NCT02047604

# Clinical Trial Protocol: C2013-0302

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|---|---|
| Study Title: | A Randomized, Double-blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the 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 Drug(s) |
| | C2013-0302 |
| **Study Number:** | 2a |
| **Study Phase:** | SAN-300 |
| **Product Name:** | **118,321** |
| **IND Number:** | Rheumatoid Arthritis |
| **Indication:** | Multicenter |
| **Investigators:** | Santarus, Inc. |
| **Sponsor:** | Santarus, Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International |
| **Sponsor's Medical Monitor:** | 400 Somerset Corporate Boulevard<br>Bridgewater, NJ 08807 |
| **Study Contact:** | Salix Pharmaceuticals, Inc.<br>8510 Colonnade Center Drive<br>Raleigh, NC 27615 |

| | Date |
|---|---|
| **Original Protocol:** | 13 August 2013 |
| **Amendment 1:** | 04 February 2014 |
| **Amendment 2:** | 24 February 2014 |
| **Amendment 3:** | 05 June 2014 |
| **Amendment 4:** | 15 September 2014 |
| **Amendment 5:** | 28 March 2016 |

## Confidentiality Statement

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3/29/16
Date

Vice President, Clinical and Medical Affairs

Valeant Pharmaceuticals, Inc. on behalf of its Affiliate Santarus, Inc.

[redacted]

3/29/16
Date

Senior Director, Clinical Operations
Valeant Pharmaceuticals, Inc. on behalf of its Affiliate Santarus, Inc.

# SYNOPSIS

**Sponsor:**
Santarus, Inc.

**Name of Finished Product:**
SAN-300

**Name of Active Ingredient:**
SAN-300

**Study Title:**
A Randomized, Double-blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the 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 Drug(s)

**Study Number:**
C2013-0302

**Study Phase:** 2a

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

**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

**Study Design:**
This is a multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose study to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), preliminary efficacy, and immunogenicity of subcutaneous (SC) administration of SAN-300 in five cohorts of patients with active RA with inadequate response to disease-modifying anti-rheumatic drug(s) (DMARDs). Planned dose cohorts for Study C2013-0302 are as follows:

| | Number of Patients to be Dosed | | |
|---|---|---|---|
| **Cohort** | **SAN-300** | **Placebo** | **SAN-300 Dose** |
| 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

This is a multiple ascending dose study that will enroll patients sequentially into Cohorts A through F. All patients from each cohort will receive a total of 6 weeks of exposure to SAN-300 or placebo at their assigned dose and administration frequency. For the purposes of this protocol, the term “study drug” will include both SAN-300 and placebo.

Safety and tolerability findings will be reviewed in a blinded manner, after each Cohort is fully enrolled and subjects have completed the 6-week Treatment Period (defined as completion of the Week 7 visit) to assess the study drug safety profile and determine whether enrollment will begin in the next 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. The safety review will include, at minimum, the following information: adverse events (AEs); safety laboratory results; vital sign measurements; and reasons for premature study withdrawal.

The decision to begin enrollment in the next cohorts will be based upon the results of the safety review. In addition, based on the findings from the safety review, the Sponsor may elect to modify the dose in the next cohort to a lower dose or terminate any further dose escalation.

Individual patient dosing will be stopped if the patient experiences any of the following: a confirmed reduction in absolute neutrophil count (ANC) to < 1.0 x $10^3$/µL; a clinically significant atypical or opportunistic infection (including those listed in Appendix 1); or a clinically significant adverse event related to study participation, in the opinion of the investigator. Study enrollment will be temporarily halted if any of the following occur: two or more patients in the study experience a confirmed reduction in ANC to < 1.0 x $10^3$/µL, any one patient experiences a clinically significant atypical or opportunistic infection (including those listed in Appendix 1), or any other significant safety risk occurs, as noted by the Sponsor. Resumption of study enrollment will be contingent upon further safety review.

All patients will attend a minimum of 10 study visits: one Screening Visit, seven visits during the Treatment Period, and two follow-up visits. Additionally, all enrolled patients will be required to visit the clinic between certain study drug administrations for blood draws for the assessment of PK/PD endpoints. Patients are expected to remain on their existing, background RA regimen for at least the duration of the Follow-up Period. For a more detailed list of individual assessments, refer to the Schedule of Assessments in Appendix 2 and the Specialty PK and PD Laboratory Testing Schedule in Appendix 3.

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 made 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 once-weekly injections of study drug 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.

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.

**Study Population:**

It is planned that approximately 40 patients (approximately 8 per cohort) with active RA will be enrolled into this study.

**Inclusion Criteria:**

1. Written informed consent
2. Diagnosed with RA for ≥ 6 months according to American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Classification Criteria 2010 (Appendix 4)
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 and randomization
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 disease-modifying anti-rheumatic drug (DMARD).
7. 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 folinic 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 B-cell/lymphocyte-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 8 g cholestyramine 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.

   Note: Females who have been surgically sterilized (e.g., hysterectomy or bilateral tubal ligation) or who are postmenopausal (total cessation of menses for > 1 year) will not be considered “females of childbearing potential”.

**Exclusion Criteria**

Medical History

1. Functional Class IV as defined by ACR classification of functional status in RA (Appendix 5)
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 any 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, endocrinologic, 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 Amendment #3
15. Treatment with another investigational agent, investigational device, or approved therapy for investigational use within the 4 weeks before randomization or within five 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 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) < $2.0 \times 10^3$/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.
22. Positive for hepatitis C virus (HCV) antibody or hepatitis B surface antigen (HBsAg) (Note: patients with positive HCV antibody who have previously received a curative treatment regimen 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 (450mL or more) within 1 month before Screening
30. Nursing mothers or women who are planning to become pregnant during the study

**Test Product, Dose, and Mode of Administration:**
SAN-300 is a humanized anti-very late antigen-1 (VLA-1) monoclonal antibody (mAb). A total of six cohorts (Cohorts A, B, C, D, E and F) will be administered the appropriate weight-based volume dose of SAN-300 or matching volume of placebo in SC injections.

**Duration of Treatment:**
The total duration of study participation will be up to approximately 13 weeks. Patients will be screened for participation within 3 weeks of dosing (Days -21 to -1). The Treatment Period will consist of injections of SAN-300 or placebo over a period of 6 weeks, concluding with the End-of-Treatment Visit (Days 1 to 43). The Follow-up Period will consist of an additional 4 weeks (Days 43 to 71).

**Safety Assessments:**
Safety assessments will consist of the following: physical examinations, vital sign measurements, 12-lead electrocardiograms (ECGs), laboratory parameters, AEs, and concomitant therapy use.

**Pharmacokinetic Assessments:**
Pharmacokinetic parameters for SAN-300 will be estimated using a population based approach with nonlinear mixed-effect modeling, in accordance with the FDA Draft Guidance on Population Pharmacokinetics (1999). In addition, exploratory assessments of linearity across doses/regimens, accumulation after repeated dosing and pharmacokinetic/pharmacodynamic relationships will be performed.

**Pharmacodynamic Assessments:**
PD parameters will consist of VLA-1 receptor occupancy (VLA-1 saturation assay); an immunophenotyping panel (CD3, CD4, CD8, CD14, CD19, CD45, CD45RO, and CD49α); CRP; and cytokines (interferon-gamma [IFNγ], tumor necrosis factor-alpha [TNFα], interleukin-6 [IL-6]).

**Efficacy Assessments:**
Efficacy evaluations will consist of changes from baseline in the Disease Activity Score with 28-joint count using CRP (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 Outcome Measures in Rheumatology Clinical Trials (OMERACT) RA MRI scoring (RAMRIS) system.

Primary Efficacy Endpoint:

DAS28-CRP mean change from baseline to the End-of-Treatment Visit

Secondary Efficacy Endpoints:

- 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 HAQ-DI at the End-of-Treatment Visit
- MRI findings of the hand and wrist most clinically affected by RA at the End-of-Treatment Visit

**Other Laboratory Assessments:**
Other laboratory parameters include anti-SAN-300 antibody levels, rheumatoid factor (RF), antinuclear antibody (ANA), and anti-citrunillated peptide antibodies (ACPA).

**Statistical Methods:**
All endpoints in this study will be summarized by descriptive statistics. Descriptive statistics for continuous variables will include the mean, standard deviation, median, first and third quartiles, minimum, and maximum; categorical variables will be presented as counts and percentages. All statistical tests will be conducted at the two-sided $\alpha = 0.05$ level of significance. All tests of binomial proportions will be conducted using the chi-square test unless more than one cell in a 2 x 2 table has an expected value of < 5, in which case the Fisher's Exact Test will be used. All tests of continuous variables will be conducted using the Wilcoxon Rank-Sum Test. For all efficacy endpoints, patients will be analyzed according to the treatment to which they were randomized. For all safety endpoints, patients will be analyzed according to the treatment they received. Parameters presented by "treatment group" will compare the 6 patients on SAN-300 from each cohort with the 10 pooled patients on placebo.

Safety:

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentages of patients reporting at least one occurrence of each AE will be tabulated by system organ class and preferred term. The number and percentages of patients reporting at least one occurrence of each AE by system organ class and preferred term will also be tabulated by severity and by the relationship to study drug. For multiple occurrences of the same AE in a patient that differ in severity, the AE with the highest level of severity will be tabulated. For multiple occurrences of the same AE in a patient that differ in relationship to study drug (e.g., related and not related), the AE will be tabulated as related. All AEs for all patients will be presented in a data listing.

All other safety parameters will be summarized using descriptive statistics and presented by time point and treatment group (6 active patients from each cohort and 10 pooled patients on placebo). All other safety parameters will be presented for individual patients in data listings.

Pharmacokinetics:

Population pharmacokinetic parameter estimates for SAN-300 will be presented by treatment groups in a tabular format as described in the Population Pharmacokinetic/Pharmacodynamic Analysis Plan, which will be finalized prior to data analysis.

Pharmacodynamics

PD parameters will be summarized using descriptive statistics and presented by time point and treatment group in tabular format. PD parameters for individual patients will be presented in data listings. Time-dependent PD parameters will be presented in figure format. PK/PD modeling will be conducted as described in the Population Pharmacokinetic/Pharmacodynamic Analysis Plan.

Efficacy:

Efficacy will be compared for the SAN-300 dose groups (0.5, 1.0, 2.0 and 4.0mg/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 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. The percentages of patients achieving a DAS28-CRP ≤ 3.2 and < 2.6 will be compared across treatment groups using the chi-square test.

All components of the ACR Core Set will be summarized using descriptive statistics and presented by time point and treatment group. The percentages of patients 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.

Other Laboratory Values:

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. Laboratory parameters will be presented in figure format.

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# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ACPA | anti-citrunillated peptide antibodies |
| ACR | American College of Rheumatology |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANA | antinuclear antibody |
| ANC | absolute neutrophil count |
| aPTT | activated partial thromboplastin time |
| AST | aspartate aminotransferase |
| AUC | area under the concentration-time curve |
| $AUC_{(0-t)}$ | area under the concentration-time curve from time 0 to the last time point evaluated |
| $AUC_{(0-inf)}$ | area under the concentration-time curve from time 0 and extrapolated to infinity |
| CBC | complete blood count with differential and platelet count |
| CL/F | apparent clearance |
| $C_{max}$ | peak serum concentration |
| CFR | Code of Federal Regulations |
| CRA | clinical research associate |
| CRF | case report form |
| CRO | contract research organization |
| Ct | last measurable serum concentration |
| CV | curriculum vitae |
| DAS28-CRP | Disease Activity Score with 28-joint count using C-reactive protein |
| DMARD | disease-modifying anti-rheumatic drug |
| ECG | electrocardiogram |
| eCRF | electronic case report form |
| ESR | erythrocyte sedimentation rate |
| EULAR | European League Against Rheumatism |
| FAAN | Food Allergy and Anaphylaxis Network |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMP | Good Manufacturing Practice |
| HAQ-DI | Health Assessment Questionnaire - Disease Index |
| HBsAg | hepatitis B surface antigen |
| hCG | human chorionic gonadotropin |
| HCV | hepatitis C virus |

| Abbreviation | Definition |
|---|---|
| HIV | human immunodeficiency virus |
| HREC | Human Research Ethics Committee |
| CRP | C-reactive protein |
| IB | Investigator's Brochure |
| ICF | informed consent form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IL-6 | interleukin-6 |
| IND | Investigational New Drug |
| IFNγ | interferon-gamma |
| IM | intramuscular(ly) |
| INR | international normalized ratio |
| IRB | Institutional Review Board |
| ITT | Intent-to-Treat |
| IV | intravenous(ly) |
| IVRS/IWRS | Interactive Voice/Web Response System |
| JC virus | John Cunningham virus |
| $k_{el}$ | terminal elimination rate constant |
| mAb | monoclonal antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MCP | metacarpophalangeal |
| MRI | magnetic resonance imaging |
| NIAID | National Institute of Allergy and Infectious Disease |
| NOAEL | no observed adverse effect level |
| NSAID | nonsteroidal anti-inflammatory drugs |
| OMERACT | Outcome Measures in Rheumatology Clinical Trials |
| OTC | over-the-counter |
| PCR | polymerase chain reaction |
| PD | pharmacodynamic(s) |
| PGA | Physician's global assessment |
| PK | pharmacokinetic(s) |
| PML | progressive multifocal leukoencephalopathy |
| PP | Per Protocol |
| PT | prothrombin time |
| QFT | QuantiFERON®-TB Gold test |

| **Abbreviation** | **Definition** |
|---|---|
| RA | rheumatoid arthritis |
| RAMRIS | Rheumatoid Arthritis Magnetic Resonance Imaging Score |
| RF | rheumatoid factor |
| SAE | serious adverse event |
| SC | subcutaneous(ly) |
| $T_{½}$ | elimination half-life |
| TB | tuberculosis |
| TEAE | treatment-emergent adverse event |
| $T_{max}$ | time to peak serum concentration |
| TNFα | tumor necrosis factor-alpha |
| UA | urinalysis |
| US | United States |
| VAS | visual analogue scale |
| Vd/F | apparent volume of distribution |
| VLA-1 | very late antigen-1 |

# 1 INTRODUCTION

Santarus is developing SAN-300 (previously known as BG00004) as a potential new therapy for the treatment of rheumatoid arthritis (RA). SAN-300 is a recombinant humanized murine antibody directed against very late antigen 1 (VLA-1; also known as $\alpha 1\beta 1$ integrin).

