16.1.9 Documentation of Statistical Methods

Statistical Analysis Plan, Version 2.0, 20Mar2017

NCT02047604

STATISTICAL ANALYSIS PLAN

Study Protocol Number: C2013-0302

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE ASCENDING DOSE STUDY TO EVALUATE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS AND EFFICACY OF ESCALATING DOSES OF SAN-300 IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS WITH INADEQUATE RESPONSE TO DISEASE MODIFYING ANTI-RHEUMATIC DRGUG(S)

Date of Original Protocol: 13 August 2013

Amendment 5: 28 March 2016

Prepared by:

Edetek, Inc.
101 College Road East, 2nd Floor
Princeton, NJ 08540 USA

Reviewed by:

Edetek, Inc.
101 College Road East, 2nd Floor
Princeton, NJ 08540 USA

Final: 10 March 2017

Confidential

Approval

The undersigned have reviewed and approved the statistical analysis plan and find the document to be consistent with the requirements of the Protocol.

REVISION HISTORY

Version Number	Version Date	Description of Significant Changes from Previous Approved Version
1.0	10March2017	Not Applicable – Original Version
2.0	20March2017	• Appendix 2 "List of Table, Figures and Listings" was update for tables to appear in consecutive order. • Tables 14.2.2.7 and 14.2.2.8 "ANCOVA Analysis of The Mean Change from Baseline to the End-of-Treatment Visit for HAQ-DI" for ITT and PP populations were added • Tables 14.2.3.9 and 14.2.3.10 titles were changed to clarify analysis performed in these tables • Listing 16.2.9.4 "Abnormal ECG Measurement" for All Randomized Subjects was added

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	Anti-Citrunillated Peptide Antibodies
ACR	American College of Rheumatology
ACR20	American College of Rheumatology 20 responder rate
ACR50	American College of Rheumatology 50 responder rate
ACR70	American College of Rheumatology 70 responder rate
AE	Adverse event
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
ANCOVA	Analysis of Covariance
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\tau}$	Area under the concentration-time curve from time 0 to the last time point evaluated
CBC	Complete Blood Count with Differential and Platelet Count
C_{max}	Peak serum concentration
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DAS28-CRP	Disease Activity Score with 28-joint count using C-reactive protein
DMARD	Disease-Modifying Anti-Rheumatic Drug
ECG	Electrocardiogram
EOT	End of treatment
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HAQ-DI	Health Assessment Questionnaire - Disease Index
HAV	Hepatitis A virus
HAQ	Health Assessment Questionnaire
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C Virus
Hep B	Hepatitis B virus

Abbreviation	Definition
HIV	Human Immunodeficiency Virus
ITT	Intent-to-treat
IV	Intravenous(ly)
IUD	Intrauterine device
IWRS	Interactive Web Response System
mAb	Monoclonal Antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OMERACT	Outcome Measures in Rheumatology Clinical Trials
OTC	Over-The- Counter
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per protocol
PSAP	Pharmacokinetics statistical analysis plan
QFT	QuantiFERON®-TB Gold test
RA	Rheumatoid Arthritis
RAMRIS	Rheumatoid Arthritis Magnetic Resonance Imaging Score
RF	Rheumatoid Factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SD	Standard deviation
TEAE	Treatment-emergent adverse event
UA	Urinalysis
VAS	Visual Analogue Scale
VLA-1	Very Late Antigen-1
WHODRUG	World Health Organization Drug

1 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the details of the statistical analyses to be performed, and the rules and conventions to be used in the presentation of the results and analyses in the evaluation of safety, preliminary efficacy, and immunogenicity of subcutaneous (SC) administration of SAN-300 in six treatment cohorts (A ,B, C, D, E, and F, with cohort F being optional) of patients with active RA with inadequate response to disease-modifying anti-rheumatic drug(s) (DMARDs). Lists of summary tables, figures and by subject data listings are included at the end of this SAP (see Appendix 2). Analyses of pharmacokinetic data will be described separately in the Pharmacokinetics Statistical Analysis Plan (PSAP).

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study objectives

2.1.1.1 Primary Objective

- To evaluate the safety and tolerability of repeat doses of SAN-300 in patients with active rheumatoid arthritis (RA).

2.1.1.2 Secondary Objectives

- To evaluate the pharmacokinetics and pharmacodynamics of repeat doses of SAN-300 in patients with active RA
- To evaluate the preliminary efficacy of repeat doses of SAN-300 in patients with active RA
- To evaluate the immunogenicity of repeat doses of SAN-300 in patients with active RA.

2.2 Endpoints

2.2.1 Efficacy Endpoints

2.2.1.1 Primary Efficacy Endpoint

- Disease Activity Score with 28-joint count using C-reactive protein (DAS28-CRP) mean change from baseline to the End-of-Treatment Visit

2.2.1.2 Secondary Endpoints

The secondary endpoints for this study are:

- Pharmacodynamic (PD) analysis of SAN-300
- Maximum plasma concentration (C_{max}) of SAN-300 by dose group
- Area under the plasma concentration-time curve over the dosing interval ($AUC_{0-\tau}$) of SAN-300 by dose group
- The immunogenicity of repeat doses of SAN-300
- American College of Rheumatology 20 (ACR20) responder rate at the End-of-Treatment Visit
- DAS28-CRP ≤ 3.2 and < 2.6 responder rates at the End-of-Treatment Visit
- ACR50 and ACR70 responder rates at the End-of-Treatment Visit
- Change in Health Assessment Questionnaire - Disease Index (HAQ-DI) at the End-of-Treatment Visit
- Magnetic Resonance Imaging (MRI) findings of the hand and wrist most clinically affected by RA at the End-of-Treatment Visit

The details of the statistical analyses on pharmacokinetic (PK) data for the definition of related to PK analyses endpoints will be documented in a Population Pharmacokinetic/Pharmacodynamic Statistical Analysis Plan (PSAP).

2.2.2 Safety Endpoints

The safety and tolerability will be assessed by the following endpoints:

- Incidence of treatment-emergent adverse events (TEAEs).
- Changes from baseline in clinical laboratory parameters.

