELP3, HAQHELP4, HAQDI10, HAQDI11,	# patients and % /category, by visit (4 categories for HAQDI items: Without any difficulty/With some difficulty/With much difficulty/Unable to do; 2 categories for HAQAID and HAQHELP items: Used/not used)

HAQDI12, HAQDI3, HAQDI4, HAQDI5, HAQDI6, HAQDI7, HAQDI8, HAQDI9, HAQD20, HAQAID10, HAQAID11, HAQAID12, HAQAID13, HAQAID14, HAQAID15, HAQAID16, HAQAID17, HAQHELP5, HAQHELP6, HAQHELP7, HAQHELP8)	
HAQ-DI pain because of illness past week, mm (HAQPAIN)	n, mean (95% CI), sd, median, min, max, by visit
HAQ-DI total score (derived, see Section 3.6)	n, mean, sd, median, min, max, by visit
Change of HAQ-DI total score at week 4 compared to baseline (derived, see Section 3.6)	N, mean, sd, median, min, max, by visit
FACIT Fatigue Scale completed (FACITYN)	# patients and % /category, by visit (2 categories: Yes/no)
FACIT Fatigue Item responses (FACIT1, FACIT2, FACIT3, FACIT4, FACIT5, FACIT6, FACIT7, FACIT8, FACIT9, FACIT10, FACIT11, FACIT12, FACIT13)	# patients and % /category/item, by visit (5 categories per item; Not at all/A little bit/Somewhat/Quite a bit/Very much)
FACIT Fatigue total subscale score (derived, see Section 3.6)	n, mean, sd, median, min, max, by visit
Change of FACIT-Fatigue total subscale score at week 4 compared to baseline (derived, see Section 3.6)	n, mean, sd, median, min, max, by visit
Proportion of subjects achieving ACR response assessed by ACR 20 (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving ACR 20)
Proportion of subjects achieving ACR response assessed by ACR 50 (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving ACR 50)
Proportion of subjects achieving ACR response assessed by ACR 70 (derived, see Section 3.6)	# patients and % /category (2 categories: Achieving/Not achieving ACR 70)

6.1.3 Description of tertiary efficacy variables

Variable (CRF annotation)	**How to be presented**
Sample collected for Cytokines (BIOPERF)	# patients and % /category, by visit (2 categories: Yes/no)
Cytokines sample Date (BIODT)	Listing only

Cytokines sample Time (BIOTM)	Listing only
CXCL13 (pg/mL) (cytokines data)	n, mean, sd, median, min, max, by visit
IL-1β (pg/mL) (cytokines data)	n, mean, sd, median, min, max, by visit
IL-6 (pg/mL) (cytokines data)	n, mean, sd, median, min, max, by visit
IL-10 (pg/mL) (cytokines data)	n, mean, sd, median, min, max, by visit
IL-6/ IL-10 ratio (derived, see Section 3.6)	n, mean, sd, median, min, max, by visit
TNF-α (pg/mL) (cytokines data)	n, mean, sd, median, min, max, by visit
Change in CXCL13 at week 4 compared to baseline (pg/mL) (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max
Change in IL-1β at week 4 compared to baseline (pg/mL) (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max
Change in IL-6 at week 4 compared to baseline (pg/mL) (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max
Change in IL-10 at week 4 compared to baseline (pg/mL) (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max
Change in IL-6/ IL-10 ratio at week 4 compared to baseline (pg/mL) (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max
Change in TNF-α at week 4 compared to baseline (pg/mL) (derived, see Section 3.6)	n, mean (95% CI), sd, median, min, max

6.1.4 Description of other efficacy variables

Variable (CRF annotation)	**How to be presented**
Subject completed global and pain VAS (PGPVAS)	# patients and % /category, by visit (2 categories: Yes/No)
Global and Pain VAS Date (PGPDT)	Listing only
Patient Assessment of Pain Today, cm (PAP)	n, mean (95% CI), sd, median, min, max, by visit
Patient Global Assessment of Disease Activity Today VAS, cm (PGADA, dataset VAS)	n, mean (95% CI), sd, median, min, max, by visit

Investigator completed Investigator Global VAS (IGVAS)	# patients and % /category, by visit (2 categories: Yes/No)
Investigator Global VAS Date (IGVASDT)	Listing only
Investigator Global Assessment of Disease Activity Today VAS, cm (IGADA, dataset VAS)	n, mean (95% CI), sd, median, min, max, by visit
C-Reactive Protein (CRP), mg/L (derived from CRP and CRP_U, see Section 7.9.2)	n, mean, sd, median, min, max, by visit
C-Reactive Protein (CRP), Out of range and Clinically significantly abnormal (CRP_OR, CRP_CS)	# patients and % /category (1 category CRP_OR; Yes, 2 categories CRP_CS; Yes/No), by visit

6.2 Exploratory Analysis

Variables are listed below (CRF annotation presented in parenthesis), along with a short description of how they will be presented.

For a list of proposed tables, see Appendix 4.

Variable (CRF annotation)	**How to be presented**
Plasma concentrations of AP1189 (ng/mL)	Listing only

7 SAFETY AND TOLERABILITY ANALYSES

All safety parameters (vital signs, ECG, AEs/SAEs, laboratory abnormalities, etc.) will be summarized by treatment as well as for all subjects in total, by time point. Individual subject listings will also be prepared for all safety variables. Listings will include flagging of clinically notable vital sign abnormalities, as defined in protocol Table 5.

Patients with no post randomization data who cannot be contacted will not be counted in frequency tables. If included, such patients would reduce the frequency of Adverse Events.

Patients will be tabulated according to treatment received. Patients who have not received any trial medication (neither active treatment nor placebo) will not be included in frequency tables.

Variables are listed below (CRF annotation presented in parenthesis), along with a short description of how they will be presented.

For a list of proposed tables, see Appendix 4.

7.1 Medical history variables

Variable (CRF annotation)	How to be presented
Any relevant medical and/or surgical history (MHYN)	# patients and % /category (2 categories: Yes/no)
Medical diagnosis/surgical procedure (MHTERM, MHONG)	# patients and % per diagnosis/procedure (unknown no. of categories)
Medical diagnosis/surgical procedure start date (MHSTDAT)	Listings only

7.2 Prior and concomitant medication variables

Variable (CRF annotation)	How to be presented
Any concomitant medications (screening) or changes since last visit (CMYN)	# patients and % /category (2 categories: Yes/No), by visit
Reported generic name of medication (CMTRT)	Listing only
Total daily dose (CMDOSE)	Listing only
Unit (CMDOSU)	Listing only
Route of administration (CMROUTE)	Listing only
Frequency (CMDOSFRQ)	Listing only
Start date (CMSTDC)	Listing only
Stop date (CMENDC)	Listing only
Ongoing (CMONG)	Listing only
Indication (CMIND)	Listing only
AE no, if given to AE (CMAENO)	Listing only

7.3 Pregnancy test

Pregnancy test taken (PTYN, PTREAS, UPTYN, UPTREAS)	# patients and % /category, by visit (2 categories: Yes/no)
Date of pregnancy test (PTDAT, UPTDAT)	Listing only
Result of pregnancy test (PTRES, UPTRES)	# patients and % /category, by visit (2 categories: Negative/Positive)