## 1.1 Role of VLA-1 in Inflammation

Inhibition of the human VLA-1 pathway using a specific monoclonal antibody such as SAN-300 is expected to interfere with VLA-1-dependent cellular functions, which are thought to be critical in the pathogenesis of RA. VLA-1 is expressed on activated cells, including T cells (specifically the subset of activated peripheral effector memory T cells), monocytes, macrophages, and natural killer cells. Elevated numbers of VLA-1+ cells have been observed in the synovial fluid taken from RA patients. Data suggest that VLA-1 function is critical to the migration, retention, and proliferation of these cells at sites of inflammation, thereby resulting in secretion of pro-inflammatory cytokines including tumor necrosis factor-$\alpha$ (TNF$\alpha$) and interferon-$\gamma$ (IFN$\gamma$). VLA-1-mediated adhesion has also been demonstrated to inhibit macrophage exit from inflammatory lesions (Becker, 2013).

Consistent with a role for VLA-1 in the pathogenesis of RA, complete or partial loss of VLA-1 function is associated with a decrease in disease severity in models of acute and chronic inflammation.

SAN-300 prevents the VLA-1 molecules on the surface of activated effector memory T cells and activated monocytes/macrophages from binding to their ligands in the extracellular matrix, primarily collagens and laminin. Thus, in RA patients, it is anticipated that blocking VLA-1/collagen interactions with a VLA-1–specific monoclonal antibody (SAN-300) will decrease the presence of VLA-1-expressing cells in chronically inflamed joints by inhibiting the migration, retention, proliferation, and survival of these cells at areas of inflammation. There is also evidence to specifically suggest that blockade of VLA-1 may be a useful treatment for those patients whose disease is inadequately controlled by anti-TNF therapies, which is an area of high unmet medical need (Ben-Horin, 2007).

## 1.2 Nonclinical Studies of Anti-VLA-1 Antibodies

### 1.2.1 Pharmacology

SAN-300 binds to the I domain of the human $\alpha 1$ integrin subunit with high affinity at low SAN-300 concentrations. This binding gives SAN-300 specificity for $\alpha 1\beta 1$ integrin (VLA-1), as $\alpha 1$ integrin only associates with $\beta 1$ integrin and no other $\beta$ subunits (Pribila, 2004).

Anti-mouse VLA-1 antibodies have been shown to be effective in murine models of arthritis, including murine anti-collagen II mAb arthritis, murine collagen-induced arthritis, and rat adjuvant arthritis. Anti-VLA-1 antibodies have also been shown to be effective in a variety of other inflammatory disease models including colitis, psoriasis, corneal transplant rejection, asthma, and atherosclerosis. The efficacy demonstrated in these studies is thought to be mediated through blockade of T-cell and/or monocyte/macrophage migration into and retention and proliferation at sites of inflammation.

### 1.2.2 Pharmacokinetics

The in vivo pharmacokinetic (PK) profiles of SAN-300 and the anti-murine VLA-1 antibodies Ha31/8 (hamster anti-murine VLA-1 mAb) and mHa31/8 (murinized Ha31/8) have been examined in the

cynomolgus monkey and the mouse, respectively. The metabolism and elimination of SAN-300 is expected to be similar to that of endogenous human antibodies. Both SAN-300 and the anti-murine VLA-1 antibodies (mHa31/8 or Ha31/8) exhibited dose-dependent PK characteristics. In cynomolgus monkeys, SAN-300 half-life ($T_{1/2}$) increased with dose, ranging from 38.4 hours at 5 mg/kg to 154 hours at 50 mg/kg. SAN-300 showed bioavailability of approximately 50% to 60% by subcutaneous (SC) or intramuscular (IM) administration in the monkey, indicating SC and IM are viable alternative dosing routes for clinical use. Monkey anti-SAN-300 antibodies were observed upon repeat dosing in cynomolgus monkeys.

### 1.2.3 Preclinical Toxicology

The in vivo toxicologic assessments were performed in the cynomolgus monkey as the most suitable species. SAN-300 has similar affinity for human and non-human primate VLA-1, and thus it is reasonable to expect the toxicity of SAN-300 in the cynomolgus monkey to be predictive for humans.

In single-dose toxicity studies, SAN-300 was well tolerated at doses of up to 50 mg/kg via intravenous (IV) infusion. In a subsequent 3-month study, repeated twice-weekly administration of SAN-300 at doses up to 20 mg/kg IV or SC had no direct effects on mortality, clinical signs, physical examinations, cytokine levels, body weights, food consumption, ophthalmologic examinations, electrocardiography, clinical chemistry results, urine chemistry results, organ weights, macroscopic or microscopic observations, or the generation of antibody responses to foreign antigens. However, recrudescence of *Plasmodium* infection was observed in 6/60 animals, and *Trichomonas* parasites were observed in the gastrointestinal tract of 2/60 animals. As a result of these findings, a no observed adverse effect level (NOAEL) was not established in this study, and further studies were initiated.

A second repeat-dose primate toxicology study was performed, this time using animals that had been pre-screened by PCR analysis for *Plasmodium* and excluding those animals that had a positive test result. There was no toxicity related to the test article at any dose level used in this study. Based on these results, the NOAEL for SAN-300 in male and female cynomolgus monkeys under the conditions of this study was considered to be ≤ 5 mg/kg.

In addition, a set of host-resistance, immune-challenge studies were performed in mice. These studies indicated that exposure to treatment with the anti-murine VLA-1 antibody mHa31/8 had no specific inhibitory effects on the clearance of the bacterial and viral infections tested.

## 1.3 Clinical Experience with SAN-300

A total of 66 healthy volunteer subjects and two patients with active RA participated in Phase 1 Study C2011-0301 (301), in which 45 healthy subjects and one patient with active RA received single doses of SAN-300 via IV infusion or SC injection. Detectable serum SAN-300 concentrations were not observed in the majority of subjects receiving SAN-300 0.03 mg/kg to 0.3 mg/kg IV. In subjects receiving SAN-300 0.6 to 2.0 mg/kg, there was a trend towards increasing serum SAN-300 concentrations with increasing dose. Receptor occupancy was essentially complete (≥ 90%) over a wide range of doses tested for both the IV and SC formulations (by 72 hours postdose for > 0.8 mg/kg IV and by 24 hours postdose for 2.0 to 6.0 mg/kg SC). Receptor occupancy was also durable, with median occupancy remaining at approximately ≥ 70% at Day 8 for all dose groups administered SAN-300 SC.

SAN-300 was generally well tolerated in this study. Mild to moderate infusion reactions occurred upon IV administration of SAN-300 doses from 0.8 to 2.0 mg/kg; all events improved with or without treatment by 72 hours and none led to withdrawal from the study. Among subjects receiving SC SAN-300 at doses ranging from 2.0 to 6.0 mg/kg, headaches and mild injection-site reactions were most common. No severe or serious infections were reported in any group. No clinically meaningful changes from baseline were observed after SAN-300 dosing for biochemistry parameters and for the majority of hematologic parameters tested. Transient, Grade I/II reductions from baseline in absolute neutrophil count (ANC) were observed in 12 subjects who received SAN-300. None of these cases were associated with concurrent infections, and all resolved. Two subjects tested positive for treatment-emergent anti-SAN-300 antibodies; no immunogenicity-related adverse events were observed in these subjects. The safety findings from this Phase 1 study support further development with the proposed multiple ascending dosing regimen in patients with RA.

The primary objective of the Phase 1 study was to evaluate the safety and tolerability of single ascending doses of SAN-300, and the study mainly enrolled healthy subjects. In addition, efficacy parameters were collected and analyzed in two RA patients. These RA patients received either a single dose of 2.0 mg/kg SAN-300 or placebo IV over 4 hours and were evaluated in the clinic for 24 hours and at follow-up assessments on Days 3, 8, 15, 22, and 29. The RA patient who received SAN-300 experienced a reduction in DAS28-CRP from 3.97 at baseline to 2.31 (-1.66) at Day 15 and to 3.05 (-0.92) at Day 29 and met the American College of Rheumatology (ACR) criteria for ACR50 at these time points. The RA patient who received placebo started with a baseline DAS28-CRP of 3.47, experienced a reduction to 3.24 (-0.24) at Day 15, followed by an increase to 3.77 (+0.30) at Day 29, and did not meet criteria for ACR20 any time point. However, any conclusions regarding efficacy drawn from this small sample of RA patients must necessarily be limited.

# 2 STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is:

- To evaluate the safety and tolerability of repeat doses of SAN-300 in patients with active RA

## 2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the PK and pharmacodynamics (PD) 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

# 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, PD, preliminary efficacy, and immunogenicity of SC administration of SAN-300 in five cohorts of patients with active RA. The study will recruit approximately 40 patients (30 SAN-300; 10 placebo) with active RA to evaluate repeat doses of SAN-300 compared with placebo. The study will be conducted at multiple study centers in the United States.

A study design schematic describing the progression of cohorts in this ascending-dose study is provided in Figure 1. Refer to Section 5.2 for the method of treatment group assignment.

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.

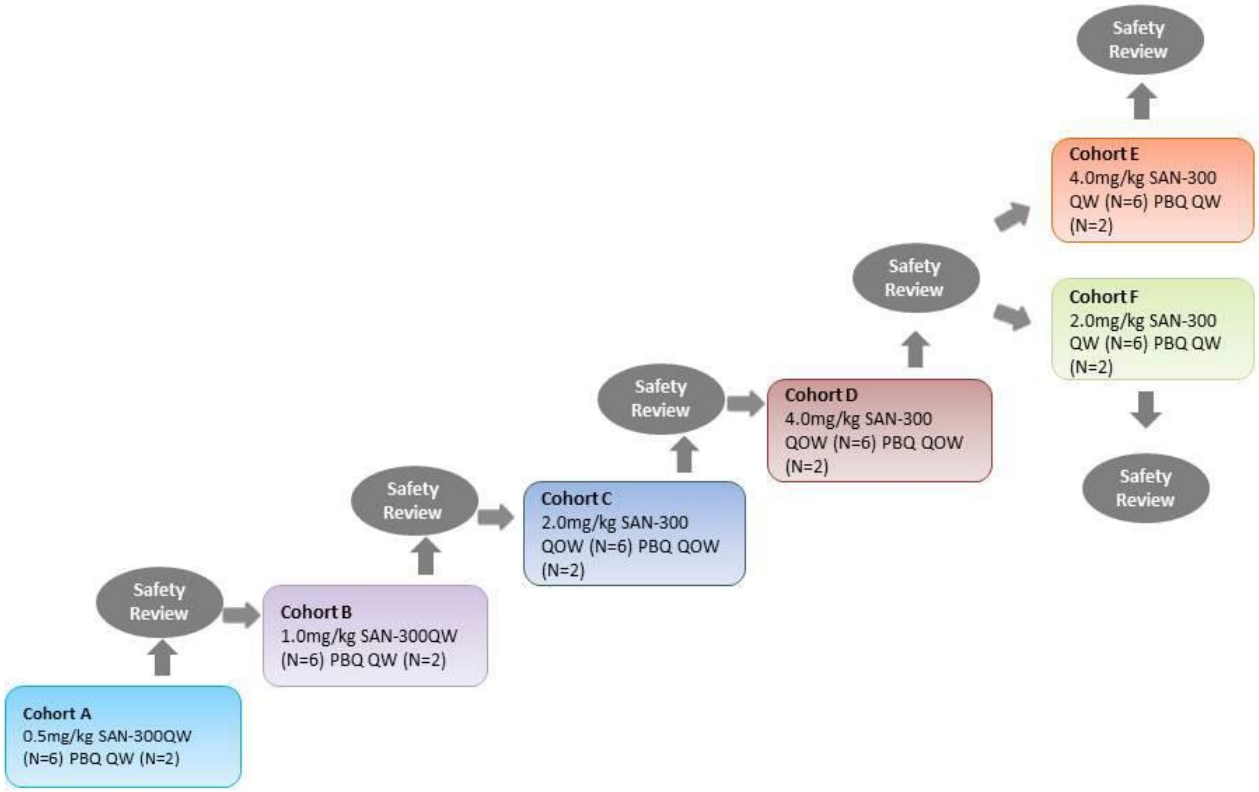
Any subject who withdraws prior to the end of the 6-week Treatment Period will not be replaced and the Study Safety Committee will review the data from all subjects regardless of duration of participation in the study.