- Changes from baseline in vital sign measurements.
- Changes from baseline in electrocardiogram measurements.
- Symptom driven physical examinations

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, tolerability, PK, pharmacodynamics (PD), preliminary efficacy, and immunogenicity of SC administration of SAN-300 in five cohorts of patients with active RA. Planned dose cohorts for Study C2013-0302 are as follows:

Cohort	Number of Patients to be Dosed		SAN-300 Dose
	SAN-300	Placebo	
A	6	2	0.5 mg/kg SC once weekly
B	6	2	1.0 mg/kg SC once weekly
C	6	2	2.0 mg/kg SC every other week
D	6	2	4.0 mg/kg SC every other week
E	6	2	4.0 mg/kg SC once weekly
F	6	2	2.0 mg/kg SC once weekly

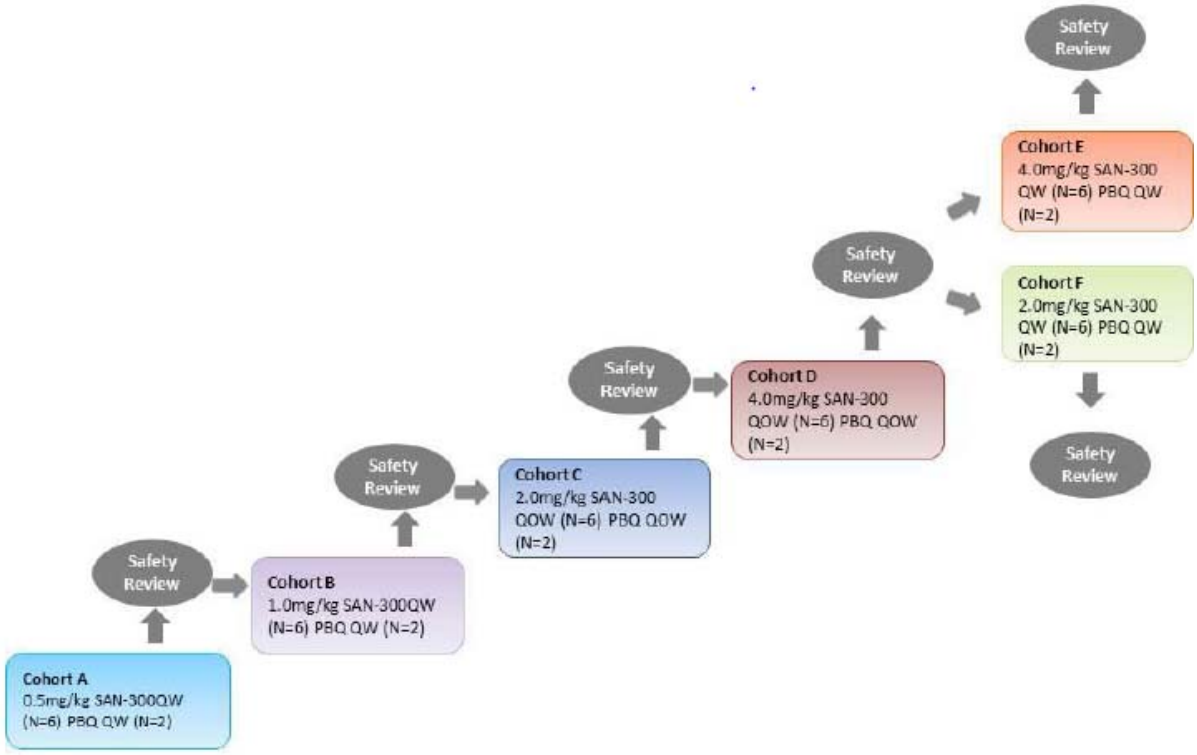
Abbreviations: SC = subcutaneous
The sponsor may elect to modify the dose in the next cohort to a lower dose or terminate any further dose escalation

This is a multiple ascending dose study that was planned to enroll patients sequentially into Cohorts A through F, with cohort F as optional cohort. All patients from each cohort received a total of 6 weeks of exposure to SAN-300 or placebo at their assigned dose and administration frequency. The study was planned to recruit approximately 48 patients with active RA to evaluate repeat doses of SAN-300 compared with placebo.

A study design schematic describing the progression of cohorts in this ascending-dose study is provided in Figure 1.

The study will initially enroll patients in Cohort A, in which patients will receive six once-weekly SC administrations of 0.5 mg/kg SAN-300 or placebo. After Cohort A has completed the 6-week Treatment Period (defined as completion of the Week 7 visit), a Study Safety Committee will conduct a blinded Safety Committee Review (including, but not limited to; adverse events (AEs), safety laboratory assessments, vital sign assessments, and reasons for premature study withdrawal) for all patients. If the Study Safety Committee determines that the safety profile is acceptable, then Cohort B can begin enrollment. Subsequent Safety Committee Reviews will take place following each dosing cohort. If the Study Safety Committee determines that the safety profile continues to be acceptable, then enrollment can begin into the next cohort.