7.4 Physical Examination

Physical examination performed (PEYN)	# patients and % /category, by visit (2 categories: Yes/no)
Date of physical exam (PEDT)	Listing only
General appearance, normal/abnormal, clinically significant (GENAPP, GENAPP_DES, GENAPP_CS)	# patients and % /category, by visit (3 categories for GENAPP: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for GENAPP_CS: Yes/no)
Dermatological, normal/abnormal, clinically significant (SKIN, SKIN_DES, SKIN_CS)	# patients and % /category, by visit (3 categories for SKIN: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for SKIN_CS: Yes/no)
Thyroid, normal/abnormal, clinically significant (THYR, THYR_DES, THYR_CS)	# patients and % /category, by visit (3 categories for THYR: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for THYR_CS: Yes/no)
Head, neck, throat, normal/abnormal, clinically significant (HNT, HNT_DES, HNT_CS)	# patients and % /category, by visit (3 categories for HNT: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for HNT_CS: Yes/no)
Heart / Lungs, normal/abnormal, clinically significant (RESP, RESP_DES, RESP_CS)	# patients and % /category, by visit (3 categories for RESP: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for RESP_CS: Yes/no)

Abdomen, normal/abnormal, clinically significant (ABDOM, AB_DES, AB_CS)	# patients and % /category, by visit (3 categories for ABDOM: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for ABDOM_CS: Yes/no)
Lymph nodes, normal/abnormal, clinically significant (LYMPH, LYMP_DES, LYMP_CS)	# patients and % /category, by visit (3 categories for LYMPH: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for LYMP_CS: Yes/no)
Musculoskeletal, normal/abnormal, clinically significant (MUSKU, MUSKU_DES, MUSCU_CS)	# patients and % /category, by visit (3 categories for MUSKU: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for MUSCU_CS: Yes/no)
Cardiovascular, normal/abnormal, clinically significant (HEART, HEART_DES, HEART_CS)	# patients and % /category, by visit (3 categories for HEART: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for HEART_CS: Yes/no)
Neurological, normal/abnormal, clinically significant (NEUR, NEUR_DES, NEUR_CS)	# patients and % /category, by visit (3 categories for NEUR: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for NEUR_CS: Yes/no)
Joints, normal/abnormal, clinically significant (JOINT, JOIN_DES, JOIN_CS)	# patients and % /category, by visit (3 categories for JOINT: Normal/Abnormal/Not Done, plus any description if abnormal; 2 categories for JOIN_CS: Yes/no)

7.5 Height and Weight

Height (HEIGHT)	Listing only
Weight (WEIGHT)	Listing only
Weight, clinically significant (WEIGHT_CS)	Listing only

7.6 Vital Signs

Variable (CRF annotation)	How to be presented
Vital signs measured (VSYN)	# patients and % /category (2 categories: Yes/No), by visit
Date of vital signs (VSDT)	Listing (and used to define visit)
Time of vital signs (VSTM)	Listing only
Systolic BP, mmHg (SBP)	n, mean, sd, median, min, max, by visit
Systolic BP, clinically significant (SBP_CS)	# patients and % /category (2 categories: Yes/No), by visit
Diastolic BP, mmHg (DBP)	n, mean, sd, median, min, max, by visit
Diastolic BP, clinically significant (DBP_CS)	# patients and % /category (2 categories: Yes/No), by visit
Heart rate, bpm (HR)	n, mean, sd, median, min, max, by visit
Heart rate, clinically significant (HR_CS)	# patients and % /category (2 categories: Yes/No), by visit
Respiratory rate, breaths/min (RR)	n, mean, sd, median, min, max, by visit
Respiratory rate, clinically significant (RR_CS)	# patients and % /category (2 categories: Yes/No), by visit

7.7 Lead ECGs

Variable (CRF annotation)	How to be presented
ECG performed (EGPERF)	# patients and % /category, by visit (2 categories: Yes/No)
ECG Date (EGDT)	Listing only
Rhythm, bpm (ECRHYT, ECRHYOT)	# patients and % /category, by visit (7 categories: Sinus normal/Tachycardia/Atrial fibrillation/Atrial flutter/Bradycardia/ Ventricular fibrillation/Other, plus any specification for other)

RR Interval, beats/min (EGRR)	n, mean, sd, median, min, max, by visit
PR Interval, msecs (EGPR)	n, mean, sd, median, min, max, by visit
QRS Duration, msecs (EGQRS)	n, mean, sd, median, min, max, by visit
QT Interval, msecs (EGQT)	n, mean, sd, median, min, max, by visit
QTcF Interval, msecs (EGQTCF). Derived from RR Interval (EGRR) and QT Interval (EGQT) if missing, see Section 3.6.	n, mean, sd, median, min, max, by visit
Overall interpretation (EGINTPRT)	# patients and % /category, by visit (4 categories: Normal/Abnormal, clinically insignificant/ Abnormal, clinically significant/ Unable to Evaluate)
Description of abnormal findings (EGDESC)	List of descriptions, by visit

7.8 X-Rays

Variable (CRF annotation)	**How to be presented**
Chest X-ray taken (XRCYN)	# patients and % /category (2 categories: Yes/No)
Chest X-ray Date (XRCDT)	Listing only
Hands and feet X-ray taken (XRHF)	# patients and % /category (2 categories: Yes/No)
Hands and feet X-ray Date (XRHFDT)	Listing only

7.9 Laboratory Assessments

7.9.1 Haematology

Variable (CRF annotation)	**How to be presented**
Blood sample collected for analysis of Haematology (BLHPERF)	# patients and % /category, by visit (2 categories: Yes/No)
Haematology sample Date (BLHDT)	Listing only
Haematology sample Time (BLHTM)	Listing only

HbA1c, collected unit[1] (HBA1C, HBA1C_U)	Listing only (units converted to mmol/L)
HbA1c, mmol/mol (derived from HBA1C above)	n, mean, sd, median, min, max, by visit
HbA1c, Out of range and Clinically significantly abnormal (HBA1C_OR, HBA1C_CS)	# patients and % /category (1 category HBA1C_OR; Yes, 2 categories HBA1C_CS; Yes/No), by visit
White blood cell, collected unit (WBCC, WBCC_U)	Listing only (units converted to 10E9/L)
White blood cell, 10E9/L (derived from WBCC above)	n, mean, sd, median, min, max, by visit
White blood cell, Out of range and Clinically significantly abnormal (WBCC_OR, WBCC_CS)	# patients and % /category (1 category WBCC_OR; Yes, 2 categories WBCC_CS; Yes/No), by visit
Neutrophils, collected unit (NEUT, NEUT_U)	Listing only (units converted to 10E9/L)
Neutrophils, 10E9/L (derived from NEUT above)	n, mean, sd, median, min, max, by visit
Neutrophils, Out of range and Clinically significantly abnormal (NEUT_OR, NEUT_CS)	# patients and % /category (1 category NEUT_OR; Yes, 2 categories NEUT_CS; Yes/No), by visit
Lymphocytes, collected unit (LYMPO, LYMPO_U)	Listing only (units converted to 10E9/L)
Lymphocytes, 10E9/L (derived from LYMPO above)	n, mean, sd, median, min, max, by visit
Lymphocytes, Out of range and Clinically significantly abnormal (LYMPO_OR, LYMPO_CS)	# patients and % /category (1 category LYMPO_OR; Yes, 2 categories LYMPO_CS; Yes/No), by visit
Monocytes, collected unit (MONOC, MONOC_U)	Listing only (units converted to 10E9/L)
Monocytes, 10E9/L (derived from MONOC above)	n, mean, sd, median, min, max, by visit
Monocytes, Out of range and Clinically significantly abnormal (MONOC_OR, MONOC_CS)	# patients and % /category (1 category MONOC_OR; Yes, 2 categories MONOC_CS; Yes/No), by visit
Eosinophils, collected unit (EOSIN, EOSIN_U)	Listing only (units converted to 10E9/L)
Eosinophils, 10E9/L (derived from EOSIN above)	n, mean, sd, median, min, max, by visit