Based on the findings of the Study Safety Committee, the Sponsor may elect to modify the dose in the next cohort to a lower dose or terminate any further dose escalation.

For the purposes of this protocol, the term “study drug” will include both SAN-300 and placebo.

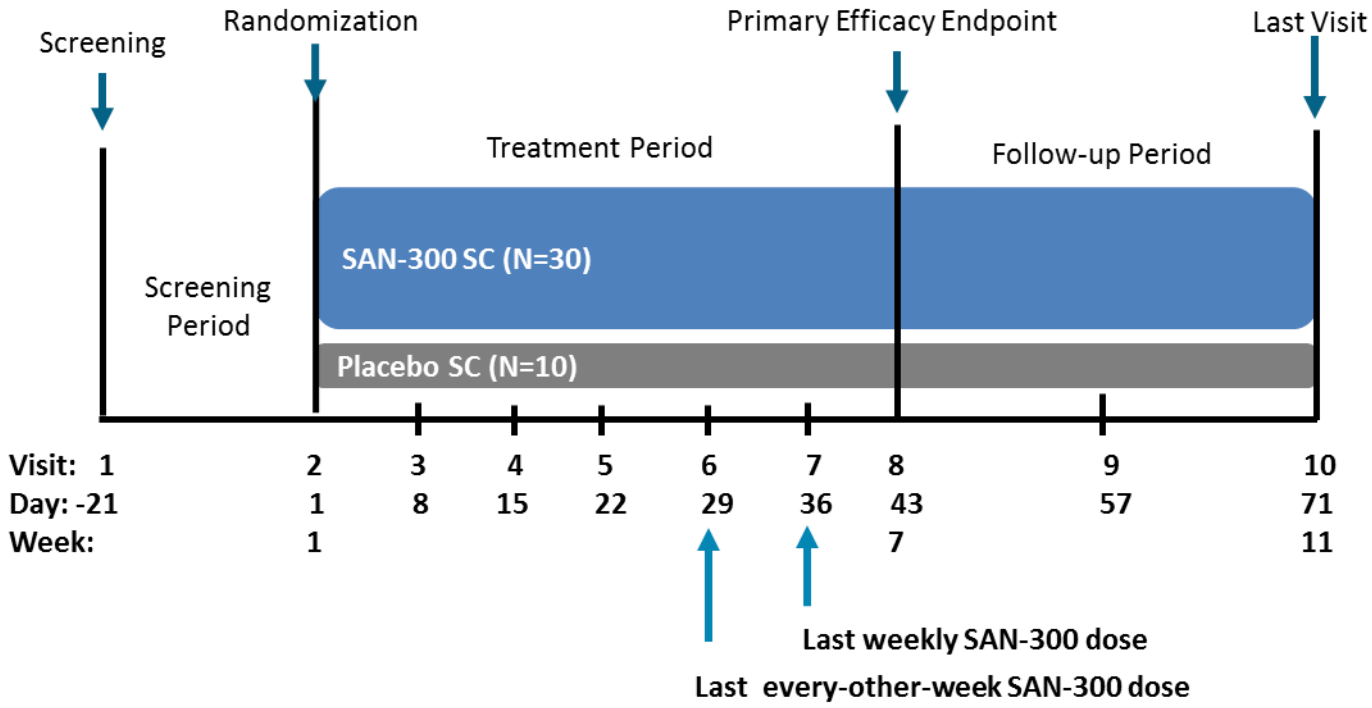
Figure 2 provides a study schematic indicating visit structure for each individual cohort. After initial Screening, eligible patients will return to the study site at weekly intervals throughout the Treatment Period for study drug administration and safety, PK, PD, efficacy, and other assessments. Enrolled 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 1. Study Design for Study C2013-0302




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. 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.

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.

Study procedures at each visit are described in the Schedule of Assessments, provided as Appendix 2.

## 3.2 Rationale for Study Design and Control Group

### 3.2.1 Rationale for Dosing Regimen

The planned doses (0.5 mg/kg once weekly through 4.0 mg/kg every week) and duration of study treatment are based on the observed safety, PK, and PD profile of SAN-300 (including VLA-1 receptor occupancy) in Phase 1 single-dose Study 301 and data from up to 3 months of dosing in non-human primate studies (Section 1.2.3). Based on receptor occupancy data, SAN-300 2.0 mg/kg SC resulted in durable VLA-1 receptor occupancy through Day 8 and the 4.0 mg/kg SC dose extended this receptor occupancy through approximately Day 15. These results suggest that weekly or every-other-week dosing may be sufficient to maintain a therapeutic effect.

In Study 301, single doses of SAN-300 up to 6.0 mg/kg SC were tolerated in a healthy volunteer population. To ensure patient safety, the design of the current multiple ascending dose study stipulates a Safety Review to occur after each dosing Cohort. The overall drug exposure in each cohort is as follows:

**Table 1 Overall Study Drug Exposure by Cohort**

| Cohort | SAN-300 Dose Regimen | Overall Exposure |
|---|---|---|
| A | 0.5 mg/kg QW | 3.0 mg/kg |
| B | 1.0 mg/kg QW | 6.0 mg/kg |
| C | 2.0 mg/kg QOW | 6.0 mg/kg |
| D | 4.0 mg/kg QOW | 12.0 mg/kg |
| E | 4.0 mg/kg QW | 24.0 mg/kg |
| F | 2.0 mg/kg QW | 12.0 mg/kg |

Abbreviations: QOW = every other week; QW = every week

Both weekly and every-other-week dosing will be explored to investigate appropriate dosing parameters for SAN-300. Should every-other-week dosing be a viable option for treatment of patients with RA, this dosing regimen would decrease patient burden.

### 3.2.2 Rationale for Control Group

In every cohort, 6 patients will be randomized to receive SAN-300 and 2 patients will be randomized to receive placebo. Placebo injections will be the best control for potential injection-site AEs, which were observed in the Phase 1 Study 301. Regardless of the cohort, all patients randomized to receive placebo will be administered a total of six once-weekly injections of placebo. In Cohorts C and D, patients randomized to receive SAN-300 will be administered three every-other-week injections of SAN-300 and three every-other-week injections of placebo on alternating weeks. In this way, cohorts with patients receiving every-other-week study drug injections will have matched placebo controls while, at the same time, patients on placebo from all six cohorts (totaling N = 10) can be pooled for safety and efficacy analyses.

### 3.2.3 Rationale for Study Population

The proposed population for this study includes patients between 18 and 75 years of age who have been diagnosed with RA for at least 6 months, have a minimum of six swollen and six tender joints, and

have previously demonstrated an inadequate response or unacceptable toxicity from at least one traditional or biologic disease-modifying anti-rheumatic drug (DMARD). Patients will be required to remain on a stable background dose of methotrexate for ≥ 6 weeks before randomization and during the study. These criteria are intended to identify an appropriate study population for this initial multiple-dose experience with SAN-300, are consistent with ACR recommendations for the use of biologic DMARDs in patients with RA (Singh, 2012), and are aligned with the draft FDA industry guidance for the clinical development of new therapies for RA (FDA, 2013). The proposed patient population is also similar to that described in the published literature for several recent biologic DMARD programs (Keystone, 2009; Fleishmann, 2012; Weinblatt, 2010). Recent clinical studies for biologic DMARD agents for RA have enrolled patients with similar inclusion criteria, including established diagnosis of RA for at least 3 to 6 months, background therapy with methotrexate at comparable doses as those proposed in this study, similar numbers of affected joints (usually six or more tender and swollen joints), and previous intolerance and/or inadequate response to a limited number of DMARDs. Methotrexate was also selected as a required background medication because of its widespread use in RA and the high likelihood that SAN-300, if eventually approved for commercial use, would be frequently used in combination with methotrexate.

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 guide the design of future efficacy and safety studies.

## 3.3 Study Duration

The total duration of study participation will be up to approximately 13 weeks. Patients will be screened for participation within 3 weeks of dosing (Days -21 to -1). The Treatment Period will consist of injections of study drug over a period of 6 weeks and conclude with the End-of-Treatment Visit (Days 1 to 43). The Follow-up Period will consist of an additional 4 weeks (Days 43 to 71).

## 3.4 Stopping Rules for Individual Patient Dosing and for Study Enrollment

The investigator must notify the Clinical Project Manager immediately (via telephone or email) if a patient experiences any of the events listed in the individual patient dosing or study enrollment stopping rules.

### 3.4.1 Stopping Rules for Individual Patient Dosing

The dosing of an individual patient will be stopped under the following circumstances:

- The patient experiences a confirmed reduction in ANC to < $1.0 \times 10^3$/μL.
- The patient experiences a clinically significant atypical or opportunistic infection (including those listed in Appendix 1).
- The patient experiences a clinically significant adverse event related to study participation, in the opinion of the investigator or Sponsor.

### 3.4.2 Stopping Rules for Study Enrollment

New patient enrollment into the study will be temporarily halted, pending review by the Study Safety Committee, under the following circumstances:

- Two or more patients in the study experience a confirmed reduction in ANC to < $1.0 \times 10^3$/μL.

- Any one patient experiences a clinically significant atypical or opportunistic infection (including those listed in Appendix 1).
- Any other significant safety risk occurs, as noted by the Sponsor.

### 3.4.3 Resumption of Study Enrollment

Resumption of study enrollment will be contingent upon review and approval by the Study Safety Committee.

## 3.5 Study Safety Committee

The Study Safety Committee will be composed of, at a minimum, a Sponsor representative and two independent expert physicians. This committee will review ongoing blinded study safety data, decide whether dose escalation is appropriate (see Section 3.1 for the role of safety reviews in dose escalation), recommend any modifications in dosing, and evaluate whether resumption of individual patient dosing or study enrollment is permissible after any interruption triggered by the stopping rules for patient dosing and for study enrollment (see Section 3.4).

# 4 STUDY POPULATION SELECTION

## 4.1 Study Population

It is planned that approximately 40 patients (approximately 8 per cohort) with active RA will be enrolled into this study.

## 4.2 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study:

1. Written informed consent
2. Diagnosed with RA for ≥ 6 months according to ACR/European League Against Rheumatism (EULAR) Classification Criteria 2010 (Appendix 4)
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 and randomization
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 folinic 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 8 g cholestyramine 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 (eg, 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.

Note: Females who have been surgically sterilized (eg, hysterectomy or bilateral tubal ligation) or who are postmenopausal (total cessation of menses for > 1 year) will not be considered "females of childbearing potential".

## 4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

*Medical History*

1. Functional Class IV as defined by ACR classification of functional status in RA (Appendix 5)
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, endocrinologic, 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 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 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
    - ANC < $2.0 \times 10^3$/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.
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

# 5 TREATMENTS TO BE ADMINISTERED

## 5.1 Planned Dose Cohorts

Eligible patients will be enrolled into a dose cohort and randomized (3:1) to receive either SAN-300 via SC injection over 6 weeks or a matching volume of placebo. More than one SC injection may be required (maximum volume of 1.2 mL per SC injection) depending on the total dose administered and the weight of the individual patient. Dosing by cohort is provided in Table 2.

**Table 2. Dose Cohorts for Study C2013-0302**

| | Number of Patients to be Dosed | | |
|---|---|---|---|
| **Cohort** | **SAN-300** | **Placebo** | **SAN-300 Dose** |
| 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

Safety and tolerability findings will be reviewed in a blinded manner for all patients in a cohort after the 6-week Treatment Period to determine whether or not enrollment will begin in the next 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. The safety review will include, at minimum, the following information: AEs; safety laboratory results; vital sign measurements; and reasons for premature study withdrawal.

The decision to begin enrollment in the next cohort will be based upon the results of the safety review. In addition, based on the findings of the Study Safety Committee, the Sponsor may elect to modify the dose in the next cohort to a lower dose or terminate any further dose escalation.

Refer to Section 3.4 for patient and study stopping rules.