Figure 1. Study Design



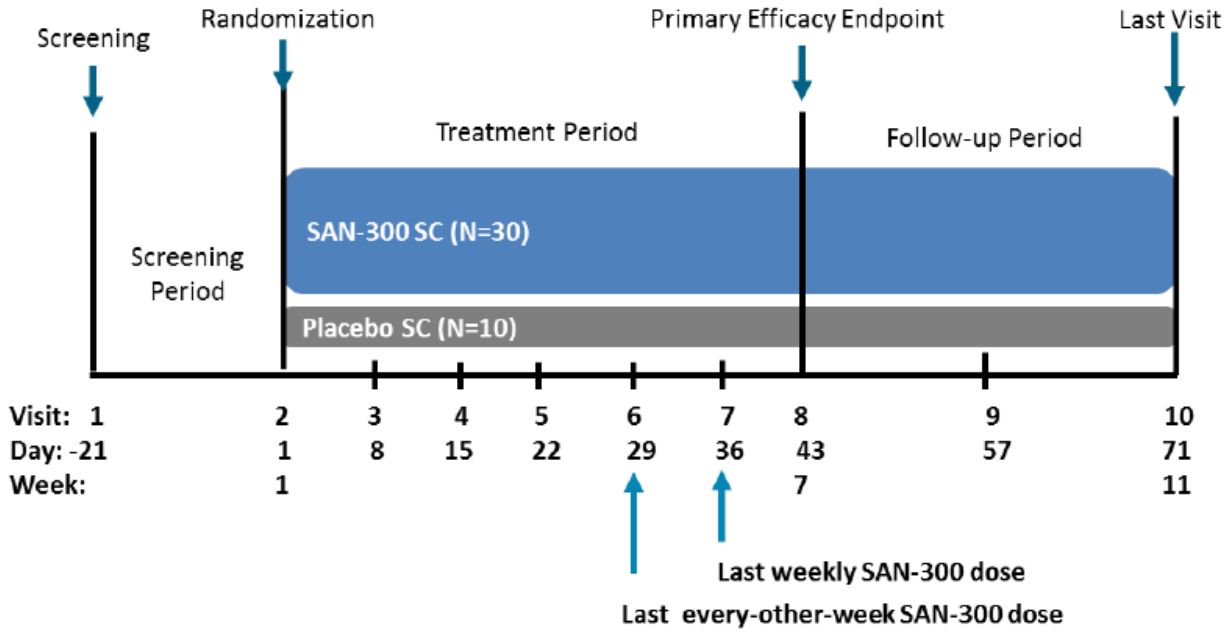
Abbreviation: PBO = placebo; QW = every week; QOW = every other week.

Notes: Patients will be randomized to each cohort in a 3:1 ratio of SAN-300 to placebo. A Safety Committee Review will occur after patients have completed the 6-week Treatment Period of

each cohort. Any subject who withdraws prior to the end of the 6-week Treatment Period will not be replaced and the Study Safety Committee will review the data from all subjects regardless of duration of participation in the study.

Figure 2 provides a study schematic indicating visit structure for each individual cohort. After initial Screening, eligible patients will return to the study site at weekly intervals throughout the Treatment Period for study drug administration and safety, PK, PD, efficacy, and other assessments. Enrolled patients will also return to the study site between study drug administration visits for the assessment of PK/PD endpoints. Primary and secondary efficacy endpoints will be assessed at the End-of-Treatment Visit on Day 43. During the 4-week Follow-up Period, patients will return to the study site at 2 weeks and 4 weeks after the end of the Treatment Period for additional assessments.

Figure 2. Study Design for Individual Cohorts



Abbreviation: SC = subcutaneously.

Screening: Between Days -21 and -1. Informed consent will be obtained before any study specific procedures are performed. Eligibility assessments will be performed.

Treatment Period: Days 1 to 43. Baseline assessments and measurements will be performed before dosing with study drug. Patients will receive SC injections of study drug as follows:

- For all cohorts, patients randomized to receive placebo will be administered a total of six once-weekly injections of placebo on Days 1, 8, 15, 22, 29, and 36.

- In Cohorts A, B, E and F, patients randomized to receive SAN-300 will be administered a total of six weekly injections of SAN-300 on Days 1, 8, 15, 22, 29, and 36.
- In Cohorts C and D, patients randomized to receive SAN-300 will be administered a total of three every-other-week injections of SAN-300 on Days 1, 15, and 29 and will be administered a total of three every-other-week injections of placebo on Days 8, 22, and 36.

Study assessments and measurements will be performed on Days 1, 8, 15, 22, 29, 36, and 43. Patients will also visit the clinic between study drug administration visits for the assessment of PK/PD endpoints. The primary and secondary efficacy endpoints will be assessed at the End-of-Treatment Visit on Day 43.

Study procedures at each visit are described in the Schedule of Assessments, provided as Appendix 1.

Follow-up Period: Days 43 to 71. Study patients will return for follow-up visits on Days 57 and 71 for safety and efficacy assessments. The Exit Visit will occur on Day 71. Patients who withdraw early from the study must return to the clinic to complete the Exit Visit assessments.

3.2 Selection of Subjects

3.2.1 Inclusion Criteria

A subject will be eligible for inclusion in this study if he/she meets all of the following criteria:

1. Written informed consent
2. Diagnosed with RA for ≥ 6 months according to American College of Rheumatology (ACR)/European League Against Rheumatism
3. 18 to 75 years of age, inclusive, at the time of informed consent
4. Swollen joint count of ≥ 6 (66-joint count) and tender joint count of ≥ 6 (68-joint count) at Screening
5. This criterion was removed in Amendment #3

6. Inadequate response to therapy or discontinuation of therapy because of unacceptable toxicity from at least one prior traditional or biologic DMARD.

7. Remain on a stable dose of methotrexate (≥ 15 mg/week and ≤ 25 mg/week) for ≥ 6 weeks before randomization; a lower dosage of methotrexate (≥ 10 mg/week) is allowed if there is documented intolerance to dosages of ≥ 15 mg/week; folic acid ≥ 5 mg/week (or an equivalent dose of folic acid) is required for all patients. If taking hydroxychloroquine in combination with methotrexate, the patient must remain on a dose of ≤ 400 mg/day hydroxychloroquine that has been stable for ≥ 6 weeks before randomization. (Note: If discontinued from hydroxychloroquine, the patient must remain on this revised treatment regimen for at least 4 weeks before randomization.)

All other DMARDs must have been discontinued for at least the following periods of time:

- Oral DMARDs and etanercept at least 4 weeks before randomization
- Rituximab and any other lymphocyte/B-cell-depleting therapy at least 1 year before randomization
- All other biologic DMARDs, including infliximab, adalimumab, golimumab, certolizumab pegol, abatacept, and tocilizumab, at least 8 weeks before randomization
- Patients who have been on leflunomide must have not received leflunomide for at least 4 weeks before randomization and must undergo treatment to facilitate drug elimination with 8gcholestyramine three times daily for 3 days to be eligible for participation.