Eosinophils, Out of range and Clinically significantly abnormal (EOSIN_OR, EOSIN_CS)	# patients and % /category (1 category EOSIN_OR; Yes, 2 categories EOSIN_CS; Yes/No), by visit
Basophils, collected unit (BASO, BASO_U)	Listing only (units converted to 10E9/L)
Basophils, 10E9/L (derived from BASO above)	n, mean, sd, median, min, max, by visit
Basophils, Out of range and Clinically significantly abnormal (BASO_OR, BASO_CS)	# patients and % /category (1 category BASO_OR; Yes, 2 categories BASO_CS; Yes/No), by visit
Hemoglobin, collected unit (HB, HB_U)	Listing only (units converted to mmol/L)
Hemoglobin, mmol /L (derived from HB above)	n, mean, sd, median, min, max, by visit
Hemoglobin, Out of range and Clinically significantly abnormal (HB_OR, HB_CS)	# patients and % /category (1 category HB_OR; Yes, 2 categories HB_CS; Yes/No), by visit
Red blood cells (RBC), collected unit (RBC, RBC_U)	Listing only (units converted to 10E12/L)
Red blood cells (RBC), 10E12/L (derived from RBC above)	n, mean, sd, median, min, max, by visit
Red blood cells (RBC), Out of range and Clinically significantly abnormal (RBC_OR, RBC_CS)	# patients and % /category (1 category RBC_OR; Yes, 2 categories RBC_CS; Yes/No), by visit
Thrombocytes, collected unit (THRC, THRC_U)	Listing only (units converted to 10E9/L)
Thrombocytes, 10E9/L (derived from THRC above)	n, mean, sd, median, min, max, by visit
Thrombocytes, Out of range and Clinically significantly abnormal (THRC_OR, THRC_CS)	# patients and % /category (1 category THRC_OR; Yes, 2 categories THRC_CS; Yes/No), by visit

[1] Different laboratories might use different units. All values collected in different units than the units to be used for analysis will be converted, see section 3.6.

7.9.2 Biochemistry

Variable (CRF annotation)	**How to be presented**

Blood sample collected for analysis of Biochemistry (BLBPERF)	# patients and % /category, by visit (2 categories: Yes/No)
Biochemistry sample Date (BLBDT)	Listing only
Biochemistry sample Time (BLBTM)	Listing only
Alanine transaminase (ALT), collected unit[1] (ALT, ALT_U)	Listing only (units converted to U/L)
Alanine transaminase (ALT), U/L (derived from ALT above)	n, mean, sd, median, min, max, by visit
Alanine transaminase (ALT), Out of range and Clinically significantly abnormal (ALT_OR, ALT_CS)	# patients and % /category (1 category ALT_OR; Yes, 2 categories ALT_CS; Yes/No), by visit
Aspartate transaminase (AST), collected unit (AST, AST_U)	Listing only (units converted to U/L)
Aspartate transaminase (AST), U/L (derived from AST above)	n, mean, sd, median, min, max, by visit
Aspartate transaminase (AST), Out of range and Clinically significantly abnormal (AST_OR, AST_CS)	# patients and % /category (1 category AST_OR; Yes, 2 categories AST_CS; Yes/No), by visit
γ−glutamyltransferase (GGT), collected unit (GGT, GGT_U)	Listing only (units converted to U/L)
γ−glutamyltransferase (GGT), U/L (derived from GGT above)	n, mean, sd, median, min, max, by visit
γ−glutamyltransferase (GGT), Out of range and Clinically significantly abnormal (GGT_OR, GGT_CS)	# patients and % /category (1 category GGT_OR; Yes, 2 categories GGT_CS; Yes/No), by visit
Bilirubin (total), collected unit (BILIT, BILIT_U)	Listing only (units converted to µmol/L)
Bilirubin (total), µmol/L (derived from BILIT above)	n, mean, sd, median, min, max, by visit
Bilirubin (total), Out of range and Clinically significantly abnormal (BILIT_OR, BILIT_CS)	# patients and % /category (1 category BILIT_OR; Yes, 2 categories BILIT_CS; Yes/No), by visit

Bilirubin (conjugated), collected unit (BILIC, BILIC_U)	Listing only (units converted to µmol/L)
Bilirubin (conjugated), µmol/L (converted from BILIC above)	n, mean, sd, median, min, max, by visit
Bilirubin (conjugated), Out of range and Clinically significantly abnormal (BILIC_OR, BILIC_CS)	# patients and % /category (1 category BILIC_OR; Yes, 2 categories BILIC_CS; Yes/No), by visit
Bilirubin (unconjugated), µmol/L, calculated (BILICALC)	n, mean, sd, median, min, max, by visit
Bilirubin (unconjugated), Out of range and Clinically significantly abnormal (BILIUN_OR, BILIUN_CS)	# patients and % /category (1 category BILIUN_OR; Yes, 2 categories BILIUN_CS; Yes/No), by visit
Alkaline phosphatase (ALP), collected unit (ALP, ALP_U)	Listing only (units converted to U/L)
Alkaline phosphatase (ALP), U/L (derived from ALP above)	n, mean, sd, median, min, max, by visit
Alkaline phosphatase (ALP), Out of range and Clinically significantly abnormal (ALP_OR, ALP_CS)	# patients and % /category (1 category ALP_OR; Yes, 2 categories ALP_CS; Yes/No), by visit
Glucose (non-fasting), collected unit (GLUC, GLUC_U)	Listing only (units converted to mmol/L)
Glucose (non-fasting), mmol/L (derived from GLUC above)	n, mean, sd, median, min, max, by visit
Glucose (non-fasting), Out of range and Clinically significantly abnormal (GLUC_OR, GLUC_CS)	# patients and % /category (1 category GLUC_OR; Yes, 2 categories GLUC_CS; Yes/No), by visit
Potassium, collected unit (POT, POT_U)	Listing only (units converted to mmol/L)
Potassium, mmol/L (derived from POT above)	n, mean, sd, median, min, max, by visit
Potassium, Out of range and Clinically significantly abnormal (POT_OR, POT_CS)	# patients and % /category (1 category POT_OR; Yes, 2 categories POT_CS; Yes/No), by visit
Sodium, collected unit (SOD, SOD_U)	Listing only (units converted to mmol/L)