## 5.2 Method of Assigning Patients to Treatment Groups

Fixed allocation will be used to randomize patients in a ratio of three on SAN-300 to one on placebo within each cohort of approximately 8 total patients.

Cohort A will be enrolled first, with 6 patients randomly assigned to receive SAN-300 and 2 patients randomly assigned to receive matching placebo in two blocks of four patients (three on SAN-300, one on placebo). After Cohort A has completed the 6-week Treatment Period, a Study Safety Committee will conduct a blinded safety review. If the Study Safety Committee determines that the safety profile is acceptable, then Cohort B can begin enrollment. Additional Safety Committee reviews will occur following completion of the 6-week Treatment Period for each of the subsequently enrolled cohorts.

Randomization will be central and occur after a patient has been deemed eligible. Randomization will be performed by Interactive Voice/Web Response System (IVRS/IWRS). The unblinded pharmacist or designated study center personnel assigned to this role will be responsible for obtaining the treatment assigned to each patient in each cohort by contacting the IVRS/IWRS system by phone or Web site. This unblinded person will then prepare the study drug and provide it to the Investigator. The study drug will then be administered by qualified, blinded study personnel on the day of or within 24 hours after randomization.

## 5.3 Blinding

Study drug will be prepared by unblinded pharmacy staff or designated study center personnel.

The randomization code that assigns treatments to patients will be available in confidence only to personnel responsible for preparation of the study drug for administration. Except in circumstances of immediate threat to patient safety (e.g., medical emergencies) detailed in Section 5.4, the code will not be broken until after all data entry is completed, the validity of the data is checked, all queries are resolved, the statistical analyses are defined, and the database is locked.

## 5.4 Breaking the Blind

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. To discuss breaking of the blind please contact the Clinical Project Manager at Santarus, Inc. by using the following contact information:

Protocol C2013-0302 Medical Monitor
Jason Vittitow, PhD
Santarus, Inc., a wholly owned subsidiary of Valeant Pharmaceuticals International
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807
Phone: + 1 908-541-3060

If the investigator breaks the blind for an individual subject, the reason must be recorded in the subject's source documents and the subject will be removed from the study.

## 5.5 Treatment Compliance

The Investigational Product will be administered to study patients by the study staff. Therefore, no patient compliance measures with regard to the Investigational Product are necessary.

All used and unused Investigational Product will be retained for verification by the Study Monitor.

## 5.6 Description of Treatments

### 5.6.1 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 °C to 8 °C, 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.

### 5.6.2 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 °C to 8 °C, protected from light.

## 5.7 Packaging and Labeling

Packaging, labeling, and shipping of study drug will be done by Catalent Pharma Solutions, LLC, located in Kansas City, MO, USA. Contracted regional drug distribution facilities will provide drug supplies to the investigational study centers.

## 5.8 Storage and Accountability

### 5.8.1 Receipt of Supplies

When supplies of study materials are received by the unblinded study personnel, he/she will acknowledge receipt by signing and dating documentation enclosed with the shipment, and returning it as instructed on the documentation. A copy will be retained for the Investigator File.

### 5.8.2 Storage of Supplies

Study materials will be stored by the study personnel according to the documentation provided with the study materials. The Sponsor reserves the right to inspect the Investigational Product storage area before and during the study. A written record will be made of the storage condition of the study materials and retained for the Investigator File.

### 5.8.3 Control of Supplies

Dispensing of the Investigational Product will be carefully recorded on appropriate Investigational Product accountability forms and will be verified periodically by an unblinded Study Monitor.

The accountability logs should include dates, quantities, batch numbers, expiration dates (if applicable), and any unique numbers assigned to the patient. The accountability logs will also include general

details related to the study, including the Protocol/Amendment number, Sponsor, indication, and the Investigator.

## 5.9 Investigational Product Retention

The Investigator must maintain accurate records demonstrating dates and amount of Investigational Product received and dispensed and accounts of any Investigational Product accidentally or deliberately destroyed. Sufficient quantities of study drug will be kept by the Sponsor to reconfirm specifications if the need arises. These samples should be retained until the analyses of study data are complete or as required by the applicable regulatory requirement.

An unblinded Study Monitor will review the Investigational Product accountability logs and check all Investigational Product returns (both unused and used) before authorizing the destruction of used Investigational Product by the study site.

# 6 CONCOMITANT THERAPY

The efficacy and safety of immunization during periods of SAN-300 therapy have not been adequately studied. It is recommended that a patient's vaccination record and possible vaccination requirements be reviewed and, if necessary, the patient be administered any required vaccination or booster at least 4 weeks before randomization. Review of the patient's immunization status and their need for the following vaccinations is recommended: tetanus; diphtheria; influenza; pneumoccocal polysaccharide; varicella; measles, mumps, and rubella; and hepatitis B vaccines. Immunization with a live vaccine is specifically prohibited within 4 weeks before randomization and throughout the study.

Folic acid ≥ 5 mg/week (or an equivalent dose of folinic acid) is required for all patients.

Patients must 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. 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 the revised treatment regimen for at least 4 weeks before randomization.

All other DMARDs are to be discontinued for at least the following periods of time:

- Oral DMARDs and etanercept at least 4 weeks before randomization
- Rituximab and any other B-cell/lymphocyte-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 leflunomide withdrawn for at least 4 weeks before randomization and must undergo treatment to facilitate drug elimination with 8 g cholestyramine three times daily for 3 days to be eligible for participation

Patients receiving treatment with prednisone (or equivalent dose of another corticosteroid) that is either over 10.0 mg/day or is not stable for at least 4 weeks before randomization are to be excluded. Intra-articular corticosteroid injection(s) are not permitted within 4 weeks of randomization and should not be given during the course of the study.

Patients receiving treatment with opioids or other narcotics are to be excluded. Note: Patients receiving 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.

Patients are to remain on their stable RA treatment regimen (i.e., the RA treatment they are receiving at the time of randomization) throughout the course of the study, including the Follow-up Period. Concomitant use of other anti-arthritic treatments, including approved or experimental agents, therapies, or devices is not permitted.

All patients should be instructed not to start taking any new medications or therapies, including non-prescribed drugs, unless they have received permission from the Investigator. Any medication and any non-drug therapy or procedure used starting from signing of the Informed Consent Form (ICF) until

the completion of the study must be recorded in the patient's CRF according to the instructions for CRF completion.

# 7 PATIENT WITHDRAWAL AND STUDY TERMINATION

## 7.1 Reasons for Withdrawal

Participation in the study is strictly voluntary. A patient has the right to withdraw from the study at any time for any reason. If he/she chooses to withdraw, the patient must inform the Investigator immediately and will be asked to make an Early Withdrawal Visit. If feasible, it is also highly recommended that the patient schedule a Follow-up Visit for a safety evaluation 4 weeks after their last dose of study drug. The Investigator has the right to terminate participation of any patient at any time if it is deemed to be in the patient's best interest. The reason and circumstances for premature discontinuation will be documented in the patient's electronic case report form (eCRF). Possible examples for reasons of premature study withdrawal include:

- Withdrawal of consent
- Intolerable AE
- Intake of non-permitted concomitant medication
- Significant non-compliance with the protocol
- Positive pregnancy test in a female patient
- Clinical or administrative reason consistent with the requirements of the protocol at the Investigator's discretion
- Clinically significant worsening of RA that, in the opinion of the Investigator, requires immediate, specific medical treatment

## 7.2 Procedures for Early Withdrawal

When it is determined that a patient should withdraw from the study, the reason(s) must be recorded, final assessments must be scheduled, and provisions for the continued treatment of RA within the standards of care must be discussed with the patient. Safety and study endpoint evaluations for the Early Withdrawal Visit (see Sections 10.2.6 and 10.3.1) will be performed as soon as possible after the decision is made to withdraw the patient.

Additional interventions (concomitant medications or therapies) may be prescribed as needed by the patient. The patient's history and preferences should be considered and discussed when prescribing a new medication for RA.

Appropriate medical follow-up with the patient should be conducted as clinically indicated after the Early Withdrawal Visit. Telephone contacts between the patient and the study staff should be conducted 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. The responsible IEC/IRB should be notified of any AEs and/or circumstances leading to early withdrawal.

If a patient is withdrawn from study participation because of pregnancy, Product Safety and IEC/IRB should be informed by the site within 24 hours of awareness. All pregnancies occurring in female patients must be reported. The pregnancy will be reported according to the procedures provided in Section 9.8. Should the patient have a spontaneous abortion or complications during the pregnancy, then the event must be captured as an SAE. Sites are obligated to follow the patient until the outcome of the pregnancy is known. The patient and/or her treating physician should be encouraged to report any future medical problems the child develops of which they become aware that are considered related to the study drug.

Patients who are randomized and who subsequently withdraw from the study will not be replaced.

### 7.3 Sponsor's Termination of Study

Santarus reserves the right to discontinue the study at any time for clinical or administrative reasons.

If the study is prematurely terminated or suspended for any reason, the Investigator must inform all study patients currently receiving study drug and assure appropriate follow-up. Santarus should promptly inform the Investigators/institutions and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension in accordance with applicable regulations. The IEC/IRB should also be informed promptly and provided with the reason(s) for the termination or suspension by Santarus or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

## 8 STUDY ASSESSMENTS

### 8.1 Demographic Data/Medical History

Demographic data, current medications (including existing RA therapy), and medical history will be recorded at Screening. In addition, a separate detailed RA history including date of diagnosis and all prior treatments will be recorded.

### 8.2 Physical Examination

The physical examination will be conducted according to the Schedule of Assessments provided in Appendix 2 and will include the following: examination of general appearance, skin, head, neck (including thyroid), eyes, ears, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system. Height will be recorded at Screening only.

### 8.3 Vital Signs

Vital signs will include the following: body temperature (°C), pulse, respiratory rate, blood pressure, and weight. Vital signs will be assessed at all study site visits. On visits when study drug is to be administered vital signs will be assessed before dosing and blood pressure and pulse will be assessed at the end of the 1 hour observation period. Vital signs should be assessed prior to any blood draws.

### 8.4 12-Lead ECG

A 12-lead electrocardiogram (ECG) will be collected according to the Schedule of Assessments provided in Appendix 2. Patients should be in a resting, supine position for 10 minutes before ECG

collection. The Investigator (or a designated, qualified observer at the investigational site) will interpret the ECG using one of the following categories: within normal limits, abnormal but not clinically significant, or abnormal and clinically significant.

## 8.5 Clinical Laboratory Tests

### 8.5.1 Laboratory Parameters

Blood samples for clinical laboratory assessments will be collected according to the Schedule of Assessments provided in Appendix 2. Patients will be in a seated or in a supine position during blood collection. Safety and Screening laboratory tests will include those listed in Table 3 and will be performed at a central laboratory.

## Table 3. List of Laboratory Tests

**Hematology:**

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)

**Urinalysis:**

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen
- Urine human chorionic gonadotropin (hCG) (only for females of childbearing potential)

**Additional Assessments:**

- Serum Immunoglobulin
- Serum tryptase
- Histamine
- C-reactive protein (CRP)
- Erythrocyte sedimentation rate (ESR) (conducted at site)

**Serum Chemistry:**

- Albumin (ALB)
- Alkaline phosphatase (ALK-P)
- Alanine aminotransferase (ALT; SGPT)
- Aspartate aminotransferase (AST; SGOT)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Carbon dioxide ($CO_2$)
- Chloride (Cl)
- Creatinine
- Creatine kinase
- Gamma-glutamyl transferase (GGT)
- Globulin
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid
- Serum hCG (only for females of childbearing potential)

**Coagulation:**

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)
- International normalized ratio (INR)

**Serology:**

- Hepatitis B surface antigen (HBsAg)
- Hepatitis C virus (HCV) antibodies
- Human immunodeficiency virus (HIV) antibodies
- QuantiFERON®-TB Gold test (QFT)

## 8.6 Pharmacokinetic Assessments

For patients in each cohort, serum SAN-300 concentrations will be determined from blood samples collected according to the Schedule of Assessments provided in Appendix 2 and the Specialty PK and PD Laboratory Testing Schedule provided in Appendix 3. Pharmacokinetic parameters for SAN-300 will be estimated using a population based approach with nonlinear mixed-effect modeling, in accordance with the FDA Draft Guidance on Population Pharmacokinetics (1999). Population PK methods will be used to estimate the relevant PK parameters for the population as well as for each patient who received SAN-300 and had sufficient blood samples in which SAN-300 was quantifiable. The details of the analysis will be documented in a Population Pharmacokinetic/Pharmacodynamic Analysis Plan.

## 8.7 Pharmacodynamic Assessments

The following PD parameters will be determined for all patients from blood samples collected at the same time as PK blood samples according to the Schedule of Assessments provided in Appendix 2 and the Specialty PK and PD Laboratory Testing Schedule provided in Appendix 3:

- VLA-1 receptor occupancy
- An immunophenotyping panel (CD3, CD4, CD8, CD14, CD19, CD45, CD45RO, and CD49α)
- Cytokines: IFNγ, TNFα, interleukin-6 (IL-6)
- CRP

Exploratory PK/PD modeling will be conducted as described in the Population Pharmacokinetic/Pharmacodynamic Analysis Plan.