8. Male or Female

Females of childbearing (reproductive) potential must have a negative serum pregnancy test at screening and agree to use an acceptable method of contraception throughout their participation in the study. Acceptable methods of contraception include double barrier methods (condom with spermicidal jelly or a diaphragm with spermicide), hormonal methods (e.g., oral contraceptives, patches or medroxyprogesterone acetate), or an intrauterine device (IUD) with a documented failure rate of less than 1% per year. Abstinence or partner(s) with a vasectomy may be considered an acceptable method of contraception at the discretion of the investigator. Men of reproductive potential must also agree to use an acceptable method of contraception.

3.2.2 Exclusion Criteria

A subject will **not** be eligible for inclusion in this study if any of the following criteria apply:

Current or Past Medical History

1. Functional Class IV as defined by ACR classification of functional status in RA.
2. History of significant systemic involvement secondary to RA (e.g., vasculitis, pulmonary fibrosis, or Felty's syndrome).
3. History of malignancy or carcinoma in situ within the 5 years before Screening or a history of melanoma. Patients with history of excised or adequately treated non-melanoma skin cancer are eligible.
4. Evidence of clinically significant uncontrolled concurrent diseases such as cardiovascular, endocrine, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, and/or other major diseases.
5. History of recurrent clinically significant infections.
6. Current active infection or serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., pneumonia, septicemia) within 3 months before randomization.
7. Fever (body temperature > 38°C) or symptomatic viral or bacterial infection within 14 days before randomization.
8. History of drug or alcohol abuse (as defined by the Investigator) within the 1 year before Screening.
9. History of severe allergic or anaphylactic reactions to other biologic agents.
10. History of allergies to murine protein.
11. Surgery within 3 months before randomization (other than minor cosmetic surgery or minor dental procedures) or plans for a surgical procedure during the Treatment Period or Follow-up Period.

12. History of malaria; patients with a history of travel to a malaria-endemic region within 4 months before randomization may be considered for enrollment upon consultation with the Sponsor regarding confirmation of no active disease via a polymerase chain reaction (PCR). Patients should not plan to travel to a malaria-endemic region throughout the duration of the study, including Screening and the 4-week Follow-up Period.

13. History of tuberculosis or latent infection currently undergoing treatment.

Treatment History

14. This criterion was removed in Protocol Amendment #3.

15. Treatment with another investigational agent, investigational device, or approved therapy for investigational use within the 4 weeks before randomization or within 5 half-lives of the investigational agent (longer of the two).

16. Treatment regimen with prednisone that is either over 10 mg/day (or equivalent dose of another corticosteroid) or is not taken at a stable dose of ≤ 10 mg/day for at least 4 weeks before randomization.

17. Intra-articular corticosteroid injection(s) within 4 weeks before randomization.

18. Current use of opioids or other narcotics. Note: Patients receiving nonsteroidal anti-inflammatory drugs (NSAIDS) or the following opioids (tramadol, codeine and oral acetaminophen/codeine combination) at stable doses for at least 2 weeks prior to randomization will be eligible for inclusion.

19. Any live immunization/vaccination, including against Herpes zoster, within 4 weeks before randomization. Live vaccinations must also be avoided throughout the study.

Laboratory Values

20. Abnormal laboratory value at Screening or Day -1 considered clinically significant (as determined by the Investigator), or:

    - Serum creatinine > 1.6 mg/dL

- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 × ULN
- Platelet count < 100,000/μL
- Hemoglobin < 8.5 g/dL
- Absolute neutrophil count (ANC) < 2.0×10^3/μL

21. Women of childbearing potential who test positive for a serum pregnancy test at Screening or a urine pregnancy test within 12 hours before randomization.

General/Compliance

22. Positive for hepatitis C virus (HCV) antibody or hepatitis B surface antigen (HBsAg) (Note: patients with positive HCV antibody may be considered for enrollment upon consultation with the Sponsor regarding confirmation of no active disease via a PCR test).

23. Positive for human immunodeficiency virus (HIV) antibody.

24. Positive QuantiFERON®-TB Gold test (QFT) (Note: If the QFT result is indeterminate and the chest X-ray is without clinically significant findings, a second QFT may be performed. If the second QFT result is negative, the patient may be considered for enrollment. If the second QFT is positive or indeterminate, the patient is ineligible.)

25. Current enrollment in any other study with an investigational agent, investigational device, or approved therapy for investigational use).

26. Previous exposure to SAN-300

27. Unwillingness or inability to comply with the requirements of this Protocol, including the presence of any condition (physical, mental, or social) that is likely to affect the patient's returning for follow-up visits on schedule

    NOTE: Patients who cannot tolerate the magnetic resonance imaging (MRI) procedures due to physical or other limitations may be enrolled in the study

28. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the patient unsuitable for enrollment

29. Blood donation (450 mL or more) within 1 month before Screening

30. Nursing mothers or women who are planning to become pregnant during the study

3.3 Treatments

SAN-300 for Subcutaneous Injection

The Investigational Product for SC injection (SAN-300-F02) is manufactured by IntegrityBio, Inc. of Camarillo, CA, USA under Good Manufacturing Practice (GMP). The SAN-300-F02 drug product is formulated with 180 mg/mL anti-VLA-1 mAb, 30 mM histidine, 250 mM sorbitol, and 0.01% polysorbate 20 at pH 6. The drug product is filled to a total volume of 1 mL in a 2-mL USP type I glass vial with a 13-mm chlorobutyl stopper and a 13-mm aluminum seal. The storage temperature for the drug product is 2 ºC to 8 ºC, protected from light.
For SC administration, the appropriate volumetric dose of SAN-300 will be injected with a 27-gauge, ½ inch syringe needle on a weight-based calculation. More than one SC injection may be required (maximum volume of 1.2 mL per injection) depending on the total dose administered and the weight of the individual patient.

Placebo for Subcutaneous Injection

For SC administration, placebo is 30 mM histidine, 250 mM sorbitol, 0.01% polysorbate 20, and 3 µg/mL riboflavin at pH 6, with a 1-mL fill in the same container closure system as the drug product. This was also manufactured by IntegrityBio, Inc. of Camarillo, CA, USA under GMP. The appropriate volumetric dose of placebo will be injected with a 27-gauge, ½ inch syringe needle via SC injection. The volume of placebo administered SC will match the volume according to the weight-based calculations as if SAN-300 were to be administered. More than one SC injection may be required (maximum volume of 1.2 mL per injection) depending on the total dose administered and the weight of the individual patient. The intended storage temperature for the placebo product is 2 ºC to 8 ºC, protected from light.

