16 APPENDICES

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

The latest version of the protocol used during the study is provided in this section. Previous versions of the protocol are available on request.

Clinical Study Protocol (NI071F2) Version 4.0 dated 09 August 2017

Nichi-Iko Pharmaceutical Co., Ltd.

FINAL CLINICAL STUDY PROTOCOL

Protocol Number: NI071F2

A Randomized, Double-Blind, Multicenter, 3-Stage, Efficacy and Safety Study of NI-071 and US-Licensed Remicade® (Infliximab) for the Treatment of Patients with Rheumatoid Arthritis

IND Number:	126520
EudraCT Number:	2016-001064-11
Name of Product:	NI-071 (proposed infliximab biosimilar)
Phase of Development:	3
Indication:	Rheumatoid Arthritis
Sponsor Contact:	PPD, PhD PPD Nichi-Iko Pharmaceutical Co., Ltd. 1-6-21 Sogawa, Toyama City, Toyama Prefecture, Japan Tel: PPD Fax: PPD
Protocol Version:	Final Version 4.0
Protocol Date:	09 August 2017

SPONSOR APPROVAL PAGE

PPD

PPD PhD PPD

PPD

Date: PPD

PPD

PPD PhD

PPD

Date: PPD

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree:

- To assume responsibility for the proper conduct of the study at this site.
- To conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by Nichi-Iko Pharmaceutical Co., Ltd.
- Not to implement any changes to the protocol without written agreement from Nichi-Iko Pharmaceutical Co., Ltd., and prior review and written approval from the Regulatory Authorities and the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), except where necessary to eliminate an immediate hazard to patients.
- That I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Nichi-Iko Pharmaceutical Co., Ltd., including, but not limited to, the current Investigator's Brochure (IB).
- That I am aware of, and will comply with, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and all applicable regulatory requirements.
- To ensure that all persons assisting me with the study are adequately informed about the Nichi-Iko Pharmaceutical Co., Ltd., study drug and of their study-related duties and functions as described in the protocol.

Signature: _____ Date: _____

Name (print): _____
Principal Investigator

Site Number: _____

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PK and Immunogenicity Laboratory:	To be provided in the laboratory manual

1 SYNOPSIS

Title of Study:	A Randomized, Double-Blind, Multicenter, 3-Stage, Efficacy and Safety Study of NI-071 and US-Licensed Remicade® (Infliximab) for the Treatment of Patients with Rheumatoid Arthritis
Protocol Number:	NI071F2
Investigators/Study Sites:	Approximately 160 sites in the United States (US; including Puerto Rico), Western Europe, and Eastern Europe.
Phase of Development:	3
Objectives:	**Stage 1 (Biosimilarity Stage)** **Primary:** • To investigate the biosimilarity of NI-071 (proposed infliximab biosimilar) and US-licensed Remicade® (infliximab; Remicade-US) in terms of efficacy in patients with rheumatoid arthritis (RA) not adequately responding to methotrexate (MTX), by determining the percentages of patients achieving ACR20-CRP (a 20% improvement from baseline in the American College of Rheumatology [ACR] core set criteria using C-reactive protein [CRP] as the acute-phase reactant) **Secondary:** • To evaluate safety and immunogenicity of NI-071 and Remicade-US • To evaluate efficacy based on other rates of improvement in the ACR criteria, on the DAS28 (disease activity score involving 28 joints) and the RAPID3 (routine assessment of patient index data 3), and on changes in health-related quality of life **Stage 2 (Interchangeability Stage)** **Primary:** • To investigate the interchangeability between NI-071 and Remicade-US by evaluating key pharmacokinetic (PK) parameters in each treatment group following treatment switches **Secondary:** • To evaluate the safety, efficacy, and immunogenicity of NI-071 and Remicade-US **Stage 3 (Safety Follow-up Stage)** **Primary:** • To evaluate the safety of long-term treatment (follow-up through Week 62)
Study Design:	This Phase 3, randomized, double-blind, multicenter, biosimilarity, interchangeability, and safety study is designed to evaluate NI-071 versus Remicade-US for the treatment of

	patients with RA. Following a screening period, there will be 3 stages: the biosimilarity stage (Stage 1), the interchangeability stage (Stage 2), and the safety follow-up stage (Stage 3). The screening period, approximately 4 weeks long for each patient, will be used to assess eligibility. At baseline (Week 0), approximately 585 patients who are eligible will be randomized in a 2:1 ratio to the Remicade-US and NI-071 groups, respectively. This initial randomization will be stratified by CRP level (≤2, >2 mg/dL). During Stage 1, patients will receive their randomized treatment at Weeks 0, 2, 6, and 14. Primary biosimilarity efficacy assessments (specifically ACR20-CRP) will be performed at Week 22. During Stage 2, at Week 22, patients in the original Remicade-US group are re-randomized (1:1) to a Remicade-US group and a Switch group. The Switch group will receive NI-071 at Week 22, Remicade-US at Week 30, and NI-071 at Weeks 38, 46, and 54; the Remicade-US group will continue to receive Remicade-US from Week 22 through Week 54 every 8 weeks. The original NI-071 group will continue to receive NI-071 from Week 22 through Week 54 every 8 weeks. To evaluate interchangeability, a full PK similarity analysis (specifically AUC_{tau} [area under the concentration-time curve over the dosing interval] and C_{max} [maximum concentration]) will be performed for all treatment groups from samples drawn at 11 time points from pre-dose Week 46 to pre-dose Week 54. During Stage 3, the last dose of study treatment will be given at Week 54, and patients will return for 2 additional safety follow-up visits through Week 62 (end of study visit). Efficacy and safety evaluations, including assessments of anti-drug antibodies (ADAs), will be performed throughout the study. In addition, samples for determining trough concentrations will be collected prior to each infusion in the study and at the end of the study (Week 62).
Selection of Patients:	**Inclusion Criteria:** 1. Patients with a diagnosis of RA as defined by the 2010 ACR and European League Against Rheumatism (EULAR) classification criteria[8] 2. Patients have active RA, as confirmed by the following criteria: • ≥6 swollen joints and ≥6 tender joints at screening and baseline (28-joint count), and • Either CRP ≥0.7 mg/dL (≥7.0 mg/L) or erythrocyte sedimentation rate (ESR) ≥28 mm/h at screening

	3. Patients taking MTX (oral or parenteral) for at least 3 months prior to screening and at a stable dose of between 10 and 25 mg/week for at least 8 weeks. Concomitant folic/folinic acid at a dose of at least 5 mg/week is to be taken during the study; patients can start treatment with folic/folinic acid at screening if not already receiving it. 4. If the patient is currently taking non-steroidal anti-inflammatory drugs (NSAIDs), the patient must be on a stable dose for at least 4 weeks prior to screening and during the study. 5. Patients with a body weight of ≥40 kg and ≤120 kg at screening 6. Patients who are ≥18 and ≤75 years of age at screening 7. Women of childbearing potential (WOCBP) and men (if their sexual partners are WOCBP) must use at least 1 highly effective form of birth control throughout the study and for 6 months after the last dose of study treatment. Highly effective methods of birth control include true sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk, in line with the preferred and usual lifestyle of the patient), surgery (bilateral tubal ligation or occlusion, vasectomized partner), progestogen-only or estrogen/progestogen hormonal contraceptive associated with inhibition of ovulation (oral, patch, injectable, implantable, or intravaginal), intrauterine device (IUD), or intrauterine hormone-releasing system (IUS). See Section 8.7 for a definition of WOCBP and a complete description of contraceptive requirements. 8. Patients with the ability to read and understand the informed consent form and to provide written consent **Exclusion Criteria:** 1. Patients who are rated as Class IV according to the 1991 ACR revised criteria for classification of global functional status (see Section 16, Appendix 1) 2. Patients who have received disease-modifying antirheumatic drugs (DMARDs), other than MTX, within a period prior to screening shorter than the washout period appropriate to the pharmacodynamic profile of the specific drug; see Section 16, Appendix 2 for a list of DMARDs and their washout periods. (These patients may be re-screened after the appropriate washout period.) 3. Patients who have received immunosuppressive drugs within 4 weeks prior to screening. Patients on a stable

	dose of oral corticosteroids (≤10 mg/day prednisone or equivalent) for ≥4 weeks prior to screening are permitted. 4. Patients who have received intra-articular, intramuscular, intravenous, or epidural injection of corticosteroids within 4 weeks prior to screening 5. Patients who have received intra-articular sodium hyaluronate injections within 4 weeks prior to screening 6. Patients who have received surgical therapy for RA such as synovectomy or arthroplasty within 6 months prior to screening 7. Patients who have received arthrocentesis within 4 weeks prior to screening 8. Patients who have had prior treatment with infliximab 9. Patients who have had prior treatment with more than 1 biological drug other than infliximab (e.g., adalimumab, rituximab, abatacept, etanercept) for RA either as part of clinical management or during a clinical study. Patients who have had prior treatment with more than 1 protein kinase inhibitor (e.g., tofacitinib) for RA either as part of clinical management or during a clinical study. Patients who have had prior treatment with 1 biological drug AND 1 protein kinase inhibitor are allowed in the study. 10. Patients who have had prior treatment with a tumor necrosis factor alpha (TNF-α) inhibitor for RA who had lack of efficacy as per clinical judgment (primary failure). Primary failure is defined as never having achieved an adequate response, whereas secondary failure is the loss of response over time. Patients who have received prior treatment with no more than 1 biological DMARD and who have received not more than 1 prior TNF-α inhibitor (other than infliximab) and have failed it because of loss of efficacy (secondary failure) or intolerance (e.g., mild injection site reactions) are allowed in the study. Patients who have discontinued TNF-α inhibitors for RA (other than infliximab) because their insurance no longer covered the cost of treatment or they could no longer afford the cost or copays for the treatment are allowed in the study. 11. Patients who had prior treatment with cyclophosphamide or other cytotoxic agents 12. Patients who received investigational drugs in other clinical studies within 12 weeks or 5 half-lives of the