## 8.8 Efficacy Assessments

Efficacy assessments will be conducted according to the Schedule of Assessments provided in Appendix 2 and will consist of Disease Activity Score for 28-joint count using C-reactive protein (DAS28-CRP), ACR Core Set Measurements, Health Assessment Questionnaire Disease Index (HAQ-DI), and MRI of the hand and wrist most clinically affected by RA.

### 8.8.1 DAS28-CRP Assessment

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)
- Patient's global assessment of disease activity (patient)
- CRP (laboratory test)

The assessor will be an experienced rheumatology clinical assessor.

### 8.8.2 ACR Core Data Set

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 ESR), as shown below:

- Swollen and tender joint assessment (assessor – refer to Appendix 6)
- 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)
- CRP or ESR (laboratory test)

The assessor will be an experienced rheumatology clinical assessor.

#### 8.8.2.1 Physician's Global Assessment of Disease Activity

The physician's global disease assessment will be documented on a visual analogue scale (VAS) of 0 to 100 mm, ranging from 0 mm no disease activity to 100 mm (worst disease activity). The distance between the single vertical line marked by the physician will be measured in millimeters (mm) from the left end of the scale using a 100 mm ruler that will be provided. To standardize measurements, the same person should take the measurement wherever possible throughout the study.

#### 8.8.2.2 Patient Assessment of Pain

Patients will be asked to rate their current pain intensity on a VAS. The VAS consists of a 100 mm-long scale ranging from 0 mm (no pain) to 100 mm (severe pain). The distance between the single vertical line marked by the patient will be measured in mm from the left end of the scale by the study staff, using the ruler provided.

#### 8.8.2.3 Patient's Global Assessment of Disease Activity

Patient's global disease assessment will be documented on a VAS of 0 mm (no disease activity) to 100 mm (worst disease activity). The distance between the single vertical line marked by the patient will be measured in mm from the left end of the scale by the study staff, using the ruler provided.

A patient is considered to have an ACR20/50/70 response if there is an improvement of 20%/50%/70% in all of the following:

- Swollen joint count (66 joints)
- Tender joint count (68 joints) and
- At least three of the following five assessments:
  - Patient's assessment of pain
  - Patient's global assessment of disease activity
  - Physician's global assessment of disease activity
  - Patient's assessment of physical function, as measured by the HAQ-DI
  - CRP

### 8.8.3 HAQ-DI Quality of Life Assessments

Quality of life will be assessed according to the Schedule of Assessments provided in Appendix 2 using the HAQ-DI (Appendix 7).

### 8.8.4 Magnetic Resonance Imaging of Hand and Wrist

The requirements for the Magnetic Resonance Imaging (MRI) scans are as follows:

- Magnet strength: 1.5 Tesla
- The same MRI scanner should be used for all scans of any individual patient throughout the study
- Region imaged: The hand with the most clinically affected metacarpophalangeal (MCP) joints and wrist at screening. Image will include the distal radioulnar joint. The same hand and wrist will be assessed for the follow up scan.
- Sequences will include T1-weighted 3D gradient echo (GRE) coronal scans pre- and post-gadolinium contrast, axial T1-weighted GRE scans post-contrast, and coronal STIR sequences.
- Exam time should last approximately 1 hour, including all patient setup and positioning

Using a central reader, all MRI scans will be assessed by two experienced rheumatology clinical assessors (see Appendix 8 for MRI scoring criteria) and their readings will be averaged to minimize any error due to the inherent variability of the MRI scoring process.

## 8.9 Other Laboratory Assessments

Additional laboratory parameters will be assessed according to the Schedule of Assessments provided in Appendix 2 and will include the following:

- Anti-SAN-300 antibody
- Rheumatoid factor (RF), antinuclear antibody (ANA), and anti-citrunillated peptide antibodies (ACPA)

## 8.10 Assessing Hypersensitivity

For suspected cases of anaphylaxis or hypersensitivity reactions, blood samples will be obtained for laboratory assessment of tryptase and histamine concentrations. In addition, Investigators should apply the criteria outlined in the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) second symposium on the definition of anaphylaxis report (Sampson, 2006), as outlined in Table 4, to assess patients for potential anaphylactic reactions.

### Table 4. Clinical Criteria for Diagnosing Anaphylaxis

**Anaphylaxis is highly likely when any one of the following three criteria is fulfilled:**

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

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF = peak expiratory flow; BP = blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Source: Sampson, 2006

## 8.11 Appropriateness of Measurements

All procedures used to measure the safety, tolerability, and PK profile of SAN-300 in this study were considered by the Sponsor and Investigators to be appropriate and necessary to obtain the required safety, tolerability, and PK data for the investigational product. The safety assessments used in this study, such as vital signs, ECG, and clinical chemistry and hematology monitoring, are widely used and are considered appropriate for monitoring patient health and well-being in this type of study.

The efficacy measures were selected to be generally comparable to published clinical studies in RA. The Investigators consider the measures to be standard assessments and endpoints for this disease. CRP and ESR measurements reflect the general inflammatory state of a patient and are components of the ACR Core Set Measurements.

The PD markers were chosen to allow assessment of the immunological effects of SAN-300. These assessments are designed to provide information relevant to their usefulness as biomarkers and measures of potential safety and efficacy. Changes in VLA-1 on lymphocytes and monocytes as well as changes in the levels of the pro-inflammatory cytokines IFNγ, TNFα, and IL-6 will be useful as potential biomarkers and indications of potential efficacy. VLA-1+ leukocytes, TNFα, and IL-6 are thought to be important drivers of inflammation in RA; IFNγ is a cytokine secreted by VLA-1+ T cells. Changes (specifically, any potential increases) in the levels of IFNγ, TNFα, and IL-6 will also be important safety markers.

# 9 SAFETY REPORTING

Santarus maintains a robust pharmacovigilance system comprised of a governance framework and standard operating procedures supporting a systematic process for review, evaluation, and management of accumulating safety data from clinical trials and other sources to:

- Identify a potential new safety signal;
- Ensure that an investigational product's risks are adequately assessed and communicated to investigators, IRBs/ECs, and regulatory bodies during clinical development.

For this study, safety monitoring activities will include but are not limited to:

- Review and evaluation of single SAE occurrences in real-time as reported through the SAE reporting process as outlined in this section of the protocol;
- Review and evaluation, in real-time, of one or more occurrences of an uncommon SAE that is not commonly associated with product exposure;
- Findings and/or safety data obtained during this study will provide information for the overall review of safety that is conducted by Santarus on a routine basis. Santarus will report expeditiously any findings from clinical trials (ongoing or completed), epidemiological studies, pooled analysis of multiple studies, and findings from animal or in vitro testing that suggest a significant risk in humans exposed to the study product.

Safety data collection for this study begins at the time of the subject's signing of the informed consent according to the operating definitions defined in this section of the protocol.

The Investigator is responsible for reporting all AEs that occur during the study, regardless of their relationship to study drug or their clinical significance.

## 9.1 Operating Definitions for Assessing Safety

### 9.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a study product and which does not necessarily have a causal relationship with the treatment.

An AE can therefore be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study product, without any judgment about causality (i.e., whether or not considered related to the study product).

Additionally, an event that is associated with study participation (regardless of administration of or relationship to study drug) should be treated as a reportable adverse event for this protocol (e.g., complications resulting from the taking of a blood sample or performance of a protocol required procedure).

An AE **does** include the following:

- Exacerbation or worsening of a pre-existing illness.
    - NOTE: if the pre-existing illness is the disease under study, then “exacerbation” refers to an unexpected worsening from the condition at baseline.
- Increase in frequency or intensity of a pre-existing episodic event or condition.
- Condition detected or diagnosed after study product administration even though it may have been present prior to the start of the study.
- Symptom associated with disease not previously reported by the patient

An AE **does not** include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) as event terms; the condition that led to the procedure is the AE if it meets the definition of an AE.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for cosmetic elective surgery; and social and/or convenience admissions).
- Overdose of either study product or concurrent medication without any signs or symptoms.
- Symptoms associated with disease, which are consistent with the patient’s usual clinical course; unless the subject experiences worsening of their symptom(s) or the symptom(s) meet the criteria for an SAE. Any medical condition present at the time of screening but does not worsen during the course of the study should be recorded as medical history.

### 9.1.2 Serious Adverse Event

A **serious adverse event (SAE)** is any AE that fulfills any of the following criteria:

- Results in death
- Is life-threatening
  NOTE: the term “life-threatening” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which could hypothetically have caused death had it been more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization

  NOTE: Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. “In-patient” hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a casualty or emergency room.
- Results in persistent or significant disability/incapacity

  NOTE: The term disability means a substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental

trauma (e.g., sprained ankle) that may interfere or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect
- Is medically significant or requires intervention to prevent one of the outcomes listed above.
  NOTE: For example, allergic bronchospasm requiring intensive treatment in an emergency room or at home [see Section 8.10 on Assessing Hypersensitivity], blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

## 9.2 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., abnormal findings during examinations or ECG monitoring) that are judged by the investigator as **clinically significant** must be recorded as AEs or SAEs if they meet the definition of an AE or SAE. The investigator should exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment (including ECG monitoring) is clinically significant.

## 9.3 Method, Frequency, and Time Period for Detecting AEs and SAEs

At each visit, after the patient has had an opportunity to spontaneously mention any problems, the investigator should inquire about AEs by asking the following standard questions:

1. "Have you had any (other) medical problems since your last visit/assessment?"

2. "Have you taken any new medicines, other than those given to you in this study, since your last visit/assessment?"

### 9.3.1 Time Period for Detecting and Reporting of AEs and SAEs

From the time of informed consent through study completion/withdrawal, including the follow-up period.

### 9.3.2 Post-Study SAEs

Investigators are not obligated to actively seek SAE information in former study participants, but investigators are encouraged to notify the sponsor of any SAEs, of which they become aware occurring at any time after a patient has completed, discontinued or terminated study participation that they judge may reasonably be related to study treatment or study participation.

## 9.4 Documenting AEs and SAEs

All AEs that occur after the patient has signed the ICF and during the course of the study, regardless of causality or seriousness, will be assessed and recorded in the patient's medical records and in the CRF. In addition, SAEs must be documented on the paper SAE Report Form.

A separate paper SAE Report Form should be used for each SAE. However, if at the time of initial reporting, multiple SAEs are present that are temporally and/or clinically related, they may be reported on the same SAE Report Form.

The investigator should attempt to establish a diagnosis for the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and SAE and not the individual signs/symptoms.

For clinically significant abnormal laboratory findings or other abnormal assessments meeting the definition of an AE or SAE, a diagnosis, if known (or clinical signs and symptoms if diagnosis is unknown), should be recorded by the investigator. If a diagnosis is unknown and clinical signs and symptoms are not present, then the abnormal finding should be recorded. When documenting as an SAE on the SAE Report Form, relevant laboratory data should either be recorded in the 'Details of Relevant Assessments' section of the SAE Report Form (including the reference range and units) or copies of the laboratory report (with reference ranges and units) should be sent with the SAE Report Form.

The SAE Report Form should be completed as thoroughly as possible and signed by the investigator or his/her designee before transmittal to Product Safety. It is **very important** that the investigator provide his/her assessment of causality to study product at the time of initial SAE reporting.

## 9.5 Follow-up of AEs and SAEs

All AEs, regardless of seriousness, must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, relevant hospital records (i.e. discharge summary), or consultation with other health care professionals.

Product Safety may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a patient dies during participation in the study or during a recognized follow-up period, Product Safety should be provided with a copy of any postmortem findings, including histopathology.

For SAEs, new or updated information should be recorded on the originally completed paper SAE Report Form and all changes signed and dated by the Investigator or designee. By signing the SAE Report Form, the investigator or designee attests to the accuracy and completeness of the data and that he/she has reviewed and approved the report being submitted. The investigational sites IRB/IEC must be notified about SAEs in accordance with the requirements of the governing IRB/IEC.

## 9.6 Assessment of Causality

The Investigator's assessment of the relationship to study drug of an AE is part of the documentation process but is not a factor in determining whether or not it is reported. All AEs, regardless of causality, must be reported. The blind should not be broken for the purpose of making this assessment. If there is uncertainty as to whether a clinical observation is an AE, the event should be reported.