3.4 Randomization and Unblinding

Fixed allocation will be used to randomize subjects in a ratio of three on SAN-300 to one on placebo 3:1 within each cohort of approximately 8 total subjects using a randomization code generated by an Interactive Web Response System (IWRS). Central randomization will be utilized for this study.

Only in the case of an emergency, when knowledge of the study drug is essential for the clinical management or welfare of the subject, will the investigator be allowed to unblind a subject's treatment assignment. If the investigator breaks the blind for an individual subject, the reason must be in the subject's source documents and the subject will be removed from the study.

3.5 Sample Size

There is no sample size calculation, as this study is not intended to be powered to demonstrate efficacy. Results from this study will be used to design future efficacy studies.

After safety review it was decided that no dose adjustment is needed for optional cohort F, and as a result 41 subjects were randomized into study.

4 GENERAL CONSIDERATIONS FOR DATA ANALYSIS

All statistical testing will be two-sided with an alpha level of 0.05. Any p-values displayed will be rounded to four decimal places, with p-values below 0.0001 displayed as '<.0001', and p-values above 0.9999 displayed as '>.9999'.

Categorical variables will be summarized by frequency counts and percentages for subjects in each category. Percentages will contain one decimal place. In cases of zero frequency counts, the percentage will not be reported.

Continuous variables will be summarized with the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. The mean and median will be presented to one decimal place more than the captured data. The SD will be presented to two decimal places

more than the captured data. The minimum and maximum will be presented to the same precision as the captured data.

Study day will be calculated as follows:

- Assessments/events prior to the first dose date, study day will be the assessment date minus the first dose date.

- Assessments/events on or after the first dose date, study day will be the assessment date minus the first dose date plus one.

Baseline is defined to be the last non-missing assessment (including assessments measured at unscheduled visits) before receiving the first dose of the study medication.

End of treatment (EOT) value is defined as last available post-baseline value during the treatment period.

Subjects will be identified in listings by center number and subject number. Unless otherwise specified, all listings will be sorted by randomized treatment, subject identification number and visit (if applicable).

Efficacy analysis will be performed on the Intent-to-Treat (ITT) population by treatment group to which subjects were randomized. Safety analysis will be performed on the Safety population by treatment received.

Parameters presented by "treatment group" will display the patients on SAN-300 from each cohort and the pooled patients on placebo, unless otherwise indicated.

4.1 Analysis Populations

The ITT population is defined as all randomized patients who received at least one dose of a study drug. Patients in the ITT Population will be analyzed according to the treatment to which they were randomized.

The Per Protocol (PP) Population is defined as all patients in the ITT Population except for those who failed to meet Inclusion Criterion 4; or met Exclusion Criteria 1 and 2.

The Safety Population is defined as all patients who received at least one dose of a study drug; this population will be used for the safety analysis. Patients in the Safety Population will be analyzed according to the treatment they received.

The summaries and analyses of baseline characteristics and efficacy will be performed for the ITT Population. All efficacy analyses will also be performed on the PP Population as a sensitivity analysis. All safety analyses will be performed on the Safety Population.

4.2 Protocol Deviation

All protocol deviations will be listed.

5 SUBJECT DISPOSITION

Subject disposition will be summarized for all randomized subjects and will include the number of subjects randomized; number and percentage of subjects who completed or prematurely discontinued the study, classified by reasons for premature discontinuation; the number of subjects randomized at each study site; and the number and percentage of subjects who completed or discontinued the study at each study site.

The number and percentages of subjects in each population and reason for exclusion from population will be summarized for all randomized subjects.

6 DEMOGRAPHICS AND BASELINE DISEASE CHARACTERISTICS

6.1 Demographics

Demographics listed below will be summarized descriptively by treatment group and overall using the ITT population.

- Age (years);

- Sex (male/female);

- Ethnicity (Hispanic or Latino/not Hispanic or Latino);

- Race (American Indian or Alaskan Native, Asian, Black or African-American, Native Hawaiian or Pacific Islander, and White); where subjects who identified more than one race will be categorized as "Multiple";

- Height (cm);

- Weight (kg); and

- Body mass index (kg/m^2) = (Weight in kg)/ $(\text{Height in m})^2$.

6.2 Baseline Characteristics

Baseline characteristics listed below will be summarized descriptively by treatment group and overall using the ITT population.

- Disease Activity Score with 28-joint count using C-reactive protein (DAS28-CRP), ACR Core Set Measurements, the Health Assessment Questionnaire – Disability Index (HAQ-DI)

- MRI score using the Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI scoring (RAMRIS) system

- Visual Analog Scale (VAS) score

- Duration of RA disease from initial diagnosis

- Use of Methotrexate, Chloroquine, NSAIDS, Corticosteroid

6.3 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 or later and will be listed. In addition, Medical history data will be summarized by system organ class and preferred term. A separate detailed RA history also be summarized descriptively by treatment group.

7 EFFICACY ANALYSIS

Efficacy evaluations will consist of changes from baseline in the Disease Activity Score with 28-joint count using C-reactive protein (DAS28-CRP), ACR Core Set Measurements, the Health Assessment Questionnaire – Disability Index (HAQ-DI), and magnetic resonance imaging (MRI) of the hand and wrist most clinically affected by RA. Each MRI will be scored using the OMERACT RAMRIS system.

7.1 Primary Efficacy Analysis

Efficacy endpoints will be summarized and maybe compared by between the SAN-300 dose groups (0.5, 1.0, and 4.0 mg/kg once-weekly and 2.0 and 4.0 mg/kg every other week) and the pooled placebo group.

The DAS28-CRP and HAQ-DI will be calculated and presented by time point and treatment group.