	drug prior to screening, whichever is longer 13. Patients with a concomitant or past history of autoimmune connective tissue diseases other than RA, for example, systemic lupus erythematosus, Sjogren's syndrome, polymyositis, dermatomyositis, and mixed connective tissue disease 14. Patients with a history of hypersensitivity to the components of NI-071 or mouse-derived protein (e.g., mouse, chimeric, and humanized antibody) 15. Patients with the following concomitant or past history: • Chronic or recurrent infectious disease (e.g., bronchiectasis, sinusitis) • Demyelinating disease (e.g., multiple sclerosis) • Presence of New York Heart Association (NYHA) Class III/IV heart failure (see Section 12.5) • Lymphoproliferative disorder (e.g., Epstein-Barr virus [EBV]-related lymphoproliferative disorder, lymphoma, or leukemia) or myelodysplastic syndrome • Cancer other than successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix • Interstitial lung disease 16. Presence of chronic or acute infection at screening, including positive result for active tuberculosis (TB) (e.g., positive QuantiFERON® test result without any prior history of active or latent TB and without evidence of active infection) where the patient is not willing to undergo prophylactic treatment. (These patients may be re-screened after appropriate treatment for TB [see Section 12.3]). 17. Patients with an acute infection requiring parenteral antibiotics within 4 weeks of study dosing or requiring oral/topical antibiotics within 2 weeks of study dosing. (These patients may be re-screened after the appropriate washout period.) 18. Patients with mycobacterial infection or opportunistic infection (e.g., cytomegalovirus infection or invasive fungal infection such as histoplasmosis, blastomycosis, or coccidiomycosis) or who have resided in or traveled to regions where such infections are prevalent within 6 months prior to the initial administration of the investigational drug 19. Patients who have active or past infection or suspected infection in prosthetic joints that have not been removed or replaced

	20. Patients with positive results of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C antibody (HCV Ab), and/or human immunodeficiency virus antibody (HIV Ab) tests at screening (excluding patients who are tested positive for HBsAb alone due to a hepatitis B vaccination) 21. Patients who received a live vaccine within 12 weeks prior to study dosing, or who plan to receive a live vaccine during the study period or within 6 months after the last dose of study treatment. (If received prior to study dosing, these patients may be re-screened after the appropriate washout period.) 22. Patients with laboratory test results at screening that meet any of the following reference levels: • Hemoglobin ≤8.5 g/dL • White blood cells (WBCs) ≤3,500/mm^3 • Lymphocytes ≤1,000/mm^3 • Platelet count ≤100,000/mm^3 • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ upper limit of normal (ULN) x 1.5 • Serum creatinine ≥ULN x 1.5 • Glycated hemoglobin (HbA1c) ≥9.0% • Positive anti-double-stranded deoxyribonucleic acid (anti-dsDNA) assay • β-D-glucan ≥80 pg/mL (positive) 23. History of clinically significant cardiac, respiratory, renal, hepatic, hematologic, gastrointestinal, neurologic, endocrinologic, psychiatric, or any other uncontrolled medical illness 24. Female patients who are pregnant, wish to become pregnant, or are breastfeeding 25. Male patients who plan to donate sperm during the study or within 6 months after the last dose. Female patients who plan to donate eggs or undergo in vitro fertilization treatment during the study or within 6 months after the last dose. 26. Patients who are taking part in other clinical studies at screening or planning to take part in other clinical studies during the study period 27. Patients with a drug or alcohol dependence 28. Patients who are determined by the Investigator to be unsuitable for study enrollment for other reasons
Planned Sample Size:	The sample size required to be randomized in Stage 1 was derived with consideration of the required sample size needed

	for PK analysis at the end of Stage 2 and assumes a 25% drop-out of patients during Stages 1 and 2. Stage 3 will follow patients for safety after the final dose and does not have sample size requirements. To show PK similarity, the 90% geometric confidence intervals (CIs) of the ratio (Switch/Remicade-US) of the least squares means from the analysis of variance (ANOVA) of the ln-transformed AUC_{tau} and C_{max} must be within 80.00% and 125.00%. For the PK interchangeability analysis at the end of Stage 2, assuming coefficients of variation (CVs) of 49% and 33% for AUC_{tau} and C_{max}, respectively, and CIs of the ratios between 95% and 105%, at least 109 patients per treatment group are required for an 80% powered trial. In order to meet this Stage 2 requirement, in Stage 1 (at Week 0), approximately 585 patients are expected to be randomized in a ratio of 2:1 to Remicade-US (390 patients) and NI-071 (195 patients). This sample size will provide over 90% power to test for equivalence, using an asymmetric margin (-12%, 15%) and a two 1-sided test (TOST) analysis with α=0.05 for each 1-sided statistical test. Greater than 90% power is achieved when the ACR20-CRP response rate for Remicade-US at Week 22 is assumed to be 79.4% (the Remicade-US ACR20-CRP result at Week 22 from Study NI071F1 using the study's modified intent-to-treat population). Assuming a 25% drop-out rate during Stage 1, at least 292 patients in the Remicade-US group and 146 patients in the NI-071 group are expected to complete Stage 1 of the study. In Stage 2 (at Week 22), patients in the original Remicade-US group (about 292 patients) will be re-randomized in a 1:1 ratio to a Remicade-US group (146 patients) and a Switch group (146 patients). Assuming a 25% drop-out rate during Stage 2, approximately 109 patients per treatment group will be available for the PK analysis at the end of Stage 2.
Investigational Therapy:	NI-071 (proposed infliximab biosimilar) is provided as a white lyophilized pellet in a vial. Each 20-mL vial contains 100 mg of NI-071 for a final reconstitution volume of 10 mL. NI-071 is to be administered by IV infusion at a dose of 3 mg/kg at Weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54.
Reference Therapy:	Remicade-US (infliximab) is provided as a white lyophilized pellet in a vial. Each 20-mL vial contains 100 mg of Remicade-US for a final reconstitution volume of 10 mL. Remicade-US is to be administered by IV infusion at a dose of 3 mg/kg at Weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54.

Switch Therapy:	Remicade-US and NI-071, administered by IV infusion at a dose of 3 mg/kg. In Stages 2 and 3, the Switch group will receive NI-071 at Week 22, Remicade-US at Week 30, and NI-071 at Weeks 38, 46, and 54.
Treatment Duration:	The approximate maximum duration of treatment for each patient is 55 weeks (Week 0 through 54), and the approximate maximum duration of the study is 67 weeks (screening of 4 weeks, treatment of 55 weeks, follow-up of 8 weeks).
Criteria for Evaluation:	**Clinical Efficacy:** Clinical efficacy will be assessed by determining ACR core set values (tender joint count, swollen joint count, patient pain assessment, patient global assessment of disease activity, physician global assessment of disease activity, patient-completed Health Assessment Questionnaire Disability Index [HAQ-DI], CRP, and ESR) at specific visits; the DAS28-CRP and DAS28-ESR scores (DAS28 scores calculated with CRP and ESR values, respectively) at specific visits; the RAPID3 scores at specific visits; and the Medical Outcome Study 36-Item Short-Form Health Survey (SF-36) scores at specific visits. ACR20, ACR50, and ACR70 response rates will be evaluated and are defined as the percentage of patients having 20%, 50%, and 70% improvement from Week 0 (baseline) scores; these response rates will be determined using CRP changes (e.g., ACR20-CRP) and ESR changes (e.g., ACR20-ESR). Biosimilarity will be based on the ACR20-CRP at Week 22. **Pharmacokinetics:** Interchangeability will be assessed from full PK sampling and similarity analysis (specifically AUC_{tau} and C_{max}) during the dosing interval of Weeks 46 to 54. The following samples will be taken for determining the full PK profile: Week 46 pre-dose, 1 h after infusion start, at the end of infusion (EOI), at 4 h and 24 h after infusion start, and at 4 days, 7 days (Week 47), 14 days (Week 48), 28 days (Week 50), 42 days (Week 52), and 56 days (Week 54) post-dose. **Safety:** Safety will be assessed by adverse event (AE) reporting, physical examinations, vital signs, electrocardiograms (ECGs), clinical laboratory values, and immunogenicity assessments. Blinded patient safety data will be monitored on a monthly basis by the clinical team to ensure patient safety.

Study Endpoints:	**Clinical Efficacy** Primary endpoint: • ACR20-CRP at Week 22 Secondary endpoints: • Change from baseline in DAS28-CRP and DAS28-ESR scores • ACR20-CRP (at time points other than Week 22), ACR20-ESR, ACR50-CRP, ACR50-ESR, ACR70-CRP, and ACR70-ESR • Change from baseline in each item of ACR core set • Change from baseline in RAPID3 scores • Change from baseline in SF-36 domain subscores and summary scores **Pharmacokinetics** Primary endpoints: • AUC_{tau} and C_{max} during the dosing interval of Weeks 46 to 54 Secondary endpoints: • Minimum concentration (C_{min}) and time at maximum concentration (t_{max}) during the dosing interval of Weeks 46 to 54 **Safety** The safety endpoints of this study are as follows: • Incidence of treatment-emergent AEs (TEAEs) and serious AEs (SAEs) • Incidence and risk difference between treatment groups of AEs of special interest, including serious infections, malignancies, infusion-related reactions, hepatotoxicity, heart failure, and cytopenias • Incidence of ADAs and neutralizing antibodies • Clinically significant changes in laboratory values, vital signs, weight, ECG, and physical examination results
Statistical Methods and Planned Analyses:	Five analysis populations are being defined for this study: • The intent-to-treat (ITT) population will include all patients who are randomized, irrespective of any deviation from the protocol or premature discontinuation. Patients will be analyzed according to the treatment group assigned at the Stage 1 randomization. The ITT population will serve as the basis for the primary efficacy analysis in Stage 1. • The safety population will include all ITT patients who receive at least 1 dose of study drug. Patients will be analyzed according to the actual treatment they receive rather than as randomized. This population will be used for the analysis of safety.