Sodium, mmol/L (derived from SOD above)	n, mean, sd, median, min, max, by visit
Sodium, Out of range and Clinically significantly abnormal (SOD_OR, SOD_CS)	# patients and % /category (1 category SOD_OR; Yes, 2 categories SOD_CS; Yes/No), by visit
Chloride, collected unit (CHLOR, CHLOR_U)	Listing only (units converted to mmol/L)
Chloride, mmol/L (derived from CHLOR above)	n, mean, sd, median, min, max, by visit
Chloride, Out of range and Clinically significantly abnormal (CHLOR_OR, CHLOR_CS)	# patients and % /category (1 category CHLOR_OR; Yes, 2 categories CHLOR_CS; Yes/No), by visit
Calcium, collected unit (CALC, CALC_U)	Listing only (units converted to mmol/L)
Calcium, mmol/L (derived from CALC above)	n, mean, sd, median, min, max, by visit
Calcium, Out of range and Clinically significantly abnormal (CALC_OR, CALC_CS)	# patients and % /category (1 category CALC_OR; Yes, 2 categories CALC_CS; Yes/No), by visit
Albumin, collected unit (ALB, ALB_U)	Listing only (units converted to g/L)
Albumin, g/L (derived from ALB above)	n, mean, sd, median, min, max, by visit
Albumin, Out of range and Clinically significantly abnormal (ALB_OR, ALB_CS)	# patients and % /category (1 category ALB_OR; Yes, 2 categories ALB_CS; Yes/No), by visit
Creatinine, collected unit (CREA, CREA_U)	Listing only (units converted to µmol/L)
Creatinine, µmol/L (derived from CREA above)	n, mean, sd, median, min, max, by visit
Creatinine, Out of range and Clinically significantly abnormal (CREA_OR, CREA_CS)	# patients and % /category (1 category CREA_OR; Yes, 2 categories CREA_CS; Yes/No), by visit
C-Reactive Protein (CRP), collected unit (CRP, CRP_U)	Listing only (units converted to mg/L)
C-Reactive Protein (CRP), mg/L (derived from CRP above)	Presented with Secondary Efficacy Variables
C-Reactive Protein (CRP), Out of range and Clinically significantly abnormal (CRP_OR, CRP_CS)	# patients and % /category (1 category CRP_OR; Yes, 2 categories CRP_CS; Yes/No), by visit

Urea, collected unit (UREA, UREA_U)	Listing only (units converted to mmol/L)
Urea, mmol/L (derived from UREA above)	n, mean, sd, median, min, max, by visit
Urea, Out of range and Clinically significantly abnormal (UREA_OR, UREA_CS)	# patients and % /category (1 category UREA_OR; Yes, 2 categories UREA_CS; Yes/No), by visit
INR (INR)	n, mean, sd, median, min, max, by visit
INR, Out of range and Clinically significantly abnormal (INR_OR, INR_CS)	# patients and % /category (1 category INR_OR; Yes, 2 categories INR_CS; Yes/No), by visit

[1] Different laboratories might use different units. All values collected in different units than the units to be used for analysis will be converted, see section 3.6.

7.9.3 Thyroid Function

Variable (CRF annotation)	**How to be presented**
TSH, collected unit[1] (TSH, TSH_U)	Listing only (units converted to 10E3/L)
TSH, 10E3/L (derived from TSH above)	n, mean, sd, median, min, max, by visit
TSH, Out of range and Clinically significantly abnormal (TSH_OR, TSH_CS)	# patients and % /category (1 category TSH_OR; Yes, 2 categories TSH_CS; Yes/No), by visit
Total T3, collected unit (TT3, TT3_U)	Listing only (units converted to nmol/L)
Total T3, nmol/L (derived from TT3 above)	n, mean, sd, median, min, max, by visit
Total T3, Out of range and Clinically significantly abnormal (TT3_OR, TT3_CS)	# patients and % /category (1 category TT3_OR; Yes, 2 categories TT3_CS; Yes/No), by visit
Free T3, collected unit (FT3, FT3_U)	Listing only (units converted to pmol/L)
Free T3, pmol/L (derived from FT3 above)	n, mean, sd, median, min, max, by visit

Free T3, Out of range and Clinically significantly abnormal (FT3_OR, FT3_CS)	# patients and % /category (1 category FT3_OR; Yes, 2 categories FT3_CS; Yes/No), by visit
Total T4, collected unit (TT4, TT4_U)	Listing only (units converted to nmol/L)
Total T4, nmol/L (derived from TT4 above)	n, mean, sd, median, min, max, by visit
Total T4, Out of range and Clinically significantly abnormal (TT4_OR, TT4_CS)	# patients and % /category (1 category TT4_OR; Yes, 2 categories TT4_CS; Yes/No), by visit
Free T4, collected unit (FT4, FT4_U)	Listing only (units converted to pmol/L)
Free T4, pmol/L (derived from FT4 above)	n, mean, sd, median, min, max, by visit
Free T4, Out of range and Clinically significantly abnormal (FT4_OR, FT4_CS)	# patients and % /category (1 category FT4_OR; Yes, 2 categories FT4_CS; Yes/No), by visit

[1] Different laboratories might use different units. All values collected in different units than the units to be used for analysis will be converted, see section 3.6.

7.9.4 Urinalysis

Variable (CRF annotation)	**How to be presented**
Urine sample collected for analysis (UAPERF)	# patients and % /category, by visit (2 categories: Yes/No)
Urine sample Date (UADT)	Listing only
Urine sample Time (UATM)	Listing only
Urinalysis result Blood (UABLOOD)	# patients and % /category, by visit (2 categories: Negative/Positive)
Urinalysis result Protein (UAPROT)	# patients and % /category, by visit (2 categories: Negative/Positive)
Urinalysis result Glucose (UAGLUC)	# patients and % /category, by visit (2 categories: Negative/Positive)
Sample sent for urine culture (UCULTYN)	# patients and % /category, by visit (2 categories: Yes/No)

Urine culture result (UCULTRES)	# patients and % /category, by visit (Categories to be based on text entries)
Urine culture clinically significant (UCULTCS)	# patients and % /category, by visit (2 categories: Yes/No)

7.9.5 Serology

Variable (CRF annotation)	**How to be presented**
Serology blood sample collected (BLSYN)	# patients and % /category (2 categories: Yes/No)
Serology blood sample Date (BLSDT)	Listing only
Rheumatoid Factor (RF) Test result (RF, RFND)	# patients and % /category (3 categories: Negative/Positive/Not done)
Anti-CCP Test result (ACCP, ACCPND)	# patients and % /category (3 categories: Negative/Positive/Not done)
HBsAg Test result (HBSAG)	# patients and % /category (3 categories: Negative/Positive/Not done)
HBV antibody Test result (HBVANTI)	# patients and % /category (3 categories: Negative/Positive/Not done)
HCV antibody Test result (HCVANTI)	# patients and % /category (3 categories: Negative/Positive/Not done)

7.9.6 MC1R Genotype Analysis

Variable (CRF annotation)	**How to be presented**
Blood sample Date	Listing only
MC1R genotype result	# patients and % /category (2 categories: MC1R Present/Not present)