The relationship of the event to the study drug should be determined by the Investigator according to the following criteria:

| | |
|---|---|
| **Not related** | An event for which sufficient data exist to indicate that the etiology is unrelated to the drug. |

| | |
|---|---|
| **Unlikely related** | An event that does not follow a reasonable temporal sequence relative to administration of the drug. However, causality from the drug cannot be ruled out. |
| **Possibly related** | An event that follows a reasonable temporal sequence relative to administration of the drug; that follows a known or expected pattern of response to the drug; but that could readily have been produced by other factors. |
| **Probably related** | An event that follows a reasonable temporal sequence relative to administration of the drug; that follows a known or expected pattern of response to the suspected drug; and that could not be reasonably explained by the known characteristics of that patient's clinical state. |

## 9.7 Prompt Reporting of SAEs to Product Safety

SAEs must be reported promptly to Product Safety once the investigator determines that the event meets the protocol definition of a SAE.

Prompt reporting of a SAE requires:

- Completion and transmission of the SAE Report Form to Product Safety via fax within 24 hours of the investigator's knowledge of the event. In parallel, a corresponding AE with the SAE details should be entered into the AE CRF within 48 hours of submitting the paper SAE Report Form.
- Prompt reporting of additional information for previously reported SAEs should follow the same reporting timeframe as initial reports. In addition, the corresponding AE in the AE CRF (as applicable) should be updated to ensure all data points documented in the AE CRF are aligned with the matching data points on the paper SAE Report Form.

## 9.8 Pregnancy Reporting

Pregnancies detected in subjects assigned to study drug should be promptly reported to Product Safety within 24 hours of awareness via fax, using the Pregnancy Notification Form. If a female patient becomes pregnant following assignment to study treatment, the study product will be immediately discontinued and the patient will be followed until the outcome of the pregnancy is known.

Product Safety should be notified promptly via fax of any updates on the status of the pregnancy by update and/or amendment of the initial pregnancy notification form.

Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication (i.e. spontaneous abortion) or elective termination of a pregnancy, for medical reasons, will be recorded as an AE or SAE and followed as such.

## 9.9 Transmission of SAE Report Forms and Pregnancy Notification Forms

Completed SAE Report Forms and completed pregnancy notification forms should be transmitted to Product Safety via the fax number provided below:

US sites: Product Safety Fax: 888-314-5934

For questions regarding SAE and/or Pregnancy reports, contact Product Safety via the phone number provided below:

US sites: Product Safety SAE Hotline: 888-314-1963

## 9.10 Regulatory Reporting Requirements for SAEs

The investigator, or responsible person per local requirements, must comply with the applicable local regulatory requirements related to the reporting of SAEs and IND safety reports to regulatory authorities and their IRB/EC.

# 10 STUDY ACTIVITIES

The study Schedule of Assessments is provided as Appendix 2, and the Specialty PK and PD Laboratory Testing Schedule is provided as Appendix 3.

## 10.1 Visit 1: Screening (Days -21 to -1)

Study specific screening procedures will begin only after the informed consent form (ICF) has been signed and the consent process conducted with the patient has been briefly described in the patient's source documents. The Screening Period will be scheduled to conduct procedures that confirm the patient is fully eligible for the study. Screening for the inclusion/exclusion criteria will occur within 3 weeks before study drug administration.

The following procedures will be performed during Screening:

- Obtain informed consent
- Evaluate inclusion and exclusion criteria
- Record patient demographics, medical history, and vital signs
- Record medication history (prescription and over the counter [OTC]) during the 8 weeks before Screening
- Record RA history and prior RA treatment(s)
- Perform a 12-lead ECG
- Perform a chest X-ray (Note: a chest X-ray is not required if a chest X-ray with no clinically significant findings was performed within 1 month of randomization)
- Perform a physical examination
- Perform a serum pregnancy test for all females of childbearing potential
- Collect blood samples on a day during Screening when the patient has fasted for 4 to 6 hours for:
  - Complete blood count with differential and platelet count (CBC) and chemistry
  - CRP
  - HCV antibody, HIV antibody, HBsAg, and QFT
  - RF and ACPA
  - ESR (done at site with the kit provided)
- Collect urine sample for urinalysis
- Inform patients of the study restrictions outlined in the inclusion/exclusion criteria
- Conduct the DAS28-CRP and ACR Core Set Measurements
- Complete the HAQ-DI

## 10.2 Treatment Period (Days 1 to 43)

The once-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.

### 10.2.1 Visit 2 (Day 1) Procedures

Eligible patients will return to the study site for enrollment, randomization, and administration of the first dose of study drug. Patients should arrive at the study site having fasted for 4 to 6 hours. The following procedures will be performed at Visit 2:

Before Randomization:

- Review inclusion and exclusion criteria and medical history
- Record all AEs since previous visit
- Record all medications (prescription and OTC) taken by the patient since Screening
- Record RA history and prior RA treatment(s)
- Record vital signs
- Perform a urine pregnancy test for all females of childbearing potential
- Collect urine for urinalysis
- MRI of the hand and wrist most clinically affected by RA (to occur within 5 days before or at Visit 2) should be performed on patients able to tolerate the MRI procedure.

Randomize the patient via the IVRS/IWRS system.

After Randomization but before Study Drug Administration:

- Collect blood samples for:
  - CBC and chemistry
  - ESR (done at site with the kit provided)
  - International normalized ratio (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT)
  - Tryptase and histamine
  - Complement (C3, C4, and CH50)
  - CRP concentration
  - Serum immunoglobulins
  - ANA
  - Anti-SAN-300 antibodies
  - Serum SAN-300 concentration
  - Cytokine assessments (IFN$\gamma$, TNF$\alpha$, IL-6)
  - Immunophenotyping panel (CD3/CD14/CD45RO/CD49a/CD45/CD4/CD19/CD8)
  - VLA-1 receptor occupancy
- Conduct the DAS28-CRP and ACR Core Set Measurements
- Complete the HAQ-DI

Administer study drug according to the randomization of the patient. Day 1 study drug administration should occur on the day of or within 24 hours after randomization.

After Study Drug Administration:

- Observe subject at minimum 1 hour post dose. Longer observation allowed if deemed necessary by investigator or designee.

- Record blood pressure and pulse at the end of the 1 hour observation period prior to the blood sample collection
- Collect blood sample at 1 hour post dose for serum SAN-300 concentration
- Collect AEs since study drug administration

### 10.2.2 Visit 2A (between Days 2 to 4) and Visit 2B (between Days 5 to 7)

Patients will come to the study site at a random, scheduled time within each of these intervals to have blood samples collected for serum SAN-300 concentration and VLA-1 receptor occupancy.

Record all AEs and medications taken since previous visit

### 10.2.3 Visits 3, 4, and 5 (Days 8, 15, and 22) Procedures

Patients should arrive at the study site having fasted for 4 to 6 hours. The following procedures will be performed at Visits 3 to 5:

- Record all medications (prescription and OTC) taken by the patient since previous visit
- Record all AEs since previous visit
- Record vital signs
- Perform a urine pregnancy test for all females of childbearing potential (Visit 5 only)
- Collect blood samples for:
  - CBC and chemistry
  - ESR (done at site with the kit provided)
  - CRP concentration
  - Anti-SAN-300 antibodies (Visit 3 only)
  - Serum SAN-300 concentration
  - Cytokine assessments (IFN$\gamma$, TNF$\alpha$, IL-6) (Visit 3 only)
  - Immunophenotyping panel (CD3/CD14/CD45RO/CD49a/CD45/CD4/CD19/CD8) (Visits 3 and 4 only)
  - VLA-1 receptor occupancy (Visits 3 and 4 only)
- Conduct the DAS28-CRP and ACR Core Set Measurements
- Administer the study drug appropriate to the randomization of the patient
- Complete the HAQ-DI
- Observe subject at minimum 1 hour post dose. Longer observation allowed if deemed necessary by investigator or designee
- Record blood pressure and pulse at the end of the 1 hour observation period
- Collect AEs since study drug administration

### 10.2.4 Visit 3A (between Days 9 to 11)

Patients will come to the study site at a random, scheduled time within this interval to have a blood sample collected for serum SAN-300 concentration.

Record all AEs and medications taken since previous visit

### 10.2.5 Visits 6 and 7 (Days 29 and 36) Procedures

Patients should arrive at the study site having fasted for 4 to 6 hours. The following procedures will be performed at Visits 6 and 7:

Before Study Drug Administration during Visits 6 and 7:

- Record all medications (prescription and OTC) taken by the patient since previous visit
- Record all AEs since previous visit
- Record vital signs
- Perform a urine pregnancy test for all females of childbearing potential (Visit 7 only)
- Collect blood samples for:
  - CBC and chemistry
  - ESR (done at site with the kit provided)
  - CRP concentration
  - Serum SAN-300 concentration
  - Cytokine assessments (IFN$\gamma$, TNF$\alpha$, IL-6)
  - Immunophenotyping panel (CD3/CD14/CD45RO/CD49a/CD45/CD4/CD19/CD8)
  - VLA-1 receptor occupancy
- Conduct DAS28-CRP and ACR Core Set Measurements
- Complete HAQ-DI

Administer the study drug appropriate to the randomization of the patient.

After Study Drug Administration during Visits 6 and 7:

- Observe subject at minimum 1 hour post dose. Longer observation allowed if deemed necessary by investigator or designee
- Record blood pressure and pulse prior to the blood sample collection
- Collect blood samples at 1 hour post dose (Visit 7 only) for:
  - Serum SAN-300 concentration
  - Cytokine assessments (IFN$\gamma$, TNF$\alpha$, IL-6)
- Collect AEs since study drug administration

### 10.2.6 Visit 6A (between Days 30 to 32), Visit 7A (between Days 37 to 39), and Visit 7B (between Days 40 to 42)

Patients will come to the study site at a random, scheduled time within each of these intervals to have blood samples collected for serum SAN-300 concentration and VLA-1 receptor occupancy.

Record all AEs and medications taken since previous visit.

### 10.2.7 Visit 8: End-of-Treatment Visit (Day 43) or Early Withdrawal Visit (Treatment Period)

Patients should arrive at the study site having fasted for 4 to 6 hours. The following procedures will be performed at the End-of-Treatment Visit (Visit 8) or at an Early Termination Visit for patients who discontinue study participation during the Treatment Period:

- Record all medications (prescription and OTC) taken by the patient since Visit 7
- Record all AEs since previous visit
- Perform a 12-lead ECG
- Perform a physical examination
- Record vital signs
- Collect urine for urinalysis
- Perform a serum pregnancy test for all females of childbearing potential
- Collect blood samples for:
  - CBC and chemistry
  - ESR (done at site with the kit provided)
  - INR, PT, aPTT
  - Complement (C3, C4, and CH50)
  - CRP concentration
  - Serum immunoglobulins
  - Anti-SAN-300 antibodies
  - Serum SAN-300 concentration
  - Cytokine assessments (IFNγ, TNFα, IL-6)
  - Immunophenotyping panel (CD3/CD14/CD45RO/CD49a/CD45/CD4/CD19/CD8)
  - VLA-1 receptor occupancy
  - RF, ANA, and ACPA
- Conduct DAS28-CRP and ACR Core Set Measurements
- HAQ-DI
- MRI of the hand and wrist most clinically affected by RA (same as screening) should be performed on patients who are able to tolerate the MRI procedure.

## 10.3 Follow-up Period (Days 43 to 71)

### 10.3.1 Visit 8A (Day 50) and Visit 9A (Day 64)

Patients will come to the study site to have blood samples collected for:

- Serum SAN-300 concentration
- VLA-1 receptor occupancy
- Immunophenotyping panel
- Anti-SAN antibodies (Visit 9A only)
- Record all AEs and medications taken since previous visit

### 10.3.2 Visit 9 (Day 57) and Visit 10 (Day 71) or Early Withdrawal Visit (Follow-up Period)

Patients should arrive at the study site having fasted for 4 to 6 hours. The following procedures will be performed at Visits 9 and 10 or at the Early Termination Visit for patients who discontinue study participation during the Follow-up Period:

- Record all medications (prescription and OTC) taken by the patient since previous visit

- Record all AEs since previous visit
- Perform a physical examination (Visit 10 and Early Termination only)
- Record vital signs
- Collect urine for urinalysis (Visit 10 and Early Termination only)
- Collect blood samples for:
  - CBC and chemistry
  - ESR (done at site with the kit provided)
  - INR, PT, aPTT (Visit 10 and Early Termination only)
  - Complement (C3, C4, and CH50) (Visit 10 and Early Termination only)
  - CRP concentration
  - Serum immunoglobulins (Visit 10 and Early Termination only)
- Conduct DAS28-CRP and ACR Core Set Measurements
- Complete the HAQ-DI

# 11 PLANNED STATISTICAL METHODS

## 11.1 General Considerations

All endpoints in this study will be summarized by descriptive statistics. Descriptive statistics for continuous variables will include the mean, standard deviation, median, first and third quartiles, minimum, and maximum value; categorical variables will be presented as counts and percentages. All statistical tests will be conducted at the two-sided $\alpha = 0.05$ level of significance. All tests of binomial proportions will be conducted using the chi-square test unless more than one cell in a 2 x 2 table has an expected value of < 5, in which case the Fisher's Exact Test will be used. All tests of continuous variables will be conducted using the Wilcoxon Rank-Sum Test. For all efficacy endpoints, patients will be analyzed according to the treatment to which they were randomized. For all safety endpoints, patients will be analyzed according to the treatment they received. Parameters presented by "treatment group" will compare the 6 patients on SAN-300 from each cohort with the 10 pooled patients on placebo.