	• The full analysis set (FAS) will include all patients in the safety population with at least 1 post-baseline ACR20 efficacy assessment. Patients will be analyzed according to the treatment group assigned at the most recent randomization. This population will be used for the secondary efficacy analyses, as well as a sensitivity analysis for the primary efficacy endpoint. • The per-protocol (PP) population will include all patients in the FAS with no major protocol deviations in Stage 1, and sufficient time in study. Sufficient time will be defined as having at least the Week 22 ACR20-CRP efficacy assessment and all study drug administrations up to and including the Week 14 study drug administration. Since this population excludes patients with major protocol deviations, patients will be analyzed according to the treatment they were randomized to and received during Stage 1. This population will be used for a sensitivity analysis of the primary efficacy analysis. • The PK population will include all patients in the FAS population in Stage 1 who have valid PK assessments through Stage 2. This includes only patients who have received all and complete treatments required per protocol through Stage 2. This population will be used for the analysis of interchangeability in Stage 2. **Clinical Efficacy** The primary clinical efficacy endpoint for biosimilarity, the ACR20-CRP response rate at Week 22, will be analyzed using the ITT population. Patients who do not have an ACR20-CRP assessment at Week 22, as well as patients who do not receive study drug up to and including the Week 14 administration, will be considered to have not achieved ACR20-CRP. Because these patients are considered non-responders for this analysis, the primary analysis is considered an analysis on the composite endpoint of both ACR20-CRP response and adherence to study drug treatment. To determine biosimilarity, two standard 1-sided asymptotic Wald tests of the difference between NI-071 and Remicade-US response rates will be performed. If the null hypotheses of both tests are rejected at α=0.05, the equivalence in efficacy is achieved. The hypotheses that will be evaluated are stated, as follows, where P_{NI-071} is the response rate in the NI-071 arm and $P_{Remicade-US}$ is the response rate in the Remicade-US arm: Ho: $P_{NI-071} - P_{Remicade-US} \leq -12\%$ Ho: $P_{NI-071} - P_{Remicade-US} \geq 15\%$ Ha: $-12\% < (P_{NI-071} - P_{Remicade-US}) < 15\%$

	Sensitivity analyses of the primary efficacy endpoint will be performed. Secondary clinical endpoints include ACR20-CRP (at time points other than Week 22), ACR20-ESR, ACR50-CRP, ACR50-ESR, ACR70-CRP, ACR70-ESR, ACR core set items, DAS28-CRP, DAS28-ESR, RAPID3 scores, and SF-36 scores. Summary statistics (including number of patients, mean, standard deviation, minimum, median, maximum) of numerical endpoints for DAS28-CRP and DAS28-ESR (value and change from baseline for visit) will be calculated and presented by visit and treatment group. Point estimate and 95% CI of differences between NI-071 and Remicade-US for DAS28-CRP and DAS28-ESR will also be presented. Frequency tables of the number and percentage of patients achieving ACR20-CRP, ACR20-ESR, ACR50-CRP, ACR50-ESR, ACR70-CRP, and ACR70-ESR will be calculated and presented by visit and treatment group. ACR core set items will be summarized (value and change from baseline for visit) descriptively. RAPID3 scores will be summarized (value and change from baseline for visit) descriptively. SF-36 domain subscores and summary scores will be summarized (value and change from baseline for visit) descriptively. **Pharmacokinetics** To determine PK similarity, the 90% CIs of the ratios (Switch/Remicade-US) of least squares means from the ANOVA of the ln-transformed AUC_{tau} and C_{max} will be evaluated at the alpha level of 0.05 for the PK population during the dosing interval of Weeks 46 to 54. If the CI is within the range of 80.00% to 125.00%, PK similarity is achieved. Secondary PK parameters include C_{min} and t_{max} during this dosing interval. Wilcoxon's test will be performed on t_{max}, and C_{min} will be summarized descriptively. Additional PK analyses may be performed. **Interim Analysis** An interim analysis of the primary clinical efficacy endpoint, the ACR20-CRP response rate, will be performed after the last patient has completed the last visit in Stage 1, the Week 22 visit (the visit of the assessments for the primary efficacy endpoint). This analysis will be performed by an unblinded statistician not otherwise affiliated with the study. An independent data monitoring committee (IDMC) will be established to assess the results and determine whether the study should continue or be stopped for futility.

	Multiplicity A hierarchical procedure will be applied to account for multiplicity of the confirmatory nature of the study. The Stage 2 interchangeability assessment will be regarded as confirmatory in nature only if the biosimilarity assessment at Stage 1 is positive. With this approach, no adjustment for multiplicity of the Stage 2 analysis will need to be performed. No adjustments for multiplicity are necessary following the interim analysis because the interim analysis will be checking for a stop for futility reasons only. Further, the PK analysis for the interchangeability assessment in Stage 2 is based solely on objective variables (plasma concentration data); hence, the introduction of additional bias can be excluded. **Safety** AEs will be tabulated by treatment group according to the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs and treatment-related TEAEs will be summarized by system organ class and preferred term. SAEs, AEs of special interest, and AEs resulting in treatment discontinuation will be summarized. The risk difference between treatment groups will be determined for AEs of special interest. Results and changes in laboratory data, ADAs, and vital signs will be summarized descriptively. Duration of treatment will be summarized by treatment group.

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IN-TEXT TABLES

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3 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACPA	Anti-citrullinated protein antibody
ACR	American College of Rheumatology
ACR20 (50, 70)-CRP	20% (50%, 70%) improvement from baseline in the ACR core set criteria using C-reactive protein as the acute-phase reactant
ACR20 (50, 70)-ESR	20% (50%, 70%) improvement from baseline in the ACR core set criteria using erythrocyte sedimentation rate as the acute-phase reactant
ADA	Anti-drug antibody
AE	Adverse event
ALT (SGPT)	Alanine aminotransferase (serum glutamic pyruvic transaminase)
Anti-dsDNA	Anti-double-stranded deoxyribonucleic acid
ANOVA	Analysis of variance
AST (SGOT)	Aspartate aminotransferase (serum glutamic oxaloacetic transaminase)
AUC	Area under the concentration-time curve
BCG	Bacillus Calmette-Guérin
CFR	Code of Federal Regulations
CI	Confidence interval
C_{max}	Maximum concentration
CPMP	EMA Committee for Proprietary Medicinal Products, now known as the Committee for Medicinal Products for Human Use
CRO	Contract research organization
CRP	C-reactive protein
CV	Coefficient of variation
DAS28-CRP	Disease activity score based on 28 joints calculated with CRP value
DAS28-ESR	Disease activity score based on 28 joints calculated with ESR value
DMARD	Disease-modifying antirheumatic drug
DNA	Deoxyribonucleic acid
EBV	Epstein-Barr virus
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture
EMA	European Medicines Agency
EOI	End of infusion

ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	Full analysis set
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HbA1c	Glycated hemoglobin
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV Ab	Hepatitis C antibody
HIV Ab	Human immunodeficiency virus antibody
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IDMC	Independent data monitoring committee
IGRA	Interferon Gamma Release Assay
IEC	Independent ethics committee
IND	Investigational new drug
IRB	Institutional review board
ITT	Intent-to-treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVRS/IWRS	Interactive voice or web response system
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
NRI	Non-responder imputation
NSAID	Non-steroidal anti-inflammatory drug
NYHA	New York Heart Association
PK	Pharmacokinetic
PP	Per protocol
PPD	Purified protein derivative (skin test for TB)
PT	Preferred term
RA	Rheumatoid arthritis

RAPID3	Routine assessment of patient index data 3
RF	Rheumatoid factor
SAE	Serious adverse event
SAP	Statistical analysis plan
SF-36	Medical Outcomes Study 36-Item Short-Form Health Survey
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
t_{max}	Time at maximum concentration
TNF-α	Tumor necrosis factor alpha
TOST	Two 1-sided test analysis
ULN	Upper limit of normal
US	United States
VAS	Visual analog scale
WBC	White blood cell
WOCBP	Women of childbearing potential

4 INTRODUCTION

4.1 Background on Rheumatoid Arthritis and Treatment

Rheumatoid arthritis (RA), the most common autoimmune inflammatory arthritis in adults, is characterized by the persistent and progressive inflammation of multiple synovial membranes, causing symptoms of joint pain, swelling, stiffness, and redness, and often ultimately leading to the erosion and destruction of cartilage and bone. RA causes increasing disability and decreases patients' ability to perform daily activities, thus reducing their economic and social quality of life. RA is associated with increased mortality and comorbidities (most commonly, cardiovascular disease, infections, mental health conditions, and malignancies). There is no cure, but effective treatments are increasingly available to treat RA. In patients with early RA, treatment usually starts with non-biologic disease-modifying antirheumatic drugs (DMARDs) that help reduce disease activity and prevent joint deformity. Over time as the disease activity increases, combination treatment with non-biologic and biologic DMARDs are introduced.[1,2]

Biologic therapies are designed to modify or regulate specific mechanisms involved in the proinflammatory cytokine overproduction that plays a key role in inflammatory diseases. Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that is involved in normal inflammatory and immune response, but overexpressed TNF-α has been implicated in the pathogenesis of RA and other immunological diseases. Elevated TNF-α levels have been found in the joints of RA patients and correlate with elevated disease activity; elevated levels are also found in patients with Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.[3,4]

US-licensed Remicade® (infliximab; Remicade-US), one of the biologics used to treat RA, is a chimeric human-murine IgG1 monoclonal antibody specific for human TNF-α produced in murine hybridoma cells by recombinant deoxyribonucleic acid (DNA) technology. Infliximab neutralizes the biological activity of TNF-α by binding with high affinity to the soluble and transmembrane forms of TNF-α and inhibits binding of TNF-α with its receptors. Infliximab inhibits the functional activity of TNF-α in a wide variety of in vitro bioassays. Also, infliximab prevented disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNF-α and when administered after disease onset, it allowed eroded joints to heal. In vivo, infliximab rapidly forms stable complexes with human TNF-α, a process that parallels the loss of TNF-α bioactivity. In RA, treatment with infliximab reduced infiltration of inflammatory cells into inflamed areas of the joint as well as expression of molecules mediating cellular adhesion, chemo-attraction, and tissue degradation. Also after infliximab treatment, patients exhibited decreased levels of serum interleukin 6 and C-reactive protein (CRP).[3,4]

Remicade-US is approved for use in the United States (US) for the treatment of adult patients with moderately to severely active RA, in combination with methotrexate (MTX), for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function. In addition, Remicade-US is approved for the treatment of the following other indications in the US:[3]

- Adult Crohn's Disease (indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active

disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease)

- Pediatric Crohn's Disease (indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy)
- Adult Ulcerative Colitis (indicated for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy)
- Pediatric Ulcerative Colitis (indicated for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients with moderately to severely active disease who have had an inadequate response to conventional therapy)
- Ankylosing Spondylitis (indicated for reducing signs and symptoms in patients with active disease)
- Psoriatic Arthritis (indicated for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function)
- Plaque Psoriasis (indicated for treatment of adult patients with chronic severe (i.e., extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate)

Nichi-Iko Pharmaceutical Co., Ltd., (the Sponsor) is developing NI-071, a proposed biosimilar of Remicade-US containing the active substance infliximab. The indications for NI-071 are proposed to be the same as currently approved for Remicade-US, and the dosage forms, route of administration, and dosing regimens for NI-071 are to be the same as for Remicade-US for each indication.[5]

4.2 Background on NI-071

NI-071 is a chimeric human/murine monoclonal antibody specific for human TNF-α. Each molecule is composed of 2 heterodimers in which each heterodimer consists of a heavy polypeptide chain of 450 amino acids and a light polypeptide chain of 214 amino acids. The complex intra- and inter-chain disulfide linkages contribute to the conserved folding, structural stability, and the unique function of the IgG1 molecule. The Sponsor has performed extensive analytical and functional assay testing between NI-071 and Remicade-US as part of the similarity assessment of NI-071 to the reference product.