7.10 Adverse Events

Variable (CRF annotation)	How to be presented
Any new (or changes to) AE (AEYN)	# patients and % /category (2 categories: Yes/No), by visit
AE description/Term (AETERM)	Listing only (used for MedDRA coding)
AE MedDRA term (coding performed by DM)	# patients and % /MedDRA term (x categories), by visit
AE start date (AESTDAT)	Listing only
AE end date (AEENDAT)	Listing only
AE ongoing (AEONG)	Listing only
Date site aware of AE (AEAWDT)	Listing only
AE severity (AESEV)	# patients and % /category (5 categories: Mild/Moderate/Severe/Life-threatening/Death), by visit
Relationship to study treatment (AEREL)	# patients and % /category (5 categories: Definitely not related/Probably not related/Possibly related/Probably related/Definitely related), by visit
Action taken with study drug (AEACT)	# patients and % /category (5 categories: Dose not changed/Dose interrupted/Drug withdrawn/Not applicable/ Unknown), by visit
AE outcome (AEOUT)	# patients and % /category (6 categories: Fatal, Not recovered/Not Resolved, Recovered/Resolved, Recovered/Resolved with sequelae, Recovering/Resolving Unknown), by visit
Medication given to treat AE (AETREAT)	# patients and % /category (2 categories: Yes/No), by visit

Serious Adverse Event (AESER, AESER1, AESER2, AESER3, AESER4, AESER5, AESER6)	# patients and % /category (2 categories for AESER: Yes/No, plus number of each kind of SAE: Death, Life-threatening, Inpatient hospitalisation or prolongation of existing hospitalisation, Persistent or significant disability/incapacity, Congenital anomaly or birth defect, and/or Important medical event), by visit
SAE report Date (SAEREPDT)	Listing only
Date of birth (BRTHDT)	Listing only
Sex (GENDER)	Listing only
Height, cm (HEIGHT, AE dataset)	Listing only
Weight, kg (SAEWGHT)	Listing only
SAE description (SAEDESC)	Included in SAE table
Phase of study at time of event (SAESP)	# patients and % /category (4 categories: Screening/Treatment/Wash-out/Follow-up), included in SAE table
Study Drug Information (SAESD, SAEFREQ, SAEFADT, SAELADT)	Listing only
SAE abate after stopping study medication (SAEDECH)	Listing only
SAE reappear after reintroduction of study medication (SAERECH)	Listing only
Blinding code broken (SAEBBROK, SAEBBDT)	Listing only
Concomitant medication (SAECM)	Listing only
Relevant medical history (SAEMH)	Listing only
Hospitalisation Details (SAEHOSP, SAEADT, SAEDDT)	Listing only
Death Details (SAEDEDT, SAEPCAUS, SAEAUTO, SAEINF)	Listing only

The incidence of AEs will be summarized by the reported AE term. A subject will be counted only once in the incidence count for a specific AE term, although an AE term might be reported more than once for a particular subject.

Separate summaries will be provided for relationship (yes, no) to study drug. An AE will be considered related to study drug if the investigator reported the event to be “definitely, probably, possibly, or unlikely” related to treatment on the CRF.

8 QUALITY CONTROL PROCEDURES

The statistical programming and analyses will be performed on a fully quality assured database.

The accuracy and validity of the output, tables, listings, and appendices will be ensured by performing a minimum of the following tasks:

8.1 Programming

- ✓ Validated generic code (such as pre-written and validated SAS macros) will be used whenever possible
- ✓ Any programs written for the purpose of data tabulation, data listing, or graphical presentations will be checked by comparing the output with the original database

8.2 Derived Data Sets

- ✓ All data sets derived from the study database will be checked to ensure that they contain the intended data

8.3 Data Listings

- ✓ At least 5% of data in listings will be verified against the database
- ✓ It will be assured that all patients in the study appear in data listings by checking that the number of patients in different groups add up to the correct total
- ✓ All listings will be visually checked for outliers and obvious discrepancies
- ✓ Codes used for data listings will be verified

8.4 Calculated Data

- ✓ Calculated data will be checked for obvious discrepancies
- ✓ At least 20% of the data calculated for efficacy parameters (descriptive statistics, p-values, etc.) will be recalculated

8.5 Tables

- ✓ Population sizes and percentages will be checked
- ✓ All tables will be visually checked for outliers and obvious discrepancies

8.6 Consistency of Summary Tables and Data Listings

- ✓ The consistency of summary tables and data listings will be verified

8.7 Documentation of Quality Control

The performed quality control will be documented and signed by the Biostatistician.

APPENDIX 1:
STATISTICAL ANALYSIS PLAN
AUTHENTICATION AND AUTHORISATION

Statistical Analysis Plan
Authentication and Authorisation

Study title:	A double-blind, multi-center, two-part, randomized, placebo-controlled study of the safety, tolerability, and efficacy of 4 weeks of treatment with AP1189 in early rheumatoid arthritis (RA) patients with active joint disease
Clinical study ID:	SynAct-CS002
SAP issue date:	V1.0 signed 31 March 2021 V2.0 (this version) 19 October 2021

Authentication

This statistical analysis plan presents a more comprehensive and detailed description of the statistical considerations in the referenced study protocol. The undersigned agree that the statistical analysis will be based on and in accordance with this plan.

Study-responsible biostatistician:

Inger Persson, PhD — Date: Nov 23 2021

Sponsor Signed and authorized by:

Thomas Jonassen
SynAct Pharma ApS — Date: Nov 23 -2021

APPENDIX 2: STATISTICAL SECTION(S) OF THE STUDY PROTOCOL

Separate document.

APPENDIX 3: DATA MONITORING COMMITTEE CHARTER

Separate document.

APPENDIX 4: SPECIFICATIONS FOR TABLES, FIGURES, AND LISTINGS

Separate document.

APPENDIX 5: REVISION HISTORY

Version Date		**Version 1.0, 9OCT2020**	**Version 2.0, 07OCT2021**	
Page	**Section**	**WAS**	**IS**	**Reason for change**
5	2.1.3 Primary Efficacy Objective	Effect of AP1189 vs. placebo in subjects with severe active RA (CDAI > 22), undergoing up-titration with MTX, by showing a change in CDAI from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks treatment compared to baseline.	Effect of AP1189 vs. placebo in subjects with severe active RA (CDAI > 22), undergoing up-titration with MTX, by showing a change in CDAI from severe (CDAI > 22) to moderate **or lower** (CDAI ≤ 22) after 4 weeks treatment compared to baseline.	Clarification.
6	2.2 Study Type and Design	Study Flow Chart: Study flow chart is shown in the study protocol, Table 3.	Study Flow Chart: Study flow chart is shown in the study protocol, Table 3**, section 20 Schedule of Visits**.	Clearer reference
7	3.1 Types of Analysis	Descriptive statistics (continuous and categorical variables summarized as above) will be used for an exploratory description of exposure in relation to effect.	Descriptive statistics (continuous and categorical variables summarized as above) will be used for an exploratory description of exposure~~ in relation to effect~~.	
8	3.5 Subgroup Analyses	No subgroup analyses are being planned for.	**A sub-study taking place in Bulgaria and Moldova was added to the clinical study protocol. The sub-study was added to investigate if the effect of AP1189 in newly diagnosed subjects with severe RA who are to start up-titration with methotrexate is comparable in these two countries compared to the main study. In addition to analyzing the main study and the sub-study separately, all data will be pooled to investigate the overall effect in all participating countries.** ~~No subgroup analyses are being planned for.~~	Addition of sub-study in protocol v.9.0.
8	3.6 Data Transformation and Derived Variables	Change from baseline to week 4 (value at week 4 minus value at baseline) will be calculated for the following variables:	Change from baseline to week 4 (value at week 4 minus value at baseline) will be calculated for the following variables: • CDAI	Addition of exploratory analysis