## 11.2 Determination of 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.

## 11.3 Analysis Populations

### 11.3.1 Intent-to-Treat Population

The Intent-to-Treat (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 ITT Population is the primary population for the analysis of all efficacy endpoints.

### 11.3.2 Safety Population

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.

### 11.3.3 Per Protocol Population

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

## 11.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group and will be presented for individual patients in data listings.

## 11.5 Safety Analysis

All AEs will be coded using MedDRA. The number and percentages of patients reporting at least one occurrence of each AE will be tabulated by system organ class and preferred term. The number and percentages of patients reporting at least one occurrence of each AE by system organ class and preferred term will also be tabulated by severity and by the relationship to study drug. For multiple occurrences of the same AE in a patient that differ in severity, the AE with the highest level of severity will be tabulated. For multiple occurrences of the same AE in a patient that differ in relationship to study drug (e.g., related and not related), the AE will be tabulated as related. All AEs for all patients will be presented in a data listing.

All other safety parameters will be summarized using descriptive statistics and presented by time point and treatment group. All other safety parameters will be presented for individual patients in data listings.

## 11.6 Pharmacokinetic Analysis

Population PK methods will be employed to estimate the relevant PK parameters for the population as well as for each individual patient who received SAN-300 and had at least one blood sample in which SAN-300 was quantifiable. The details of the population PK analysis will be documented in a Population Pharmacokinetic/Pharmacodynamic Analysis Plan.

PK parameters will be summarized using descriptive statistics and presented by time point and treatment group in tabular format. PK parameters for individual patients will be presented in data listings. Time-dependent SAN-300 concentrations will be presented in figure format.

## 11.7 Pharmacodynamic Analysis

PD parameters will be summarized using descriptive statistics and presented by time point and treatment group in tabular format. PD parameters will be summarized from baseline to each time point by treatment group. PD parameters for individual patients will be presented in data listings. Time-dependent PD parameters will be presented in figure format.

## 11.8 Efficacy Analysis

Efficacy will be compared for the SAN-300 dose groups (0.5, 1.0, 2.0 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 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. The percentages of patients achieving a DAS28-CRP $\leq 3.2$ and $< 2.6$ will be compared across treatment groups using the chi-square test.

All components of the ACR Core Set will be summarized using descriptive statistics and presented by time point and treatment group. The percentages of patients 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.

## 11.9 Other Laboratory Values

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. Laboratory parameters will be presented in figure format.

## 11.10 Interim Analysis

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

# 12 DATA HANDLING AND QUALITY ASSURANCE

## 12.1 Case Report Forms

As part of the responsibilities assumed by participating in the study, the Principal Investigator or Sub-investigators agree to maintain adequate case histories for the patients treated as part of the research under this protocol. The case histories include accurate eCRFs and source documentation. The primary source documents for this study will be the patients' medical records and research records maintained by the Investigators.

The Principal Investigator or Sub-investigator is responsible for ensuring that the clinical data required by the study protocol are carefully entered in the eCRFs. They are also responsible for checking that the data reported in the eCRFs correspond to those in the source files. To ensure legibility, the eCRFs will be entered in English. Data changes are documented and saved in an audit trail in the clinical trial database, and there is no deletion of entered data. In the interests of completeness of data acquisition, the questions which are repeated in each section of the eCRF should be answered in full, even if there are no changes from a previous examination. A reasonable explanation must be given by the Investigator for all missing data.

After data have been entered, reviewed, and edited and source data verification has been performed, completed eCRFs must be electronically signed by the Principal Investigator or Sub-investigator.

## 12.2 Monitoring of the Study

The study will be supervised by regional clinical research associates (CRAs). The CRAs will visit the Principal Investigator or Sub-investigator at each study facility at periodic intervals to review and discuss study progress. In addition, CRAs will maintain regular telephone, email, and letter contact with each study facility. The CRAs will maintain current personal knowledge of the study through observation, review of study records and direct access to source documentation, and discussion of the conduct of the study with the Principal Investigator and/or Sub-investigator and staff.

All aspects of the study will be carefully monitored by the CRO and Santarus for compliance with applicable government regulation with respect to current Good Clinical Practice (GCP) and current Standard Operating Procedures.

The eCRFs will be checked for completeness, plausibility, and consistency with source documents and any queries will be resolved by the Investigator.

## 12.3 Inspection of Records

Principal or Sub-investigators and institutions involved in the study will permit trial-related monitoring, audits, IEC/IRB review, and regulatory inspection(s). In the event of an audit, the Principal or Sub-investigator agrees to allow the Sponsor, representatives of the Sponsor, FDA, or other regulatory authorities access to all study records and source documentation.

The Principal Investigator or Sub-investigator should promptly notify the Sponsor and the CRO of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor.

## 12.4 Study Record Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Principal Investigator or Sub-investigator/institution as to when these documents no longer need to be retained.

# 13 ADMINISTRATIVE CONSIDERATIONS

The following administrative items are meant to guide the Principal Investigator and Sub-investigator in the conduct of the trial but may be subject to change based on industry and government Standard Operating Procedures or Working Practice Documents or Guidelines.

## 13.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient, except as necessary for monitoring and auditing by the Sponsor, its designee, Regulatory Authorities, or the IEC/IRB.

The Principal Investigator or Sub-investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

## 13.2 Independent Ethics Committee/Institutional Review Board Approval

ICH guidelines require that approval be obtained from an IEC/IRB before the participation of human patients in research studies. Before the study starts, the protocol, the ICF, advertisements to be used for patient recruitment, and any other written information regarding this study to be provided to the patient (or the patient's legal guardian) must be approved by the IEC/IRB. Documentation of all IEC/IRB approvals and of the IEC/IRB compliance with ICH Guideline E6 will be maintained by the site and will be available for review by the Sponsor or its designee. All IEC/IRB approvals should be signed by the IEC/IRB Chairman or designee and must identify the IEC/IRB name and address, the clinical protocol by title and/or protocol number and the date approval and/or favorable opinion was granted.

The Principal Investigator or Sub-investigator is responsible for obtaining notification of continued review of the clinical research at intervals not exceeding one year or otherwise specified by the IEC/IRB. The Principal Investigator or Sub-investigator must supply the Sponsor or its designee with written documentation of annual IEC/IRB review and approval of the clinical research.

## 13.3 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the Sponsor or its designee. Amendments to the protocol must be submitted in writing to the Principal Investigator's IEC/IRB for approval before patients are enrolled into an amended protocol.

## 13.4 Informed Consent

Written informed consent will be obtained from each patient before entering the study or before performing any unusual or non-routine procedure that involves risk to the patient. An agreed ICF, reviewed by the Sponsor and/or its designee, will be submitted by the Principal Investigator or

Sub-investigator to his or her IEC/IRB for review and approval before the start of the study. If the ICF is revised during the study, all active participating patients must sign the revised ICF.

Before recruitment and enrollment, each prospective patient will be given a full explanation of the study and allowed to read the IEC/IRB-approved ICF. Once the Principal Investigator or Sub-investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the ICF. The informed consent process will be briefly described in the source documents for each patient. The original and any amended signed and dated informed consent documents must be retained at the study site; and a copy must be given to the patient or the patient's legally authorized representative(s). Note: The ICF for this study will be provided as a separate document.

## 13.5 Protocol Violations and Deviations

The Principal Investigator or Sub-investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The Principal Investigator or Sub-investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to trial patients without prior IEC/IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendment(s) should be submitted to the IEC/IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol can be an unintended and/or unanticipated departure from the procedures and/or processes approved by the Sponsor and the IEC/IRB and agreed to by the Principal Investigator or Sub-investigator. Deviations usually have an impact on individual patients or a small group of patients and do not involve inclusion/exclusion or primary endpoint criteria. A protocol violation occurs when there is non-adherence to the protocol that results in a significant, additional risk to the patient, when the patient or Principal Investigator or Sub-investigator has failed to adhere to significant protocol requirements (e.g., an inclusion/exclusion criterion) and the patient was enrolled without prior Sponsor approval, or when there is non-adherence to ICH-GCP guidelines.

Protocol violations and deviations will be documented by the Principal Investigators or Sub-investigators. The IEC/IRB should be notified of protocol violations and substantial deviations that impact on the safety and integrity of the study in a timely manner. Other deviations from the protocol must also be reported to the IEC/IRB according to their requirements.

## 13.6 Study Reporting Requirements

By participating in this study the Principal Investigator or Sub-investigator agrees to submit reports of SAEs and pregnancies according to the timeline and method outlined in the protocol. In addition, the Principal Investigator or Sub-investigator agrees to submit annual reports to his/her IEC/IRB as appropriate. The Principal Investigator or Sub-investigator also agrees to provide the Sponsor with an adequate report of the Principal Investigator's or Sub-investigator's participation in the study.

## 13.7 Financial Disclosure and Obligations

Principal Investigators and Sub-investigators are required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. Note: this study may be used as part of a US submission

package and hence the appropriate CFRs need to apply to all study sites. In addition, the Principal Investigator and Sub-investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study

Neither the Sponsor nor study CROs are financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor the study CROs are financially responsible for further treatment of the patient's disease.

## 13.8 Investigator Documentation

Before beginning the study, the Principal Investigator will be asked to comply with ICH E6 8.2 guidelines and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- An original signed Investigator's Statement page of the protocol (Appendix 9)
- An IEC/IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient
- IEC/IRB approval
- FDA 1572 form
- Curriculum vitae (CV) for the Principal Investigator and each Sub-investigator. Current licensure must be noted on the CV. They will be signed and dated by the Principal Investigators and Sub-investigators at study start-up, indicating that they are accurate and current
- Financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements required under Part 54 of Title 21 of the CFR. In addition, the Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study

## 13.9 Study Conduct

The Principal Investigator agrees that the study will be conducted according to the principles of the ICH E6 Guideline on GCP and the ethical principles that have their origins in the WMA Declaration of Helsinki. The Principal Investigator will conduct all aspects of this study in accordance with all national and local laws or regulations.

## 13.10 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with Investigators to determine how the manuscript is written and edited, the number and order of authors, the publishing journal/newsletter to which it will be submitted, and other related issues. Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

# 14 REFERENCE LIST

Aletaha D, Neogi T, Silman A, Funovits J, Felson D, Bingham C, et al. 2010 Rheumatoid arthritis classification criterion. Arthritis & Rheumatism. 2010;62(9):2569-2581.

Ben-Horin S, Goldstein I, Koltakov A, Langevitz P, Ehrenfeld M, et al. The effect of blockade of tumor necrosis factor alpha on VLA-1+ T-cells in rheumatoid arthritis patients. J Clin Immunol. 2007;27(6):580-588.

Becker HM, Rullo J, Chen M, Ghazarian M, Bak S, Xiao H. α1β1 integrin-mediated adhesion inhibits macrophage exit from peripheral inflammatory lesion. J Immunol. 2013;190:4305-4314.

Fleishmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. New Eng J Med. 2012;367:495-507.

Food and Drug Administration. Guidance for industry. Clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA). 1999.

Hochberg M, Chang R, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. Arthritis & Rheumatism. 1992;35(5):498-502.

Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC. Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD study. Ann Rheum Dis. 2009;68:789-796.

Østergaard M, Peterfy C, Conaghan P, McQueen F, Bird P, Ejbjerg B, et al. OMERACT Rheumatoid Arthritis Magnetic Resonance Imaging Studies. Core set of MRI acquisitions, joint pathology definitions, and the OMERACT RA-MRI scoring system. J Rheumatol. 2003;30(6):1385-1386.

Peterfy CG, DiCarlo JC, Olech E, Bagnard MA, Gabriele A, Gaylis N. Evaluating joint-space narrowing and cartilage loss in rheumatoid arthritis by using MRI. Arthritis Res Ther. 2012;14(3):R131.

Pribila JT, Quale AC, Mueller KL, Shimizu Y. Integrins and T cell-mediated immunity. Ann Rev Immunol. 2004.22:157-180.

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson NF, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report-second National Institute of Allergy and Infectious Disease/Food Allergy and Anaplylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-397.

Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care & Research. 2012;64:625-639.

Weinblatt ME, Kavanaugh A, Genovese MC, Musser TK, Grossbard EB, Magilavy DB. An oral spleen tyrosine kinase (syk) inhibitor for rheumatoid arthritis. New Eng J Med. 2010;363:1303-1312.