The HAQ queries the ability to perform 20 activities of daily living with four response categories [without any difficulty (score 0), with some difficulty (score 1), with much difficulty (score 2), not being able to do (score 3)]. The 20 activities are classified into eight categories with two or three activities each. A score is then assigned to each of the eight categories based on the highest score of any activity within the category. Patients are also asked about the use of aids and devices, and if they need help from another person for activities in any of the eight categories. If the category score is lower than 2, it is increased to 2 in any category in which the patient uses a device or help from another person, so that underlying disability is more accurately represented.

The DAS28 assessment is a standardized measure of improvement made using four components, two made by an assessor, one made by the patient, and one laboratory value (CRP), as shown below:

- Swollen and tender joint assessment (assessor – refer to Appendix 6 of Protocol (Amendment 5))
- Patient's global assessment of disease activity (patient)
- CRP (laboratory test)

DAS28-CRP= 0.56 x sqrt(TJC28) x sqrt(SJC28) + 0.36 x ln(CRP+1) +0.014 x VAS +0.96

Where

TJC28: The number of tender joints (0-28).

SJC28: The number of swollen joints (0-28).

CRP: The C-Reactive Protein level (in mg/l

VAS General Health Assessment (from 0=best to 100=worst).

The mean change from baseline to the End-of-Treatment Visit for DAS28-CRP will be compared across treatment groups using the Wilcoxon Rank-Sum Test.

7.2 Secondary Efficacy Analysis

The percentages of patients achieving a DAS28-CRP ≤ 3.2 and < 2.6 will be compared across treatment groups using the chi-square test.

The ACR Core Data Set is a standardized measure of arthritis activity consisting of seven measures, three made by an assessor, three made by the patient, and one laboratory value (CRP or erythrocyte sedimentation rate [ESR]), as shown below:

- Swollen and tender joint assessment (assessor – refer to Appendix 6 of Protocol (Amendment 5))
- Physician's global assessment of disease activity (assessor)
- Patient assessment of pain (patient)
- Patient's global assessment of disease activity (patient)
- Patient's assessment of physical function as measured by Health Assessment Questionnaire (HAQ) (patient – refer to Appendix 7 of Protocol (Amendment 5))
- CRP or ESR (laboratory test)

The assessor will be an experienced rheumatology clinical assessor.

All components of the ACR Core Set will be summarized using descriptive statistics and presented by time point and treatment group. The percentages of subjects achieving ACR20, ACR50, or ACR70 responses will be compared across treatment groups using the chi-square test. MRI data will be summarized across the treatment groups for each time point. All MRI data will be presented for individual patients in data listings.
All efficacy assessments will be presented for individual patients in data listings.
Additional analyses may be performed, as needed, to fully evaluate potential efficacy signals and evidence of clinical benefit.

7.2.1 Pharmacokinetics of SAN-300

Statistical analysis (including exploratory data analysis and population modeling) for pharmacokinetics of SAN-300 will be described in detail in the PSAP document. The PSAP will be finalized prior to database lock.

7.3 Exploratory Efficacy Analysis

An exploratory analysis of the primary endpoint will be performed using analysis of covariance (ANCOVA) model with treatment as factor and baseline DAS28-CRP and HAQ-DI scores as covariates. Normality of the mean change from baseline of DAS28-CRP data will be tested and if necessary transformation such as but not limited to logarithmic transformation could be applied.

The ratios of the least squares (LS) geometric means and 95% confidence intervals (CI) for mean change from baseline of to the EOT Visit for DAS28-CRP from the administration of SAN-300 (“test”) relative to the administration of Placebo (“reference”), test/reference, will be calculated.

Comparison analysis for ACR20, ACR50, or ACR70 responses for pooled treatment group against placebo will be conducted using Fisher exact test. Bar chart will be plotted by SAN-300 treatment regimen to show if there is linear relationship between ACR20, ACR50, and ACR70 and SAN-300 dose level and frequency.
In addition, logistic regression model with treatment regimen as ordinal variable will be performed on to compare percentage of subjects achieved ACR20, ACR50, and ACR70 responses at the EOT Visit. Predictor variables may include swollen joint count at screening, tender joint count at screening, and methotrexate use (yes/no).

Statistical analyses will be performed and statistical tables will be generated using Statistical Analysis Software (SAS) version 9.3 or higher. Statistical significance will be assessed at the two-sided 5% level.

8 SAFETY PRESENTATION

8.1 Extent of Exposure

The number of subjects administered study drug and the extent (duration) of exposure to study drug will be summarized descriptively by treatment group (n, mean, median, SD, minimum, and maximum values). Extent of exposure is defined as last dose of study drug – first dose of study drug +1. Additionally, number and percent by duration category by week for the first 4 weeks and then by 2-week intervals thereafter will also be summarized by treatment group.

8.2 Adverse Events

Adverse events will be coded using the MedDRA version 19.0 or later coding dictionary. If an adverse event is not coded then the verbatim investigator text will be listed at the end of each applicable summary table.

8.2.1 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE started post-treatment. Summary tables will include number of subjects with treatment-emergent AEs and as percentage of number of subjects in the treatment group. The number of serious TEAEs will be summarized in the appropriate summary table. Summary tables will also be presented for the frequency of AEs by MedDRA-preferred term and severity of AE. Severity of AEs will be based on the scale as indicated in Section 8.2.2.

The subset of AEs that are considered by the Investigator to have a possible or definite relationship to study medication will be considered as treatment-related AEs. If the Investigator does not specify the relationship of the AE to study medication, the AE will be considered as treatment-related. The incidence of AEs and TEAEs will be tabulated per treatment. AEs will also be summarized by severity, using the categories described in Section 8.2.2.

8.2.2 Treatment-Emergent Adverse Events by Intensity

Adverse events are categorized for severity by the investigator as "Mild", "Moderate" or "Severe". The frequency of TEAEs by intensity will be summarized by body system, and preferred term, overall and by treatment group. TEAEs with missing intensity will be considered 'Severe' in the tabular summaries but data listings will show severity listed as missing. In case of multiple TEAEs for the same body system and preferred term for the same subject, only the TEAE with the maximum intensity will be counted in the table.