		• CDAI • HAQ-DI total score	• **DAS28** • HAQ-DI total score	
9	3.6 Data Transformation and Derived Variables	Indicators noting the following will be constructed, based on the above defined change in CDAI score from baseline to week 4: • a 5-point decrease • a 10-point decrease • a 15-point decrease	Indicators noting the following will be constructed, based on the above defined change in CDAI score from baseline to week 4: • a 5-point decrease • a 10-point decrease • a 15-point decrease • **a 20-point decrease** • **a 30-point decrease**	Addition of exploratory analyses
9	3.6 Data Transformation and Derived Variables	An indicator noting a change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline will be constructed. An indicator noting a change in DAS28 from > 3.2 to ≤ 3.2 at week 4 compared to baseline will be constructed.	~~An indicator~~ **Indicators** noting a change in CDAI score **will be constructed as follow**s: • from severe (CDAI > 22) to moderate **or lower** (CDAI ≤ 22) at week 4 compared to baseline~~ will be constructed.~~ • **from severe (CDAI > 22) to low or remission (CDAI ≤ 10) at week 4 compared to baseline** • **from severe (CDAI > 22) to remission (CDAI ≤ 2.8) at week 4 compared to baseline** ~~An indicator~~ **Indicators** noting a change in DAS28 **will be constructed as follows:** • from > 3.2 to ≤ 3.2 at week 4 compared to baseline ~~will be constructed.~~ • **from high (DAS28 > 5.1) to moderate or lower (DAS28 ≤ 5.1) at week 4 compared to baseline**	Addition of exploratory analyses
10	3.6 Data Transformation and Derived Variables	Lab values are reported in different units at different sites and will be transformed to the following units:	~~Lab values are reported in different units at different sites and will be transformed to the following units:~~ **The QT interval on the ECGs is corrected from Bazett, Hodges or ECAPS to Fridericia. The laboratory values from the different sites may be reported in different units, which will be corrected to:**	New information from sites.
11	3.6 Data Transformation and Derived Variables		Addition of Variable: **Corrected QT Interval (QTc)**	New information from sites.

11	3.6 Data Transformation and Derived Variables		Addition of Unit to be used in analyses/report: **QTc Fridericia**	New information from sites.
11	3.6 Data Transformation and Derived Variables		Addition of Conversion formula(s): **QTcF = QT/(RR1/3) [1]**	New information from sites.
11	3.6 Data Transformation and Derived Variables		Addition of Comments: **The reported QT and RR intervals will be used to calculate QTcF.**	New information from sites.
11	3.6 Data Transformation and Derived Variables	HbA1c unit	**mmol/mol** ~~mmol/L~~ Addition of Comment: **mmol/L used at sites in Moldova and Bulgaria**	New information from sites.
11	3.6 Data Transformation and Derived Variables	Variables White blood cell, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Hemoglobin, Red blood cells (RBC), Thrombocytes	Addition of Comment: **g/dl used at some sites**	New information from sites.
11	3.6 Data Transformation and Derived Variables	Variables Alanine transaminase (ALT), Aspartate transaminase (AST), γ−glutamyltransferase (GGT), Alkaline phosphate (ALP)	Addition of Comment: **µkat/L used at some sites**	New information from sites.
11	3.6 Data Transformation and Derived Variables	Footnote 1 (several places in the table)	**2** ~~1~~	New information from sites.
11	3.6 Data Transformation and Derived Variables	Variable Free T4	Addition of Comment: **Some site measure Total T4**	
12	3.6 Data Transformation and Derived Variables	Addition of footnote	**[1] https://www.clinigate.com/clinicalc/corrected-qt-interval-qtc.php**	New information from sites.
12	3.6 Data Transformation and Derived Variables	[1] http://unitslab.com/node/55	[2] http://unitslab.com/node/55	Addition of footnote above.

12	3.6 Data Transformation and Derived Variables	Site 21 measures serum biochemistry, while all the other sites measure plasma biochemistry, which means that different reference intervals must be used.	**All the clinical sites are using their local laboratory to measure safety parameters, which means that different reference intervals will apply.** ~~Site 21 measures serum biochemistry, while all the other sites measure plasma biochemistry, which means that different reference intervals must be used.~~	New information from sites.
12	3.6 Data Transformation and Derived Variables	Lab values reported as a non-numerical value (e.g., '<1') will be transformedconverted to an appropriate numerical value for numerical analyses (e.g., calculation of mean values). The team will decide the numerical value to be used before analyses.	Lab values reported as a non-numerical value (e.g., '<1') will be transformedconverted to an appropriate numerical value for numerical analyses (e.g., calculation of mean values). The team will decide the numerical value to be used before analyses. **Lab values below the level of quantification will be set to LoQ/2 for the analyses.**	Clarification on how to handle this special type of lab values.
12	3.6 Data Transformation and Derived Variables	Change from baseline to week 4 (value at week 4 minus value at baseline) will be calculated for the following variables (only Part 2, selected sites): • Percentage of polymorphs in synovial fluid • Percentage of monocytes in synovial fluid • Percentage of lymphocytes in synovial fluid	~~Change from baseline to week 4 (value at week 4 minus value at baseline) will be calculated for the following variables (only Part 2, selected sites):~~ ~~• Percentage of polymorphs in synovial fluid~~ ~~• Percentage of monocytes in synovial fluid~~ ~~• Percentage of lymphocytes in synovial fluid~~	The mentioned sub-study will not be performed.
12	3.7 Interim Analysis	An interim analysis will be performed, evaluating the first (minimum) 24 subjects from Part 1 of the trial in order to assess the safety and efficacy of the investigational product before proceeding to Part 2. All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) and efficacy	An interim analysis ~~will be~~ **has been** performed, evaluating the first (minimum) 24 subjects from Part 1 of the trial in order to assess the safety and efficacy of the investigational product before proceeding to Part 2. **Version 1 of this analysis plan was used for the interim analysis.** All safety parameters (ECG, vital signs, AEs/SAEs, laboratory abnormalities, etc.) and efficacy data for the primary efficacy endpoint ~~will be~~ **were** summarized by treatment and time point for the	The interim analysis has already been performed.