4.2.1 Nonclinical Studies

In vitro functional assays were performed to assess whether NI-071 possesses similar biological activity to Remicade-US. A comprehensive panel of binding assays and bioassays was conducted to test functionality. The results from these assays have demonstrated that NI-071 is similar analytically to Remicade-US in primary in vitro pharmacodynamics. Further information on the nonclinical studies of NI-071 is presented in the Investigator's Brochure (IB).[5]

4.2.2 Clinical Studies

Two studies have been completed in Japan using Remicade-US as the reference product. A Phase 1 study of NI-071 and Remicade-US was performed to study pharmacokinetics and safety, and a Phase 3 clinical study in RA patients was performed to evaluate efficacy in NI-071 and Remicade-US, and to provide immunogenicity and pharmacokinetic (PK) information.[5,24]

In the Phase 1 study, 96 healthy male adult volunteers were randomized and given a single dose of 3 mg/kg NI-071 or Remicade-US as a 2-hour intravenous (IV) infusion (48 subjects in the NI-071 group, and 48 subjects in the Remicade-US group). The least-squares means ratios (NI-071/Remicade-US), the 90% geometric confidence intervals (CIs), and coefficients of variation (CVs) were determined for $AUC_{0\text{-}t}$ (area under the concentration-time curve from time zero to the last non-zero concentration), $AUC_{0\text{-}inf}$ (area under the concentration-time curve from time zero to infinity), and maximum concentration (C_{max}). As shown by the CIs of the $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$, PK similarity following a single dose was demonstrated. Single-dose administration of a 3 mg/kg dose of NI-071 resulted in slightly greater immunogenic potential based on the incidence of anti-drug antibody (ADA)-positive subjects and detected increases in antibody titer and neutralizing antibody activity. No difference was observed between the 2 groups in the severity and incidence of adverse events (AEs).

The Phase 3 study evaluated Japanese RA patients for whom MTX was inadequately effective, and had a screening period and a treatment period (a double-blind period in Stage I and an open-label period in Stage II). The study design in Stage I (from randomization to before administration at Week 30) was a randomized, double-blind, positive-control, parallel-group trial, comparing the efficacy, safety, and pharmacokinetics of NI-071 and Remicade-US. NI-071 or Remicade-US was administered at a dose of 3 mg/kg by IV infusion on the first administration day, at 2 weeks, at 6 weeks, then every 8 weeks. If the effect was insufficient or decreased, the dose could be increased and the dosing interval could be shortened after the evaluation at Week 14. If the dose was increased, it was to be done stepwise and the upper limit of the dose per 1 kg body weight was to be 10 mg (if the dosing interval was 8 weeks) or 6 mg (if the dosing interval was 4 weeks). If the dosing intervals were shortened, the intervals were to be 4 weeks. The study design in Stage II (from administration at Week 30) was an open-label study in which NI-071 was administered to all patients who transitioned to Stage II to evaluate the long-term safety of NI-071.

In this study, 242 patients (126 patients in the NI-071 group, 116 patients in the Remicade-US group) were randomized, and the investigational product was administered to all 242 randomized patients. Overall, 238 (98.3%) patients completed the protocol to 14 weeks, which was the main evaluation point for efficacy, and 222 (91.7%) patients completed Stage I, which was the double-blind period (from randomization to before the administration at Week 30). The average value (standard deviation) of change in DAS28-ESR (disease activity score [DAS] measured with 28 joints and erythrocyte sedimentation rate [ESR]) from baseline to Week 14, which was the primary efficacy endpoint, was -2.15 (1.19) in the NI-071 group and -2.13 (1.18) in the Remicade-US group. The difference in average values between the NI-071 group and the Remicade-US group and the 95% CI were calculated for the change in DAS28-ESR, using analysis of covariance with DAS28-ESR at the start of administration as the covariant. As a result, the least squares

average values (standard errors) of the 2 groups were -2.13 (0.106) in the NI-071 group and -2.16 (0.112) in the Remicade-US group. The difference was 0.02, and its 95% CI was -0.280 to 0.328. The previously stipulated standard for equivalence (95% CI of the difference in average values to fall in the range -0.6 to 0.6) was satisfied. Therefore, the results indicated that the efficacy of NI-071 measured with DAS28-ESR was similar to Remicade-US.

The ACR20-CRP, ACR50-CRP, and ACR70-CRP response rates (percentages of patients achieving a 20%/50%/70% improvement from baseline in the American College of Rheumatology [ACR] core set criteria) using CRP at Week 14 in the NI-071 group were 73.2% (90 of 123 patients), 45.5% (56 of 123 patients), and 21.1% (26 of 123 patients), respectively. In the Remicade-US group, they were 69.4% (77 of 111 patients), 53.2% (59 of 111 patients), and 26.1% (29 of 111 patients), respectively. At Week 22, the ACR20-CRP, ACR50-CRP, and ACR70-CRP response rates in the NI-071 group were 84.7% (100 of 118 patients), 61.9% (73 of 118 patients), and 32.2% (38 of 118 patients), respectively. In the Remicade-US group, they were 79.4% (85 of 107 patients), 59.8% (64 of 107 patients), and 37.4% (40 of 107 patients), respectively. Similarly, ACR20-CRP, ACR50-CRP, and ACR70-CRP response rates at Week 30 in the NI-071 group were 86.8% (99 of 114 patients), 69.3% (79 of 114 patients), and 40.4% (46 of 114 patients), respectively. In the Remicade-US group, they were 84.3% (86 of 102 patients), 64.7% (66 of 102 patients), and 45.1% (46 of 102 patients), respectively. Thus, no clear difference was observed between the 2 groups.

Through Week 30 of the study, treatment-emergent AEs (TEAEs) were observed in 92 (73%) patients in the NI-071 group and 89 (76.7%) patients in the Remicade-US group. TEAEs considered related to study drug were observed in 57 (45.2%) patients in the NI-071 group and in 49 (42.2%) patients in the Remicade-US group. TEAEs seen with relatively high frequency (in at least 5% of patients in either group) were nasopharyngitis (NI-071 group: 18.3%, Remicade-US group: 23.3%), infusion-related reaction (8.7%, 6.0%), elevated alanine aminotransferase (ALT) (6.3%, 6.0%), and eczema (3.2%, 5.2%). Serious TEAEs were observed in 9 (7.1%) patients in the NI-071 group and 4 (3.4%) patients in the Remicade-US group. Each of the events was reported in only 1 patient. Serious TEAEs considered related to study drug were pancytopenia, female breast cancer, enterocolitis, peritonitis, interstitial lung disease, and pneumonia in the NI-071 group; and pyelonephritis, duodenal perforation, and *Pneumocystis jiroveci* pneumonia in the Remicade-US group. No deaths were reported. TEAEs that led to discontinuation of study treatment were reported in 11 (8.7%) patients in the NI-071 group and 10 (8.6%) patients in the Remicade-US group.

In the open-label stage (from Week 30 through Week 54) of the study, TEAEs were observed in 108 (85.7%) patients in the NI-071 group and 99 (85.3%) patients in the switch group (the patients who switched from Remicade-US to NI-071 at Week 30). There was no difference between the 2 groups in terms of the incidence of TEAEs. Moreover, the types of TEAEs did not change characteristically between up to Week 30 and Week 30 to Week 54. Thus, there was no clinical safety concern with the long-term administration of NI-071 and the switching from Remicade-US to NI-071.

4.3 Potential Benefits and Risks

In the Phase 1 study in healthy volunteers and in the Phase 3 study in patients with RA in Japan, the PK, clinical efficacy, and safety results were similar between the NI-071 and

Remicade-US groups. NI-071 is expected to have a similar benefit/risk profile to Remicade-US in patients with diseases indicated for treatment, as the active substance of NI-071 is essentially the same biological substance as the marketed formulation of infliximab.