8.2.3 Treatment-Emergent Adverse Events Related to Study Drug

Related AEs are the AEs with "Related" or "Possibly Related" for causality. TEAEs with missing relationship to study drug will be considered "related" in the tabular summaries but data listings will show relationship as missing.

8.2.4 Treatment-Emergent Serious Adverse Events

Any AE reported as serious in the Case Report Form (CRF) will be reported as a serious adverse event (SAE). The clinical database will be reconciled with the SAE database (from the Salix Safety department) before database lock.

All treatment-emergent SAEs will be summarized by body system and preferred term, overall and by treatment group.

8.2.5 Treatment-Emergent AEs that Led to Premature Discontinuation of Study

All TEAEs that led to subject discontinuation from the study will be summarized and listed separately.

8.2.6 Treatment-Emergent SAEs that Led to Premature Discontinuation of Study

All treatment-emergent SAEs that led to subject discontinuation from the study will be summarized and listed separately.

8.2.7 Deaths

Deaths will be listed.

8.3 Clinical Laboratory Evaluations

Hematology, blood chemistry, and urinalysis parameters will be summarized at baseline and at each time point. Additionally, the change from baseline in each parameter will be summarized. Laboratory values and changes from baseline in laboratory values will be summarized descriptively by treatment group.

A summary of shifts from baseline will be given for each treatment group for each parameter. The normal range for each parameter will be used to create categories of low, normal, or high. Any result higher than upper limit of normal or lower than lower limit of normal will be categorized as high or low respectively, and any result within the lower and upper limits of normal will be categorized as normal. The number and percentage of subjects in each treatment group in each shift category from baseline to final evaluation will be shown for each parameter.

Hepatitis Panel data (Hep B surface antibody, Hep B Surface antigen, Hep B core antibody total, HCV antibody and hepatitis A virus (HAV) total) collected will be listed.

8.4 Other Laboratory Evaluations

Other laboratory parameters include anti-SAN-300 antibody levels, rheumatoid factor (RF), antinuclear antibody (ANA), and anti-citrunillated peptide antibodies (ACPA). All other laboratory parameters will be summarized using descriptive statistics and presented by time point and treatment group. All other laboratory parameters will be presented for individual patients in data listings.

8.5 Prior and Concomitant Medications

All prior medications and concomitant medications captured in the Electronic Data Capture system will be coded to preferred term using World Health Organization Drug (WHODRUG) dictionary (September 2015). Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) Class term and preferred term for the Safety population.

Medication start and end dates will be used to determine whether a medication is prior, concomitant or newly initiated. When start and end dates are incomplete or missing and the medication category cannot be determined, the standard Salix estimation rule for concomitant medications will be followed.

8.5.1 Prior Medications

Prior medications are defined as any medication ended prior to the first study drug administration. All prior medications captured in CRF will be summarized and listed.

8.5.2 Concomitant and Newly Initiated Medications

Concomitant medications (medications taken at any time after first dose date including those taken prior to and continued after first dose date) and newly initiated medications (medications taken after initiation of the study drug administration) will be listed by subject and tabulated overall and by treatment group. In this summary, the number and percentage of subjects who take at least one concomitant medication and the number and percent of subjects who take each specific concomitant medication will be presented by ATC class, preferred term, and treatment group.

8.6 Vital Sign Measurements

Vital sign measurements and change from baseline including body temperature, heart rate, sitting blood pressures, and weight will be summarized at each scheduled visit descriptively by treatment group.

8.7 Physical Exam

Physical examination data will be listed.

8.8 Electrocardiogram (ECG)

Actual value and change from baseline of ECG parameters will be summarized by treatment group using descriptive statistics. In order to assess the QT interval data, corrected QT values as

suggested in the FDA QTc Guidance Document will be calculated based on the following three methods.

1) Fridericia's correction: $QTc=QT/RR^{0.33}$,

2) Bazett's Correction: $QTc=QT/RR^{0.5}$,

And

3) Correction based on linear regression techniques: Based on the data from baseline study population, the intercept(a) and slope (b) will be estimated separately for males and females using the equation QT=a+b(1-RR). Those estimates will be used to calculate the corrected QT values at post baseline time points.

A summary table will be presented of the number and percentage of subjects with worst QTc, QRS, PR, and ventricular rate abnormalities observed during the treatment period. Specific criteria to be used include the following:

ECG Parameter	**Definition**
QT_cB interval	Absolute QT_cB interval prolongation values:
	> 450 to ≤ 480 msec
	> 480 to ≤ 500 msec
	> 500 msec;
	Increase from baseline values:
	> 30 to ≤ 60 msec
	> 60 msec;
QT_cF interval	Absolute QT_cF interval prolongation values:
	> 450 to ≤ 480 msec
	> 480 to ≤ 500 msec
	> 500 msec;

ECG Parameter	Definition
	Increase from baseline values: > 30 to ≤ 60 msec > 60 msec;
QRS duration	Absolute values are abnormally low ≤ 50 msec, normal > 50 to < 120 msec, and abnormally high ≥ 120 msec;
PR interval	Absolute values are normal < 210 msec and abnormally high ≥ 210 msec;
Ventricular rate	Absolute values are abnormally low ≤ 50 bpm, normal > 50 to < 120 bpm, and abnormally high ≥ 120 bpm.

9 STATISTICAL AND ANALYTICAL ISSUES

9.1 Handling of dropouts or missing data

Subjects who prematurely discontinue before the end of the treatment will be contacted via follow-up phone call as frequently as needed. If the patient is found to have an AE or clinically significant laboratory abnormality, the patient will be followed until the event/abnormality is resolved, or until the Investigator determines that further follow-up is no longer medically indicated.

For subjects who discontinue prematurely, the last completed post-baseline assessment will be used as EOT.

Missing data will not be imputed in other analyses unless specified otherwise.

For subjects who terminate early from the study, if the study day of the EOT visit falls into a specific protocol defined scheduled visit window, the EOT visit will be reassigned to that specific scheduled visit for the analyses by protocol defined scheduled visit.

For cases where the start date of an AE is not complete, the assumption is made that the AE is a treatment-emergent event unless there is evidence to the contrary.