		data for the primary efficacy endpoint will be summarized by treatment and time point for the subjects included in Part 1 of the study, i.e., the following tables (see Appendix 4 for details) will be presented (any MedDRA coding of AEs will not be performed for the interim):	subjects included in Part 1 of the study, i.e., the following tables (see Appendix 4 for details) ~~will be~~ **were** presented (any MedDRA coding of AEs will not be performed for the interim):	
13	3.7 Interim Analysis	Listings showing the following data will also be presented:	Listings showing the following data ~~will~~ **were** also ~~be~~ presented:	The interim analysis has already been performed.
13	3.7 Interim Analysis	An independent external statistician will conduct the interim analysis. The external statistician is included in the Data Monitoring Committee (DMC) established by the sponsor. The DMC will review the unblinded data from the interim analysis and recommend one of the three study designs for Part 2 to the Safety Committee. The criteria for choice of design are described in the Data Monitoring Committee Charter (Appendix 3). All recommendations will be documented and signed by the DMC members, and they will provide a summary of the safety and tolerability data obtained in Part 1 and their design recommendation for Part 2. The independent external statistician will ensure that the interim analysis is a completely confidential process. Sponsor, investigators, and other study	An independent external statistician ~~will~~ **conducted** the interim analysis. The external statistician is included in the Data Monitoring Committee (DMC) established by the sponsor. The DMC ~~will~~ **reviewed** the unblinded data from the interim analysis and recommended one of the three study designs for Part 2 to the ~~Safety~~ **Steering** Committee. The criteria for choice of design are described in the Data Monitoring Committee Charter (Appendix 3). All recommendations ~~will be~~ **are** documented and signed by the DMC members, and they ~~will~~ provide**d** a summary of the safety and tolerability data obtained in Part 1 and their design recommendation for Part 2. The independent external statistician will ensure that the interim analysis is a completely confidential process. Sponsor, investigators, and other study personnel will be kept blind. The Steering Committee's final decision on design choices for Part 2 of the study ~~will be~~ **was** communicated to all investigators and study personnel as soon as the decision ~~is~~ **was** made.	The interim analysis has already been performed. Steering Committee's name also updated.

		personnel will be kept blind. The Steering Committee's final decision on design choices for Part 2 of the study will be communicated to all investigators and study personnel as soon as the decision is made.		
14	3.12 Documentation and Other Considerations	New text added	**Protocol Section *12.2 Primary efficacy Objective* states "Effect of AP1189 vs. placebo in subjects with severe active RA (CDAI > 22), undergoing up-titration with MTX, by showing a change in CDAI from severe (CDAI > 22) to moderate (CDAI ≤ 22) after 4 weeks treatment compared to baseline." The cut-off values for the CDAI score correspond to severe (CDAI>22) or moderate or lower (CDAI ≤ 22), which is the wording used in this analysis plan.**	Clarification.
14	3.12 Documentation and Other Considerations	However, no samples are collected to make a PK evaluation, and this will thus not be done.	However, **only one sample is taken at each visit (for some visits), with variability in the time from last dosing to sampling. Thus, the relationship between exposure and effect is not possible to evaluate, and exposure will therefore be described without relation to effect.** ~~no samples are collected to make a PK evaluation, and this will thus not be done.~~	New information, PK samples are taken once after 1, 2, 3- and 4-weeks of treatment.
18	6.1.1 Description of primary efficacy variables	Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline (derived, see Section 3.6)	Proportion of subjects with a change in CDAI score from severe (CDAI > 22) to moderate **or lower** (CDAI ≤ 22) at week 4 compared to baseline (derived, see Section 3.6)	Clarification.
21	6.1.2 Description of secondary efficacy variables		New variables added to the table: **DAS28 change from baseline to week 4 (derived, see Section 3.6)** — **n, mean (95% CI), sd, median, min, max, by visit**	Additional exploratory analysis

<table>
<tr><td>29</td><td>7.7 Lead ECGs</td><td>QTcF Interval, msecs (EGQTCF).</td><td>QTcF Interval, msecs (EGQTCF). Derived from RR Interval (EGRR) and QT Interval (EGQT) if missing, see Section 3.6.</td><td>New information from sites.</td></tr>
<tr><td>30</td><td>7.9.1 Haematology</td><td>HbA1c, mmol/L (derived from HBA1C above)</td><td>HbA1c, mmol/mol<s>L</s> (derived from HBA1C above)</td><td>Typo.</td></tr>
<tr><td>30-36</td><td>7.9.1, 7.9.2, 7.9.3</td><td>units transformed to

(at several places in the text)</td><td>units <s>transformed</s>converted to</td><td>More accurate language</td></tr>
<tr><td>36</td><td>7.9.3 Thyroid Function</td><td></td><td>New variables added to the table:

<table><tr><td>Total T4, collected unit (TT4, TT4_U)</td><td>Listing only (units converted to nmol/L)</td></tr><tr><td>Total T4, nmol/L (derived from TT4 above)</td><td>n, mean, sd, median, min, max, by visit</td></tr><tr><td>Total T4, Out of range and Clinically significantly abnormal (TT4_OR, TT4_CS)</td><td># patients and % /category (1 category TT4_OR; Yes, 2 categories TT4_CS; Yes/No), by visit</td></tr><tr><td>Total T4, collected unit (TT4, TT4_U)</td><td>Listing only (units converted to nmol/L)</td></tr></table></td><td>New variables added to CRF v.7</td></tr>
<tr><td>38</td><td>7.9.6 MC1R Genotype Analysis</td><td></td><td>New section added, with new table:

<table><tr><td>Variable (CRF annotation)</td><td>How to be presented</td></tr><tr><td>Blood sample Date</td><td>Listing only</td></tr><tr><td>MC1R genotype result</td><td># patients and % /category (2 categories: MC1R Present/Not present)</td></tr></table></td><td>Addition of sample in protocol v.8.0.</td></tr>
<tr><td>38</td><td>7.10 Adverse Events</td><td>7.9.7 Adverse Events</td><td>7.10 Adverse Events</td><td>Wrong heading numbering.</td></tr>
</table>

39	7.11 Safety Assessments Sub-study, only Part 2 (if applicable)	7.1 Safety Assessments Sub-study, only Part 2 (if applicable)	7.**11** Safety Assessments Sub-study, only Part 2 (if applicable)	Wrong heading numbering.
40	1.1 Safety Assessments Sub-study, only Part 2 (if applicable)	1.1 Safety Assessments Sub-study, only Part 2 (if applicable) Variable (CRF annotation) How to be presented Synovial biopsy performed # patients and % /category (2 categories: Yes/No), by visit Change in percentage of polymorphs in synovial fluid at week 4 compared to baseline (derived, see Section 3.6) n, mean, sd, median, min, max Change in percentage of monocytes in synovial fluid at week 4 compared to baseline (derived, see Section 3.6) n, mean, sd, median, min, max Change in percentage of lymphocytes in synovial fluid at week 4 compared to baseline (derived, see Section 3.6) n, mean, sd, median, min, max	~~1.1 Safety Assessments Sub-study, only Part 2 (if applicable)~~ ~~Variable (CRF annotation)~~ ~~How to be presented~~ ~~Synovial biopsy performed # patients and % /category~~ ~~(2 categories: Yes/No), by visit~~ ~~Change in percentage of polymorphs in synovial fluid at week 4 compared to baseline (derived, see Section 3.6)~~ ~~n, mean, sd, median, min, max~~ ~~Change in percentage of monocytes in synovial fluid at week 4 compared to baseline (derived, see Section 3.6)~~ ~~n, mean, sd, median, min, max~~ ~~Change in percentage of lymphocytes in synovial fluid at week 4 compared to baseline (derived, see Section 3.6)~~ ~~n, mean, sd, median, min, max~~	The mentioned sub-study will not be performed.
43 ff	Appendix 2, 3, and 4		Moved to separate documents	The document was growing too large, with an increased risk of crashing.
44-55	Appendix 5		Revision history added.	
Appendix 2	Whole Appendix		Text from latest available protocol used.	Protocol updated since previous version.
Appendix 4 p. 2			**The font Times New Roman will be used for all tables, figures, and listings.**	New specification.