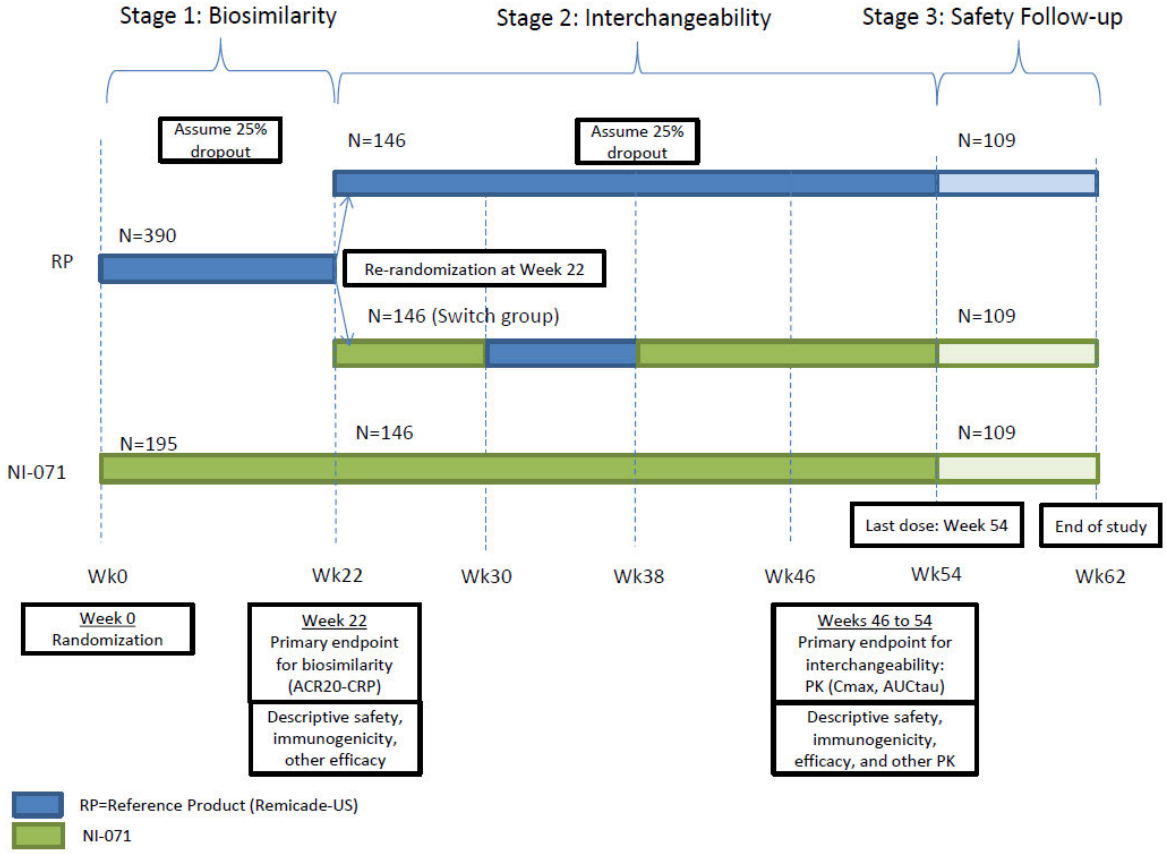
Infliximab neutralizes the biological function of TNF-α by blocking its interaction with cell surface TNF-α receptors, and modulates biological responses that are induced or modified by TNF-α. The benefit of this immunosuppression is that RA patients who have inadequate disease control can enter the study and be treated with a TNF-α inhibitor recommended by ACR treatment guidelines.[1] The main risk accompanies the same immunosuppression: an increased risk of infections and possibly malignancies. Other serious risks include hypersensitivity, hepatotoxicity, heart failure, and cytopenias. The most commonly reported AEs with Remicade-US have been mild to moderate infusion-related reactions and upper respiratory tract infections, which are easily monitored and treated.[3] Patients with a history of chronic or acute infection, including a positive test for hepatitis or untreated latent tuberculosis (TB), will not be permitted to enter the study. Patients will be monitored during the study for development of serious infections and, if required, study treatment will be promptly discontinued.

4.4 Rationale

To address any residual uncertainty in the proposed similarity of NI-071 and Remicade-US, this Phase 3 protocol will examine the therapeutic biosimilarity, the PK interchangeability, and the safety after multiple doses of double-blind study treatment. This study in the sensitive population of patients with RA will serve as the benchmark study that addresses the clinical impact of the proposed biosimilar compared with the reference biologic for all adult indications currently approved for Remicade-US.

Following a screening period, there are 3 stages: the biosimilarity stage (Stage 1), the interchangeability stage (Stage 2), and the safety follow-up stage (Stage 3). Clinical efficacy will be evaluated by the ACR20-CRP response rate at Week 22, which was the primary efficacy variable analyzed in the Phase 3 RA trials for Remicade-US. At Week 22, half of the original Remicade-US patients will be randomly assigned to a Switch group to assess the effects of switching from the reference product to the investigational product. During Stage 2, (Weeks 22 to 54), the Switch group will receive NI-071, then Remicade-US, then NI-071; the other half of the original Remicade-US group will continue on Remicade-US, and the NI-071 group will continue on NI-071. To evaluate interchangeability, a full PK similarity analysis will be performed for all treatment groups from samples drawn at 11 time points from pre-dose Week 46 to pre-dose Week 54. During Stage 3, the last dose of study treatment will be given at Week 54, and patients will return for 2 additional safety follow-up visits through Week 62. A schematic of the study design is provided in Figure 1.

Figure 1 NI071F2 Study Design



5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Stage 1 (Biosimilarity Stage) Objectives

Primary:

- To investigate the biosimilarity of NI-071 (proposed infliximab biosimilar) and Remicade-US (infliximab) in terms of efficacy in patients with RA not adequately responding to MTX, by determining the percentages of patients achieving ACR20-CRP

Secondary:

- To evaluate safety and immunogenicity of NI-071 and Remicade-US
- To evaluate efficacy based on other rates of improvement in the ACR criteria, on the DAS28 and the RAPID3 (routine assessment of patient index data 3), and on changes in health-related quality of life

5.1.2 Stage 2 (Interchangeability Stage) Objectives

Primary:

- To investigate the interchangeability between NI-071 and Remicade-US by evaluating key PK parameters in each treatment group following treatment switches

Secondary:

- To evaluate the safety, efficacy, and immunogenicity of NI-071 and Remicade-US

5.1.3 Stage 3 (Safety Follow-up Stage) Objective

Primary:

- To evaluate the safety of long-term treatment (follow-up through Week 62)

5.2 Study Endpoints

5.2.1 Clinical Efficacy Endpoints

Primary:

- ACR20-CRP at Week 22

Secondary:

- Change from baseline in DAS28-CRP and DAS28-ESR scores (DAS28 scores calculated with CRP and ESR values, respectively)
- ACR20-CRP (at time points other than Week 22), ACR20-ESR, ACR50-CRP, ACR50-ESR, ACR70-CRP, and ACR70-ESR
- Change from baseline in each item of the ACR core set
- Change from baseline in RAPID3 scores

- Change from baseline in the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) domain subscores and summary scores

5.2.2 Pharmacokinetic Endpoints

Primary:

- AUC_{tau} and C_{max} during the dosing interval of Weeks 46 to 54

Secondary:

- Minimum concentration (C_{min}) and time at maximum concentration (t_{max}) during the dosing interval of Weeks 46 to 54

5.2.3 Safety Endpoints

The safety endpoints of this study are as follows:

- Incidence of TEAEs and serious AEs (SAEs)
- Incidence and risk difference between treatment groups of AEs of special interest, including serious infections, malignancies, infusion-related reactions, hepatotoxicity, heart failure, and cytopenias
- Incidence of ADAs and neutralizing antibodies
- Clinically significant changes in laboratory values, vital signs, weight, ECG, and physical examination results

6 INVESTIGATIONAL PLAN

6.1 Description of Overall Study Design and Plan

This Phase 3, randomized, double-blind, multicenter, biosimilarity, interchangeability, and safety study is designed to evaluate NI-071 versus Remicade-US for the treatment of patients with RA. Following a screening period, there will be 3 stages: the biosimilarity stage (Stage 1), the interchangeability stage (Stage 2), and the safety follow-up stage (Stage 3).

The screening period, approximately 4 weeks long for each patient, will be used to assess eligibility. At baseline (Week 0), approximately 585 patients who are eligible will be randomized in a 2:1 ratio to the Remicade-US and NI-071 groups, respectively. This initial randomization will be stratified by CRP level (≤2, >2 mg/dL). During Stage 1, patients will receive their randomized treatment at Weeks 0, 2, 6, and 14. Primary biosimilarity efficacy assessments (specifically ACR20-CRP) will be performed at Week 22.

During Stage 2, at Week 22, patients in the original Remicade-US group are re-randomized (1:1) to a Remicade-US group and a Switch group. The Switch group will receive NI-071 at Week 22, Remicade-US at Week 30, and NI-071 at Weeks 38, 46, and 54; the Remicade-US group will continue to receive Remicade-US from Week 22 through Week 54 every 8 weeks. The original NI-071 group will continue to receive NI-071 from Week 22 through Week 54 every 8 weeks. To evaluate interchangeability, a full PK similarity analysis (specifically AUC_{tau} and C_{max}) will be performed for all treatment groups from samples drawn at 11 time points from pre-dose Week 46 to pre-dose Week 54. During Stage 3, the last dose of study

treatment will be given at Week 54, and patients will return for 2 additional safety follow-up visits through Week 62 (end of study visit).

Efficacy and safety evaluations, including assessments of ADAs, will be performed throughout the study. In addition, samples for determining trough concentrations will be collected prior to each infusion in the study and at the end of the study.

6.2 Discussion of Study Design

This Phase 3 study of NI-071 is designed to examine biosimilarity and interchangeability with Remicade-US in terms of efficacy, safety, and pharmacokinetics. This randomized, double-blind study in patients with RA is designed to evaluate the same primary efficacy endpoint as in the Phase 3 Remicade-US studies (ACR20-CRP), pharmacokinetics, and safety, including immunogenicity. The design includes primary efficacy evaluations at Week 22, followed by PK, efficacy, and safety assessments over an additional 32 weeks of treatment, and includes a randomized Switch arm that switches from Remicade-US to NI-071 to Remicade-US to NI-071. This switching of treatments in the Switch arm allows a study of the effect of interchangeability of Remicade-US and NI-071 on the pharmacokinetics, efficacy, and safety. The immunogenicity of NI-071 is assessed during the biosimilarity and interchangeability stages of the study.

The recommended therapeutic dose of Remicade-US for adults with RA is 3 mg/kg administered IV at Weeks 0, 2, and 6, then every 8 weeks. As NI-071 is being developed as a similar medicinal product to Remicade-US, it is appropriate to also administer NI-071 at a dose of 3 mg/kg IV on the same schedule. Hence, the duration of the switching intervals is also 8 weeks in the interchangeability stage of the study. During this stage, the 16 weeks on NI-071 (2 doses starting from Week 38) in the Switch group ensures a washout of the reference product before the PK analysis is performed after the final dose of study treatment at Week 54 (for the Stage 2 PK endpoint).