For cases where the start or the stop date of medication is not complete, the assumption is made that the medication is a concomitant medication unless there is evidence to the contrary.

10 INTERIM ANALYSES AND DATA MONITORING

There will be no formal interim analysis during the course of the study.

11 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. T. Uhlig, E. A. Haavardsholm, T. K. Kvien Comparison of the Health Assessment Questionnaire (HAQ) and the modified HAQ (MHAQ) in patients with rheumatoid arthritis, Rheumatology (Oxford) (2006) 45 (4): 454-458, 15 November 2005

APPENDIX 1 OVERALL TIME AND EVENTS SCHEDULE

STUDY ASSESSMENTS	Screening (21 days)	Treatment Period										Follow-up Period (28 days)	
Week:		**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 5**		**Week 6**		**Week 7**	**Week 9**	**Week 11**
Visit:	**Visit 1**	**Visit 2**		**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**		**Visit 7**		**Visit 8**	**Visit 9**	**Visit 10**
Day	**-21 to -7**	**Day 1[a]**		**Day 8[a]**	**Day 15[a]**	**Day 22[a]**	**Day 29[a]**		**Day 36[a]**		**Day 43[a]**	**Day 57[a]**	**Day 71[a]**
Timing (where applicable):		**Pre-dose**	**Post-dose**				**Pre-dose**	**Post-dose**	**Pre-dose**	**Post-dose**	**EOT**		**Exit Visit**
Eligibility Assessments													
Informed Consent	X												
Inclusions/Exclusions	X	X											
Demographics	X												
Medical History	X	X											
Medication History	X	X											
RA History and Prior RA Treatment	X	X											
HCV Antibody, HBsAg, HIV Antibody	X												
Chest X-ray[b]	X												
QuantiFERON-GOLD	X												
Dosing													
Randomization		X											
Administration of SAN-300 or Placebo[c]		X[d]		X[c]	X	X[c]	X		X[c]				
Safety Assessments													
Vital Sign Measurements	X	X	X[g]	X[g]	X[g]	X[g]	X	X[g]	X	X[g]	X	X	X
Physical Examination	X	X									X		X
CBC, Chemistry Panel	X	X		X	X	X	X		X		X	X	X
UA	X	X									X		X

STUDY ASSESSMENTS	Screening (21 days)	Treatment Period										Follow-up Period (28 days)	
Week:		**Week 1**		**Week 2**	**Week 3**	**Week 4**	**Week 5**		**Week 6**		**Week 7**	**Week 9**	**Week 11**
Visit:	**Visit 1**	**Visit 2**		**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**		**Visit 7**		**Visit 8**	**Visit 9**	**Visit 10**
Day	**-21 to -7**	**Day 1[a]**		**Day 8[a]**	**Day 15[a]**	**Day 22[a]**	**Day 29[a]**		**Day 36[a]**		**Day 43[a]**	**Day 57[a]**	**Day 71[a]**
Timing (where applicable):		**Pre-dose**	**Post-dose**				**Pre-dose**	**Post-dose**	**Pre-dose**	**Post-dose**	**EOT**		**Exit Visit**
INR, PT, aPTT, Complement		X											
Serum Immunoglobulins		X									X		X
Pregnancy Test	Serum	Urine				Urine			Urine		Serum		
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessments													
ACR Core Set Assessments, DAS28-CRP	X	X		X	X	X	X		X		X	X	X
HAQ-DI	X	X		X	X	X	X		X		X	X	X
ESR	X	X		X	X	X	X		X		X	X	X
CRP	X	X		X	X	X	X		X		X	X	X
MRI of Hand and Wrist[f]		X									X		
Other Assessments													
RF, ACPA	X										X		
ANA		X									X		

Abbreviations: ACPA = anti-citrunillated peptide antibodies; ACR = American College of Rheumatology; ANA = antinuclear antibody; aPTT = activated partial thromboplastin time; CBC = complete blood count with differential and platelet count; CCP = cyclic citrullinated peptide; DAS28-CRP = Disease Activity Score with 28-joint count C-reactive protein; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; HAQ-DI = Health Assessment Questionnaire – Disease Index; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; CRP = C reactive protein; INR = international normalized ratio; MRI = magnetic resonance imaging; PT = prothrombin time; QFT = QuantiFERON®-TB Gold test; RA = rheumatoid arthritis; RF = rheumatoid factor; UA = urinalysis.

[a] Weekly visits during the Treatment and Follow-up Periods can be scheduled for ±2 days around each of the designated Days in this schedule, but the designated Days themselves will not be shifted relative to Day 1.

b If a chest X-ray was performed with no clinically significant findings within 1 month of randomization, another chest X-ray is not required at Screening.

[c] For all cohorts, patients randomized to receive placebo will be administered a total of 6 once-weekly SC injections of placebo on Days 1, 8, 15, 22, 29, and 36. In Cohorts A, B, and D, patients randomized to receive SAN-300 will be administered a total of 6 once-weekly SC injections of SAN-300 on Days 1, 8, 15, 22, 29, and 36. In Cohorts C and E, patients randomized to receive SAN-300 will be administered a total of three every-other-week SC injections of SAN-300 on Days 1, 15, and 29 and will be administered a total of three every-other-week SC injections of placebo on Days 8, 22, and 36. Note: Subject to be observed at minimum 1 hour post- dose. Longer observation allowed if deemed necessary by investigator or designee.

[d] Day 1 dosing will occur on the day of or within 24 hours after randomization.

[e] After baseline assessment, additional assessments of tryptase and histamine to occur only in suspected cases of anaphylaxis or hypersensitivity reactions.

[f] In patients who are able to tolerate the MRI, it should be performed within 5 days prior to or at Visit 2 (Day 1, prior to dosing). MRI of hand and wrist most clinically affected by RA will be imaged at Baseline, the same wrist will be imaged at End of Treatment.

[g] Blood pressure and pulse will be collected at the end of the observation period; prior to the subject leaving the clinic. When a post-dose blood sample is collected, the blood pressure and pulse should be assessed prior to the sample collection

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