Appendix 4 p. 2			**Tables and figures for efficacy analyses will be repeated with the two AP1189 doses pooled.**	Pooling of doses missed in previous version.
Appendix 4 p. 18	Tables for Primary Efficacy Analysis	Tables for Primary Efficacy Analysis	Tables **and Figures** for Primary Efficacy Analysis	Figures added.
Appendix 4 p. 21-392	Table 11.4.1.1 to Table 11.4.1.59	"Received rescue treatment" denotes subjects who received rescue treatment during the 4-week treatment period (Footnote in several tables)	"Received rescue treatment" denotes subjects who received rescue treatment during the 4-week treatment period **or follow-up**	Rescue treatment can be given also after the study treatment period.
Appendix 4 p. 30	Tables and Figures for Primary Efficacy Analysis		Addition of Figure1, Figure2, and Figure3	Graphical representation of CDAI score in addition to summary table.
Appendix 4 p. 32	Tables and Figures for Primary Efficacy Analysis	Table 11.4.1.5 CDAI score, change from severe (CDAI > 22) to moderate (CDAI ≤ 22) at week 4 compared to baseline	Table 11.4.1.5 CDAI score, change from severe (CDAI > 22) to moderate **or lower** (CDAI ≤ 22) at week 4 compared to baseline	Clarification.
Appendix 4 p. 32	Table 11.4.1.5 Row heading	Change in CDAI score from severe to moderate	Change in CDAI score from severe to moderate **or lower**	Clarification.
Appendix 4 pp. 84-85	Tables and Figures for Primary Efficacy Analysis		Addition of **Figure4**, **Figure5**, and **Figure6**	Graphical representation of DAS28 score in addition to summary table.
Appendix 4 p. 394	New section		**Tables for Exploratory Efficacy Analysis**	Additional analyses to explore CDAI score and DAS28 score changes.
Appendix 4 pp. 394-401	Tables for Exploratory Efficacy Analysis		Addition of tables: **Table 11.4.1.60 CDAI score, change from severe (CDAI > 22) to low or remission (CDAI ≤ 10) at week 4 compared to baseline** **Table 11.4.1.61 CDAI score, change from severe (CDAI > 22) to remission (CDAI ≤ 2.8) at week 4 compared to baseline** **Table 11.4.1.62 Proportion of subjects achieving a 20- or 30-point decrease in CDAI score after 4 weeks of treatment compared to baseline**	Additional exploratory analyses.

			Table 11.4.1.63 DAS28 score, change from baseline to week 4 **Table 11.4.1.64 DAS28 score, change from high (DAS28 > 5.1) to moderate or lower (DAS28 ≤ 5.1) at week 4 compared to baseline** **Table 11.4.1.65 CXCL13, change from baseline to week 4 (pg/mL and percent change from baseline), by decrease in CDAI score** **Table 11.4.1.65 CXCL13, change from baseline to week 4 (pg/mL and percent change from baseline), by decrease in CDAI score** **Table 11.4.1.66 IL-1β, change from baseline to week 4 (pg/mL and percent change from baseline), by decrease in CDAI score** **Table 11.4.1.67 IL-6 change from baseline to week 4 (pg/mL and percent change from baseline), by decrease in CDAI score** **Table 11.4.1.68 IL-10 change from baseline to week 4 (pg/mL and percent change from baseline), by decrease in CDAI score** **Table 11.4.1.69 TNF-α, change from baseline to week 4 (pg/mL and percent change from baseline), by decrease in CDAI score** **Table 11.4.1.70 CDAI score, change from baseline to week 4, subgroup of subjects with the 25% highest CDAI score at baseline** **Table 11.4.1.71 CXCL13, change from baseline to week 4 (pg/mL and percent change from**	

			baseline), subgroup of subjects with the 25% highest CDAI score at baseline **Table 11.4.1.72 IL-1β, change from baseline to week 4 (pg/mL and percent change from baseline), subgroup of subjects with the 25% highest CDAI score at baseline** **Table 11.4.1.73 IL-6, change from baseline to week 4 (pg/mL and percent change from baseline), subgroup of subjects with the 25% highest CDAI score at baseline** **Table 11.4.1.74 IL-10, change from baseline to week 4 (pg/mL and percent change from baseline), subgroup of subjects with the 25% highest CDAI score at baseline** **Table 11.4.1.75 TNF-α, change from baseline to week 4 (pg/mL and percent change from baseline), subgroup of subjects with the 25% highest CDAI score at baseline** **Table 11.4.1.76 CXCL13, change from baseline to week 4 (pg/mL and percent change from baseline), by ACR response** **Table 11.4.1.77 IL-1β, change from baseline to week 4 (pg/mL and percent change from baseline), by ACR response** **Table 11.4.1.78 IL-6 change from baseline to week 4 (pg/mL and percent change from baseline), by ACR response** **Table 11.4.1.79 IL-10 change from baseline to week 4 (pg/mL and percent change from baseline), by ACR response**	

			Table 11.4.1.80 TNF-α, change from baseline to week 4 (pg/mL and percent change from baseline), by ACR response	
Appendix 4 p. 422	Table 12.4.2.5 Biochemistry results	? -glutamyltransferase (GGT), U/L	γ -glutamyltransferase (GGT), U/L	Typo
Appendix 4 p. 501	Tables for Safety Analysis	Table 12.4.2.7 hyroid function	Table 12.4.2.7 **T**hyroid function	Typo.
Appendix 4 p. 502	Table 12.4.2.10 Urine sample results	Column headings: Urin sample Clincally significant abnormal value	Urin**e** sample Clin**ici**ally significant abnormal value	Typos
Appendix 4 p. 512	Tables for Safety Analysis		Addition of table: **Table 12.4.2.15 MC1R Genotype**	Addition of sample in protocol v.8.0.
Appendix 4 p. 576	Tables for Safety Analysis	n = Number of patients in the safety analysis set with non-missing values Std = Standard deviation	**RR interval (beats/min) = heart rate** n = Number of patients in the safety analysis set with non-missing values Std = Standard deviation	Addition of footnote for clarity
Appendix 4 p. 600	Tables for Pharmacokinetic Analysis		Addition of table: **Table 11.4.4.1 Drug Exposure (Plasma Concentrations)**	PK analyses believed not to be performed when SAP v1.0 was written.
Appendix 4 p. 601	Tables for Pharmacokinetic Analysis		Addition of table: **Table 11.4.4.2 Time from last dosing to pharmacokinetic sample (hours)**	Timing of PK samples differ between individuals.
Appendix 4 pp. 602-689	Listing 6.4.1 to Listing 16.2.5.3	PAGESTATUS	Column deleted	Information not relevant as it does not contain collected data.