The Committee for Medicinal Products for Human Use draft “Guideline on clinical investigation of medicinal products other than non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of RA” (CPMP/EWP/556/95 Rev.2) indicates that combined measures are to be used in the documentation of efficacy in studies of RA. Validated composite endpoints that are regarded as acceptable in this guideline include the ACR response rate and the DAS28 score.[6] Both the ACR20 and DAS28 are accepted, validated endpoints that have been widely used in studies to assess DMARDs (biological and non-biological) for the treatment of RA.[7] The timing of the ACR20-CRP endpoint at Week 22 is consistent with previous studies evaluating the efficacy of biological agents to improve the signs and symptoms of RA.

7 SELECTION AND WITHDRAWAL OF PATIENTS

7.1 Inclusion Criteria

Patients must meet all of the following criteria in order to be included in the study:

1. Patients with a diagnosis of RA as defined by the 2010 ACR and European League Against Rheumatism (EULAR) classification criteria[8]
2. Patients have active RA, as confirmed by the following criteria:
   - ≥6 swollen joints and ≥6 tender joints at screening and baseline (28-joint count), and
   - Either CRP ≥0.7 mg/dL (≥7.0 mg/L) or ESR ≥28 mm/h at screening
3. Patients taking MTX (oral or parenteral) for at least 3 months prior to screening and at a stable dose of between 10 and 25 mg/week for at least 8 weeks. Concomitant folic/folinic acid at a dose of at least 5 mg/week is to be taken during the study; patients can start treatment with folic/folinic acid at screening if not already receiving it.
4. If the patient is currently taking NSAIDs, the patient must be on a stable dose for at least 4 weeks prior to screening and during the study.
5. Patients with a body weight of ≥40 kg and ≤120 kg at screening
6. Patients who are ≥18 and ≤75 years of age at screening
7. Women of childbearing potential (WOCBP) and men (if their sexual partners are WOCBP) must use at least 1 highly effective form of birth control throughout the study and for 6 months after the last dose of study treatment. Highly effective methods of birth control include true sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk, in line with the preferred and usual lifestyle of the patient), surgery (bilateral tubal ligation or occlusion, vasectomized partner), progestogen-only or estrogen/progestogen hormonal contraceptive associated with inhibition of ovulation (oral, patch, injectable, implantable, or intravaginal), intrauterine device (IUD), or intrauterine hormone-releasing system (IUS). See Section 8.7 for a definition of WOCBP and a complete description of contraceptive requirements.
8. Patients with the ability to read and understand the informed consent form (ICF) and to provide written consent

7.2 Exclusion Criteria

Patients meeting any of the following criteria are ineligible to participate in this study:

1. Patients who are rated as Class IV according to the 1991 ACR revised criteria for classification of global functional status (see Section 16, Appendix 1)
2. Patients who have received DMARDs, other than MTX, within a period prior to screening shorter than the washout period appropriate to the pharmacodynamic profile of the specific drug (see Section 16, Appendix 2, for a list of DMARDs and

their washout periods). (These patients may be re-screened after the appropriate washout period.)

3. Patients who have received immunosuppressive drugs within 4 weeks prior to screening. Patients on a stable dose of oral corticosteroids (≤10 mg/day prednisone or equivalent) for ≥4 weeks prior to screening are permitted.
4. Patients who have received intra-articular, intramuscular, IV, or epidural injection of corticosteroids within 4 weeks prior to screening
5. Patients who have received intra-articular sodium hyaluronate injections within 4 weeks prior to screening
6. Patients who have received surgical therapy for RA such as synovectomy or arthroplasty within 6 months prior to screening
7. Patients who have received arthrocentesis within 4 weeks prior to screening
8. Patients who have had prior treatment with infliximab
9. Patients who have had prior treatment with more than 1 biological drug other than infliximab (e.g., adalimumab, rituximab, abatacept, etanercept) for RA either as part of clinical management or during a clinical study. Patients who have had prior treatment with more than 1 protein kinase inhibitor (e.g., tofacitinib) for RA either as part of clinical management or during a clinical study. Patients who have had prior treatment with 1 biological drug AND 1 protein kinase inhibitor are allowed in the study.
10. Patients who have had prior treatment with a tumor necrosis factor alpha (TNF-α) inhibitor for RA who had lack of efficacy as per clinical judgment (primary failure). Primary failure is defined as never having achieved an adequate response, whereas secondary failure is the loss of response over time. Patients who have received prior treatment with no more than 1 biological DMARD and who have received not more than 1 prior TNF-α inhibitor (other than infliximab) and have failed it because of loss of efficacy (secondary failure) or intolerance (e.g., mild injection site reactions) are allowed in the study. Patients who have discontinued TNF-α inhibitors for RA (other than infliximab) because their insurance no longer covered the cost of treatment or they could no longer afford the cost or copays for the treatment are allowed in the study.
11. Patients who had prior treatment with cyclophosphamide or other cytotoxic agents
12. Patients who received investigational drugs in other clinical studies within 12 weeks or 5 half-lives of the drug prior to screening, whichever is longer
13. Patients with a concomitant or past history of autoimmune connective tissue diseases other than RA, for example, systemic lupus erythematosus, Sjogren's syndrome, polymyositis, dermatomyositis, and mixed connective tissue disease
14. Patients with a history of hypersensitivity to the components of NI-071 or mouse-derived protein (e.g., mouse, chimeric, and humanized antibody)

15. Patients with the following concomitant or past history:
    - Chronic or recurrent infectious disease (e.g., bronchiectasis, sinusitis)
    - Demyelinating disease (e.g., multiple sclerosis)
    - Presence of New York Heart Association (NYHA) Class III/IV heart failure (see Section 12.5)
    - Lymphoproliferative disorder (e.g., Epstein-Barr virus (EBV)-related lymphoproliferative disorder, lymphoma, or leukemia) or myelodysplastic syndrome
    - Cancer other than successfully treated non-melanoma skin cancer or localized carcinoma in situ of the cervix
    - Interstitial lung disease
16. Presence of chronic or acute infection at screening, including positive result for active tuberculosis (TB) (e.g., positive QuantiFERON® test result without any prior history of active or latent TB and without evidence of active infection) where the patient is not willing to undergo prophylactic treatment. (These patients may be re-screened after appropriate treatment for TB [see Section 12.3]).
17. Patients with an acute infection requiring parenteral antibiotics within 4 weeks of study dosing or requiring oral/topical antibiotics within 2 weeks of study dosing. (These patients may be re-screened after the appropriate washout period.)
18. Patients with mycobacterial infection or opportunistic infection (e.g., cytomegalovirus infection or invasive fungal infection such as histoplasmosis, blastomycosis, or coccidiomycosis) or who have resided in or traveled to regions where such infections are prevalent within 6 months prior to the initial administration of the investigational drug
19. Patients who have active or past infection or suspected infection in prosthetic joints that have not been removed or replaced
20. Patients with positive results of hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (HBcAb), hepatitis C antibody (HCV Ab), and/or human immunodeficiency virus antibody (HIV Ab) tests at screening (excluding patients who are tested positive for HBsAb alone due to a hepatitis B vaccination)
21. Patients who received a live vaccine within 12 weeks prior to study dosing, or who plan to receive a live vaccine during the study period or within 6 months after the last dose of study treatment. (If received prior to study dosing, these patients may be re-screened after the appropriate washout period.)
22. Patients with laboratory test results at screening that meet any of the following reference levels:
    - Hemoglobin ≤8.5 g/dL
    - White blood cells (WBCs) ≤3,500/mm^3

- Lymphocytes ≤1,000/mm^3
- Platelet count ≤100,000/mm^3
- Aspartate aminotransferase (AST) or ALT ≥ upper limit of normal (ULN) x 1.5
- Serum creatinine ≥ULN x 1.5
- Glycated hemoglobin (HbA1c) ≥9.0%
- Positive anti-double-stranded deoxyribonucleic acid (anti-dsDNA) assay
- β-D-glucan ≥80 pg/mL (positive)

23. History of clinically significant cardiac, respiratory, renal, hepatic, hematologic, gastrointestinal, neurologic, endocrinologic, psychiatric, or any other uncontrolled medical illness
24. Female patients who are pregnant, wish to become pregnant, or are breastfeeding
25. Male patients who plan to donate sperm during the study or within 6 months after the last dose. Female patients who plan to donate eggs or undergo in vitro fertilization treatment during the study or within 6 months after the last dose.
26. Patients who are taking part in other clinical studies at screening or planning to take part in other clinical studies during the study period
27. Patients with a drug or alcohol dependence
28. Patients who are determined by the Investigator to be unsuitable for study enrollment for other reasons

7.3 Withdrawal, Removal, and Replacement of Patients

Patients will be considered to have completed the study if they complete treatment and assessments through Week 62. Patients who are withdrawn from the study for any reason will not be replaced.

A patient's study treatment should be discontinued if any of the following situations occurs:

- The Investigator believes that for safety reasons it is in the best interest of the patient to stop treatment.
- The patient becomes pregnant.
- The patient is diagnosed with a malignancy, with the exception of no more than 2 localized basal cell skin cancers that are treated with no evidence of recurrence or residual disease.
- The patient is deemed ineligible according to 1 of the following TB criteria: a diagnosis of active TB is made; a patient has symptoms suggestive of active TB, but the patient cannot or will not undergo further evaluation; or a patient undergoing evaluation has a QuantiFERON test with evidence of active TB.
- The patient initiates a protocol-prohibited medication (see Section 8.6.2).
- If the patient requires parenteral antibiotics, the patient will be withdrawn from treatment but followed for resolution of the AE. If it is necessary to interrupt study drug dosing for longer than 2 weeks for treatment of an infection with an oral or topical antibiotic, the patient will be withdrawn from treatment but followed for resolution of the AE.
- The patient is noncompliant with the study visit schedule or other protocol requirements.
- The patient develops a severe allergic reaction that occurs following study treatment administration.
- The patient has a reaction resulting in myalgia and/or arthralgia with fever and/or rash (suggestive of serum sickness) occurring 1 to 14 days after an injection of study treatment.