## Appendix 1 Atypical or Opportunistic Infections

1. Mycobacterial infections: tuberculosis (TB), nontuberculosis mycobacteria
2. Viral infections: progressive multifocal leukoencephalopathy (PML) (JC [John Cunningham] virus), hepatitis B virus, Cytomegalovirus, and disseminated Herpes zoster
3. Systemic/invasive fungal infections: coccidioidomycosis, aspergillosis, cryptococcosis, histoplasmosis, blastomycosis, Pneumocystis jirovecii, and invasive or systemic candidiasis
4. Protozoal infections: malaria (Plasmodium)
5. Other infections: nocardiosis

## Appendix 2 Schedule of Assessments for Study C2013-0302

| | Screening (21 days) | Double-blind Treatment Period (42 days [3 to 6 doses]) | | | | | | | | | | 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:** | **Day -21 to -1** | **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** | **End-of-Treatment Visit** | | **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 |
| CBC, Chemistry Panel | X | X | | X | X | X | X | | X | | X | X | X |
| UA | X | X | | | | | | | | | X | | X |
| INR, PT, aPTT, Complement | | X | | | | | | | | | X | | X |

| | Screening (21 days) | Double-blind Treatment Period (42 days [3 to 6 doses]) | | | | | | | | | | 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:** | **Day -21 to -1** | **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** | **End-of-Treatment Visit** | | **Exit Visit** |
| Tryptase, histamine[e] | | X | | | | | | | | | | | |
| Serum Immunoglobulins | | X | | | | | | | | | X | | X |
| 12-Lead ECG | 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.

## Appendix 3 Specialty PK and PD Laboratory Testing Schedule

For all cohorts, blood samples for PK and PD analysis will be collected at the specified times predose and postdose, at random times intermittently scheduled between dosing visits, and at visits within the Follow-up Period. A predose sample will be collected before every study drug administration. A postdose sample will be collected at 1 h after the first study drug administration on Day 1 and at 1 h after the last study drug administration on Day 36. In addition, all patients will return to the study site at random times within the specified intervals between certain study drug administration visits for additional sample collection. Finally, samples will be collected for all cohorts after the end of all drug dosing, on Days 43, 50, and 64.

| **SC Dose #:** | **SC #1** | | | | **SC #2** | | **SC #3** | **SC #4** | **SC #5** | | **SC #6** | | | | **End-of-Treatment Visit** | **Follow-up Period** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Week:** | **Wk 1** | | | | **Wk 2** | | **Wk 3** | **Wk 4** | **Wk 5** | | **Wk 6** | | | | **Wk 7** | **Wk 8** | **Wk 10** |
| **Visit:** | **Visit 2** | | **Visit 2A** | **Visit 2B** | **Visit 3** | **Visit 3A** | **Visit 4** | **Visit 5** | **Visit 6** | **Visit 6A** | **Visit 7** | | **Visit 7A** | **Visit 7B** | **Visit 8** | **Visit 8A** | **Visit 9A** |
| **Day:** | **Day 1** | **Day 1** | **Day 2-4** | **Day 5-7** | **Day 8** | **Day 9-11** | **Day 15** | **Day 22** | **Day 29** | **Day 30-32** | **Day 36** | **Day 36** | **Day 37-39** | **Day 40-42** | **Day 43** | **Day 50** | **Day 64** |
| **Timing:** | **Pre-Dose** | **1 h Post-Dose** | **Random** | **Random** | **Pre-Dose** | **Random** | **Pre-Dose** | **Pre-Dose** | **Pre-Dose** | **Random** | **Pre-Dose** | **1 h Post-Dose** | **Random** | **Random** | | | |
| PK | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Cyto | X | | | | X | | | | X | | X | X | | | X | | |
| RO | X | | X | X | X | | X | | X | X | X | | X | X | X | X | X |
| IPT | X | | | | X | | X | | X | | X | | | | X | X | X |
| ADA | X | | | | X | | | | | | | | | | X | | X |

Abbreviations: ADA = anti-drug (SAN-300) antibody; Cyto = cytokines (IFNγ, TNFα, IL-6); IPT = immunophenotyping panel (CD3, CD4, CD8, CD45, CD45RO, CD14, CD19, and CD49α); PK = pharmacokinetics; RO = receptor occupancy (VLA-1); SC = subcutaneous. Note: At each visit, AEs and medications taken should be recorded.

# Appendix 4 ACR / EULAR RA Classification Criteria

## ACR / EULAR RA Classification Criteria (2010)

| | |
|---|---|
| Target population (Who should be tested?):<br>1. Patients who have at least one joint with definite clinical synovitis (swelling)[1]<br>2. Patients whose synovitis is not better explained by another disease[2] | |
| Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥ 6/10 is needed for classification of a patient as having definite RA)[3] | |
| A. Joint involvement[4] | |
| 1 large joint[5] | 0 |
| 2-10 large joints | 1 |
| 1-3 small joints (with or without involvement of large joints)[6] | 2 |
| 4-10 small joints (with or without involvement of large joints) | 3 |
| > 10 joints (at least 1 small joint)[7] | 5 |
| B. Serology (at least 1 test result is needed for classification)[8] | |
| Negative RF and negative ACPA | 0 |
| Low-positive RF or low-positive ACPA | 2 |
| High-positive RF or high-positive ACPA | 3 |
| C. Acute-phase reactants (at least 1 test result is needed for classification)[9] | |
| Normal CRP and normal ESR | 0 |
| Abnormal CRP or abnormal ESR | 1 |
| D. Duration of symptoms[10] | |
| < 6 weeks | 0 |
| ≥ 6 weeks | 1 |

Abbreviations: ACPA = anti-citrunillated peptide antibody; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; RA = rheumatoid arthritis; RF = rheumatoid factor.

[1] The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of RA with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria, should be classified as having RA.

[2] Differential diagnoses vary among patients with different presentations but may include conditions such as systemic lupus erythematosus, psoriatic arthritis, and gout. If it is unclear which of the relevant differential diagnoses to consider, an expert rheumatologist should be consulted.

[3] Although patients with a score of < 6/10 are not classifiable as having RA, their status can be reassessed, and the criteria might be fulfilled cumulatively over time.

[4] Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints, and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement.

[5] "Large joints" refers to shoulders, elbows, hips, knees, and ankles.

[6] "Small joints" refers to the metacarpophalangeal joints, proximal interphalangeal joints, second through fifth metatarsophalangeal joints, thumb interphalangeal joints, and wrists.

[7] In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (e.g., temporomandibular, acromioclavicular, sternoclavicular, etc.).

[8] Negative refers to International Unit (IU) values that are less than or equal to the upper limit of normal (ULN) for the laboratory and assay; low-positive refers to IU values that are higher than the ULN but ≤ 3 times the ULN for the laboratory and assay; high-positive refers to IU values that are > 3 times the ULN for the laboratory and assay. Where RF information is only available as positive or negative, a positive result should be scored as low-positive for RF.

[9] Normal/abnormal is determined by local laboratory standards.

[10] Duration of symptoms refers to patient self-report of the duration of signs or symptoms of synovitis (e.g., pain, swelling, tenderness) of joints that are clinically involved at the time of assessment, regardless of treatment status.

Source: Aletaha, 2010

# Appendix 5 ACR Revised Criteria for Classification of Global Functional Class in RA

## ACR Revised Criteria for Classification of Global Functional Class in RA (1991)

| Class | Definition |
|---|---|
| Class I: | Completely able to perform usual activities of daily living (self-care, vocational, and avocational)[1] |
| Class II: | Able to perform usual self-care and vocational activities, but limited in avocational activities. |
| Class III: | Able to perform usual self-care activities, but limited in vocational and avocational activities. |
| Class IV: | Limited in ability to perform usual self-care, vocational and avocational activities. |

[1] Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Vocational (school, work, homemaking) and avocational (recreational and/or leisure) activities are patient-desired and age- and sex-specific.

Source: Hochberg, 1992

## Appendix 6 Swollen and Tender Joint Assessment

An experienced assessor will evaluate joint counts.

**Joints to be Assessed for Swelling and Tenderness**

The joints to be assessed for tenderness (68 joints) and swelling (66 joints) consist of the following:

- Temporomandibular joint
- Sternoclavicular joint
- Acromioclavicular joint
- Shoulders*
- Elbows*
- Wrists*
- Interphalangeal on digit 1*
- Distal interphalangeal joints on digits 2 – 5
- Proximal interphalangeal joints on digits 2 – 5*
- Metacarpophalangeal joints on digits 1 – 5*
- Hips (tenderness only)
- Knees*
- Ankles
- Metatarsals
- Interphalangeal joints on toes 1 – 5
- Metatarsophalangeal joints on toes 1 – 5

Joints assessed for swelling are the same, with the exception of the hips, which are excluded.

* The 28 joints used to calculate the DAS28.

## Appendix 7 HAQ-DI Total Score and Individual Dimensions

The physical functional status of the patient will be assessed using the HAQ. This is a widely used patient self-report tool which assesses the degree of difficulty a person has had in accomplishing tasks in eight functional areas, over the previous week.

The eight categories assessed by the HAQ are

(1) dressing and grooming,

(2) rising,

(3) eating,

(4) walking,

(5) hygiene,

(6) reach,

(7) grip,

(8) common daily activities.

For each of these categories, patients report the amount of difficulty they have in performing two or three specific activities. There are four possible responses for the HAQ questions: without ANY difficulty (0), with SOME difficulty (1), with MUCH difficulty (2) and UNABLE to do (3). The scores for each of the eight categories are calculated. The HAQ is then derived by adjusting the score for each of these categories, if necessary, based upon the patient's use of an aid, device, or assistance for that category, totaling the sum of the category scores and dividing by the number of categories answered. The HAQ score can range between 0 and 3.

## Appendix 8 Scoring the Magnetic Resonance Imaging Scans

Each MRI will be scored using the published OMERACT RA MRI Score (RAMRIS) (Østergaard, 2003) and cartilage loss scoring (Peterfy, 2012).

**Scoring of Bone Erosion:**
Erosion will be scored at the following 25 locations: the distal radius and ulna, the eight carpal bones, including the trapezium, trapezoid, capitate, hamate, pisiform, scaphoid, lunate, and triquetrum, as well as the five metacarpal bases, the five metacarpal heads, and the five proximal phalangeal bases.

Bone erosion is scored 0-10, according to the proportion (in increments of 10%) of erosion of articular bone: 0: 0%, 1: 1%-10%, 2: 11%-20%, ……..10: 91%-100%

**Scoring of Osteitis:**
Osteitis will be scored at the same 25 bone locations as erosion: the distal radius and ulna, the eight carpal bones, including the trapezium, trapezoid, capitate, hamate, pisiform, scaphoid, lunate, and triquetrum, as well as the five metacarpal bases, the five metacarpal heads, and the five proximal phalangeal bases.

Osteitis is scored 0-3 according to the proportion (in increments of 33%) of involvement of original articular bone: 0: 0%, 1: 1%-33%, 2: 34%-66%, 3: 67%-100%

**Scoring of Synovitis:**
Synovitis will be scored at the following eight joint locations: the distal radioulnar joint, the radiocarpal joint, the intercarpal and carpometacarpal joints together, and the five metacarpophalangeal (MCP) joints.

Synovitis is scored 0-3 according to the proportion of volume enhancement:
0: 0%, 1: 1%-33%, 2: 34%-66%, 3: 67%-100%

**Scoring of Cartilage Loss:**
Cartilage loss will be assessed in the MRI images of the hand with the most clinically significant synovitis (25 joints). Joints that will be assessed include MCP joints 1-5, proximal inter-phalangeal joints (1-5), as well as the following joints of the wrist:

- Four carpometacarpal (CMC) joints 2-5
- Scaphotrapezoid joint
- Scaphotrapezium joint
- Trapezoid-trapezium joint
- Radioscaphoid joint
- Radiolunate joint
- Lunate-triquetrum joint
- Hamate-triquetrum joint
- Capitate-hamate joint
- Capitate-lunate joint
- Scaphocapitate joint
- Capitate-trapezoid joint

The following joints are *not* scored: CMC joint 1, scapholunate joint, triquitropisiform joint, and the radioulnar joint.

Cartilage loss is scored 0-4 according to the following scale:

| Score | Definition |
|---|---|
| 0 | Normal |
| 0.5 | Equivocal |
| 1.0 | Mild (definitive narrowing) |
| 1.5 | Mild-moderate |
| 2.0 | Moderate |
| 2.5 | Moderate-severe, including partial bone-on-bone narrowing |
| 3.0 | Severe, complete bone-on-bone narrowing (bilateral cartilage denuding) |
| 3.5 | Partial ankylosis |
| 4.0 | Complete ankylosis |

## Appendix 9 Investigator's Signature

**Study Title:** A Randomized, Double-blind, Placebo-Controlled, Multiple Ascending Dose Study to Evaluate the 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 Drug(s)

**Study Number:** C2013-0302

**Final Date:** 15 Sep 2014

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

<enter name and credentials>
<enter title>
<enter affiliation>

<enter address>

<enter phone number>