Also, discontinuation of study treatment should be considered for patients who develop a serious or opportunistic infection, congestive heart failure, demyelinating disease, lupus-like syndrome, cytopenia (for example, anemia, leukopenia, or neutropenia), or liver abnormalities.

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Patient withdrawal of consent: At any time, a patient's participation in the study may terminate at his/her request. The specific reason for patient withdrawal will be noted on the electronic case report form (eCRF).

- Lost to follow-up: The patient stops coming for visits, and study personnel are unable to contact the patient after repeated attempts (e.g., telephone calls, mail, or email).
- This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her site for any reason including safety or low enrollment.

7.4 Follow-Up for Drug Discontinuation/Patient Withdrawal from Study

If a patient's study treatment is discontinued during Stage 1 and the patient maintains consent to contribute additional outcome information, the patient should continue to be followed through Week 22 for all key safety and efficacy assessments. Investigators will be trained about the importance of retention and steps to prevent missing data.

When a patient withdraws or is withdrawn before completing the study, the date and reason for withdrawal are to be documented in the eCRF. The study site must immediately notify the medical monitor. Patients who withdraw prematurely are to attend an early discontinuation visit if possible, at which time they will complete all assessments described in Table 2 under the Week 62 visit.

In the event that a patient discontinues prematurely from the study due to a TEAE or serious TEAE, the TEAE or serious TEAE will be followed until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to be no longer clinically significant.

Once a patient is withdrawn from the study, the patient may not re-enter the study.

8 TREATMENTS

8.1 Details of Study Treatments

NI-071 is a proposed infliximab biosimilar to be administered as an IV infusion. Each 20-mL vial contains 100 mg of NI-071 in the form of a lyophilized (freeze-dried) white pellet, for a final reconstitution volume of 10 mL and a final concentration of 10 mg/mL. Excipients include sucrose, polysorbate 80, monobasic sodium phosphate, and dibasic sodium phosphate.

Remicade-US (infliximab) is the reference product to be administered as an IV infusion. Only US-licensed Remicade will be used in this study. Each 20-mL vial contains 100 mg of infliximab in the form of a lyophilized (freeze-dried) white pellet, for a final reconstitution volume of 10 mL and a final concentration of 10 mg/mL. Excipients include sucrose, polysorbate 80, monobasic sodium phosphate, and dibasic sodium phosphate.

Basic information about the study treatments is provided in Table 1. All vials of study drug will be provided by the Sponsor.

Table 1 Details of Study Treatments

	Preparations to be Administered	
	NI-071	**Remicade (All US-licensed)**
Manufacturer	Binex, Co., Ltd. 7-48, Song do-dong Yeonsu-Gu, Incheon, 406-840 Republic of Korea	Janssen Biotech, Inc. Horsham, PA, US
Active ingredient	NI-071	Infliximab
Dosage	3 mg/kg at Weeks 0, 2, and 6, then every 8 weeks	3 mg/kg at Weeks 0, 2, and 6, then every 8 weeks
Route	IV	IV
Formulation	Each 20-mL vial contains 100 mg of NI-071 (as a lyophilized pellet) for a final reconstitution volume of 10 mL and a final concentration of 10 mg/mL.	Each 20-mL vial contains 100 mg of infliximab (as a lyophilized pellet) for a final reconstitution volume of 10 mL and a final concentration of 10 mg/mL.

Storage Instructions

Each vial of study treatment is individually packaged in a carton. Store unopened vials in a refrigerator at 2° to 8°C (36° to 46°F). Do not freeze. Do not use any vial beyond the expiration date. The study treatments do not contain preservatives. Detailed storage instructions will be provided in the pharmacy manual.

Instructions for Use

The reconstituted infusion solution should be prepared by a pharmacist or other trained medical professional using aseptic technique with the following procedures[3] (detailed instructions will be available in the pharmacy manual):

- Calculate the dose, total volume of reconstituted study drug solution required and the number of study drug vials needed.
- Within 3 h prior to the planned patient infusion, reconstitute each vial with 10 mL sterile water for injection, using a syringe equipped with a 21-gauge or smaller needle. After removing the top from the vial and wiping the top with an alcohol swab, insert the needle into the vial through the center of the rubber stopper and direct the stream of liquid to the glass wall of the vial. Gently swirl the solution by rotating the vial to dissolve the drug. Avoid prolonged or vigorous agitation (do not shake). Allow to stand for 5 minutes after dissolution.
- The solution should be colorless to light yellow or opalescent, and there may be a few translucent particles, as this is a protein preparation. Do not use if the lyophilized pellet has not fully dissolved, or if opaque particles, discoloration, or other foreign particles are present.

- Dilute the total volume of the reconstituted study drug solution to 250 mL with 0.9% sodium chloride for infusion. This can be done by withdrawing a volume of the sodium chloride solution from the 250 mL infusion bottle or bag equal to the volume of reconstituted study drug. Slowly add the total volume of reconstituted study drug solution to the infusion bottle or bag. Gently mix.

- Label the infusion bottle or bag in a blinded manner per the pharmacy manual and give to the appropriate blinded study staff for patient infusion.

The blinded Investigator or designated study staff will administer the study drug in the following manner:

- Start IV administration within 3 h after reconstitution and dilution. Use an independent line for administration. Do not mix the study drug with other infusion solutions. Use an infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 1.2 µm or less).

- Prior to administration, visually inspect the infusion solution for particulates or discoloration. If opaque particles, discoloration, or other foreign particles are present, do not use the solution.

- Prior to administration of the study drug, patients may be given antihistamines and/or acetaminophen (paracetamol) per standard of care. Emergency equipment, such as adrenaline, antihistamines, corticosteroids, and an artificial airway must be available in the event of infusion-related reactions.

- Administer the infusion solution over a period of 2 h. Observe the patient for at least 30 minutes post-infusion for acute infusion-related reactions, including anaphylaxis. See Section16, Appendix 3 for guidelines on diagnosing anaphylaxis.

- Do not store or reuse any unused portion of the infusion solution. Any unused product or waste material should be disposed of in accordance with local requirements.

8.2 Dosage Schedule

Study treatment is to be administered by IV infusion at a dose of 3 mg/kg at Weeks 0, 2, 6, 14, 22, 30, 38, 46, and 54.

Every effort should be made to adhere to the dosing schedule. However, a scheduled dose should not be administered if a patient has an infection for which systemic anti-infectives are indicated or the patient has signs or symptoms of an infection or other AE that, in the Investigator's opinion, warrants holding the dose. If the patient requires parenteral antibiotics, the patient will be withdrawn from treatment but followed for resolution of the AE. If it is necessary to interrupt study drug dosing for longer than 2 weeks for treatment of an infection with an oral or topical antibiotic, the patient will be withdrawn from treatment but followed for resolution of the AE.

8.3 Study Treatment Assignment

Each patient will be allocated a unique patient number at screening and will retain this number throughout the study. At baseline (Week 0), upon confirmation of eligibility, the study staff will randomize an eligible patient using an interactive voice or web response system (IVRS/IWRS). Patients will be randomized in a 2:1 ratio to receive Remicade-US or NI-071, respectively, for Stage 1 treatments in the study (at Weeks 0, 2, 6, and 14). This initial randomization will be stratified by CRP level (≤2, >2 mg/dL).

At Week 22, patients in the original Remicade-US group will be re-randomized (1:1) to a Remicade-US group or a Switch group; the treatment assignments for all patients will remain blinded. For Stage 2 and Stage 3 treatments, the Switch group will receive NI-071 at Week 22, Remicade-US at Week 30, and NI-071 at Weeks 38, 46, and 54; the Remicade-US group will continue to receive Remicade-US from Week 22 through Week 54 every 8 weeks. The original NI-071 group will continue to receive NI-071 from Week 22 through Week 54 every 8 weeks. As the blinded re-randomization of the original Remicade-US group to a Switch group and a Remicade-US group will occur within the IVRS/IWRS, the clinical procedure for handling study treatment will remain unchanged throughout the study.

8.4 Blinding

At each dosing visit, the Investigator or designee will access the IVRS/IWRS to receive the specific study drug number for the patient; this number will be provided to the unblinded pharmacist or designee for preparing the study treatment.

The pharmacist or designee who prepares the infusion will be unblinded and not otherwise involved in the study. This staff member will prepare the study drug according to the study drug number issued by the IVRS/IWRS for each patient at each dosing visit. The prepared infusion solutions will be identical in appearance, and the preparer will label the bag or bottle in a blinded manner to include, at a minimum, the protocol number, “For Investigational Use Only”, the patient number, and the solution concentration. All other study staff, all patients, and the Sponsor and its designees conducting the study will be blinded to treatment assignments during the study.

In a medical emergency, if unblinding is required in the interest of the safety of a patient, the Investigator may break the randomization code for that patient using the IVRS/IWRS. The Investigator must inform the medical monitor and/or the Sponsor as soon as possible that the randomization code has been broken for that patient. The reason for unblinding must be documented in the eCRF.

8.5 Treatment Accountability and Compliance

The study drug supplies will be stored at the site in a locked facility with monitored temperature. Only authorized personnel will be allowed access. The pharmacist or other designated unblinded individual will maintain records of study treatment delivered to the study site; the inventory at the site; the distribution to and use by each patient; and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study patients.

Administration of study drugs will be performed by blinded study personnel. Infusion rates, volume of study drug infused, start times, and stop times will be recorded. If any study drug is discarded, the reason will be recorded in the eCRF.

8.6 Prior and Concomitant Illnesses and Medications

8.6.1 Prior and Concomitant Illnesses

Investigators should document all prior significant medical history. Additional illnesses present at the time when informed consent is given and up to the time of first dosing (Week 0) are to be regarded as concomitant illnesses. Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs in the eCRF.

8.6.2 Prior and Concomitant Medications

All medications and other treatments (including over-the-counter treatments and preventative vaccines) taken by the patient during the study, including those treatments initiated prior to the start of the study, must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

Permitted Concomitant Medications

All patients are required to take concomitant MTX and folic/folinic acid during this study. Patients must have taken MTX (oral or parenteral) for at least 3 months and at a stable dose of 10 to 25 mg/week for at least 8 weeks immediately prior to screening. Patients are to continue on this stable dose during the study. The route of administration of MTX should not change throughout the study. The patient's MTX dose can be reduced for toxicity only. If toxicity occurs, this should be recorded as an AE. The folic/folinic acid dose should be at least 5 mg/week during the study. Folic/folinic acid can be started at screening if the patient is not already receiving it. These required concomitant medications will not be provided by the Sponsor.

To minimize the risk of allergic reactions, patients may be given an antihistamine and/or acetaminophen (paracetamol) prior to each study drug infusion per standard care of the study site (For the antihistamine, 2 to 4 mg chlorpheniramine or equivalent, or 10 mg cetirizine, 30 to 60 minutes prior to dosing).

Oral corticosteroids (≤10 mg/day prednisone or equivalent) are permitted during the study if the dose has been stable for at least 4 weeks prior to screening and is continued at the same dose during the study. An increase in oral corticosteroid dose is permitted to treat concomitant conditions, e.g., asthma, only. The reason for any such increase in dose should be recorded as an AE (e.g., asthma flare). The dose must be tapered back down as soon as medically viable and within 2 weeks.

NSAIDs up to the maximum approved dose are permitted during the study if the dose has been stable for at least 4 weeks prior to screening. Patients should continue to take this stable dose during the study. The NSAID dose can be increased (not above the maximum approved dose) for up to 2 weeks to treat an RA flare. This should be documented as a change in the concomitant medication. The dose must be tapered back down as soon as medically viable and within 2 weeks. Patients who are not receiving NSAIDs may be treated with an NSAID

for up to 2 weeks, or an additional NSAID may be added to an existing NSAID regimen for up to 2 weeks to treat an RA flare.

Analgesics up to the maximum approved dose are permitted during the study but should not be taken in the 24 hours prior to efficacy evaluations (except in cases of severe pain). Other analgesics could include paracetamol/acetaminophen, combinations, alternative treatments, and psychotropic agents.

For states and countries where medical marijuana is legal, patients can take medical marijuana while in the study according to the analgesic rule above.

Patients with evidence or suspicion of latent TB at screening (see Section 12.3), may be enrolled provided that they begin prophylactic antimycobacterial treatment at least 4 weeks prior to randomization (or longer, if local guidelines specify) and commit to completing the course of treatment. The treatment should be according to local guidelines. If needed, such patients may be re-screened (see Section 9.2).

Prohibited Medications

The following treatments are prohibited during the study:

- Immunization with a live or attenuated vaccine is prohibited within 12 weeks prior to study dosing, for the duration of study, and for 6 months after administration of the last dose.
- Treatment with another investigational drug is prohibited during the study and within 12 weeks or 5 half-lives of the drug prior to screening, whichever is longer.
- Treatment with intra-articular or parenteral steroids within 28 days prior to study dosing and during the study is prohibited. If a patient is treated with an intra-articular steroid injection during the study, the Investigator should discontinue study treatment and withdraw the patient from the study. If this occurs during Stage 1 and the patient maintains consent to contribute additional outcome information, the patient should continue to be followed through Week 22 for all key safety and efficacy assessments.
- Treatment with DMARDs (other than MTX), including traditional non-biologic drugs, biologic drugs, and protein kinase inhibitors, is prohibited during the study and within a period prior to screening (a washout period) appropriate to the pharmacodynamic profile of the specific drug. See Section 16, Appendix 2, for a list of traditional non-biologic drugs, biologic drugs, and protein kinase inhibitors, along with their washout periods. If the Investigator wishes to treat a patient with a DMARD other than MTX during the study, the patient must be withdrawn from study treatment, and the reason for withdrawal must be documented in the eCRF.
- Surgical therapy and radiosynovectomy for RA is prohibited. If surgery is performed on a joint, the joint will be unevaluable (excluded from joint counts) for the remainder of the study.
- Arthrocentesis is prohibited during the study and within 4 weeks prior to screening.
- Treatment with an agent that might confound efficacy or safety evaluation in this study (e.g., RANKL [receptor activator of nuclear factor kappa-B ligand] inhibitors for osteoporosis and immunomodulators for asthma) is prohibited within 5 half-lives

of the drug concerned prior to the first dose of study treatment and during the study. Examples of RANKL inhibitors include Prolia/Xgeva (denosumab) for osteoporosis and Xolair (omalizumab) for asthma.

- Cytapheresis is prohibited during the study.

8.7 Study Restrictions

All WOCBP and all men (if their sexual partners are WOCBP) must use at least 1 highly effective method of contraception during the study and for 6 months after the last dose of study treatment. A woman is considered as a WOCBP (fertile) following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception include the following:

- Combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation. Delivery may be oral, intravaginal, or transdermal.
- Progestogen-only hormonal contraception associated with inhibition of ovulation. Delivery may be oral, injectable, or implantable.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Bilateral tubal ligation or occlusion.
- Vasectomy (provided that the male has a medical assessment of surgical success).
- True sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk, in line with the preferred and usual lifestyle of the patient).

All patients will be strongly advised that they (or the female partners of male patients) should not become pregnant while on study treatment or for 6 months after the last dose. Female patients will be advised that if they believe they may be pregnant, they must report immediately to the study site for pregnancy testing and appropriate management.

9 STUDY PROCEDURES

Table 2 outlines the timing of procedures, and assessments to be performed throughout the study. Additional details of study procedures are provided in Sections 10, 11, and 12.

Table 2 Schedule of Assessments

	Screening	Stage 1						Stage 2								Stage 3	
Visit at Week (±3 days)	**(Day -28 to Day -7)**	**0 (Day 1)**	**2**	**6**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**54**	**58**	**62[a]**
Informed consent	X																
Inclusion/exclusion criteria	X	X															
Medical history	X																
Demographics	X																
NYHA classification	X																
Vital signs, weight, height[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chest x-ray	X[b]								X[b]								X[b]
Physical examination	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]
Electrocardiogram	X																X[l]
Clinical laboratory tests[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum immunology tests[e]	X																
Pregnancy test[f]	X	X	X	X	X		X		X		X		X		X		X
QuantiFERON TB test	X								X								X
RF and ACPA tests[g]	X																
Joint assessment[g,h,i,m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
2010 ACR/EULAR RA classification	X																
CRP test[g,h,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ESR test[g,h,i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAQ-DI[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient global assessment[h,i,j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient pain assessment[h,j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RAPID3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physician global assessment[h,j]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening	Stage 1						Stage 2								Stage 3	
Visit at Week (±3 days)	**(Day -28 to Day -7)**	**0 (Day 1)**	**2**	**6**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**54**	**58**	**62[a]**
SF-36		X			X		X				X						X
Concomitant medication review	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X*					X**										
Administration of study drug		X	X	X	X		X		X		X		X		X		
MTX and folic acid reminder	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse event monitoring		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-drug antibodies (pre-dose)		X	X	X	X		X		X		X		X		X		X
Trough PK sample[k] (pre-dose)		X	X	X	X		X		X		X		X		X		X
Full PK sample[k] (Weeks 46 to 54)													X	X	X		

Abbreviations: ACPA=anti-citrullinated protein antibody; ACR=American College of Rheumatology; ACR20(50, 70)=a 20%(50%, 70%) improvement from baseline in the ACR core set criteria; anti-dsDNA=anti-double-stranded deoxyribonucleic acid; CRP=C-reactive protein; DAS28=disease activity score involving 28 joints; EOI=end of infusion; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; HAQ-DI=Health Assessment Questionnaire-Disability Index;HbA1c=glycated hemoglobin; HBcAb=hepatitis B core antibody; HBsAb=hepatitis B surface antibody; HBsAg=hepatitis B surface antigen; HCV Ab=hepatitis C antibody; HIV Ab=human immunodeficiency virus antibody; NYHA=New York Heart Association; PK=pharmacokinetic; RA=rheumatoid arthritis; RAPID3=routine assessment of patient index data 3; RF=rheumatoid factor; SF-36=Medical Outcomes Study 36-Item Short-Form Health Survey; TB=tuberculosis

[a]Or early discontinuation visit.

[b]Chest x-rays (anterior-posterior and lateral views) are to be done only if the TB test is positive; also, at screening, only if the patient has not had x-rays within 12 weeks prior to screening.

[c]A limited physical examination to verify continued patient eligibility and to follow up any changes (symptom-driven) will be performed at these visits.

[d]Standard hematology, blood chemistry, and urinalysis tests; at screening, also HbA1C.

[e]Screening serum immunology tests include HBsAg, HBsAb, HBcAb, HCV Ab, HIV Ab, anti-dsDNA, and β-D-glucan.

[f]Only in women of childbearing potential. Serum test is to be done at screening; urine test is to be done locally at other specified time points.

[g]Assessment contributes to the 2010 ACR and EULAR RA classification at screening.

[h]Assessment contributes to the ACR core set criteria for determining ACR20, ACR50, and ACR70 at all post-screening visits.

[i]Assessment contributes to the DAS28 scores at all post-screening visits.

[j]Measured on a visual analog scale (VAS) of 0 to 100 mm. VAS for patient assessment of pain goes from “no pain” to “pain as bad as it can be”; VAS for patient global assessment of disease activity goes from “very well” to “very poor”; VAS for physician global assessment of disease activity goes from “none” to “extremely active.”

[k]Trough PK sampling should be done within 1 h prior to dosing. Full PK sampling during Weeks 46 to 54 includes the following time points: pre-dose, 1 h after

	Screening	Stage 1						Stage 2								Stage 3	
Visit at Week (±3 days)	**(Day -28 to Day -7)**	**0 (Day 1)**	**2**	**6**	**14**	**18**	**22**	**26**	**30**	**34**	**38**	**42**	**46**	**50**	**54**	**58**	**62[a]**

infusion start, at the end of infusion (EOI), at 4 h and 24 h after infusion start, and at 4 days, 7 days (Week 47), 14 days (Week 48), 28 days (Week 50), 42 days (Week 52), and 56 days (Week 54) post-dose. Sampling windows for the blood draws are ±15 minutes for the 1 h time point, +15 minutes for the EOI, and ±15 minutes for the 4 h time point; ±2 h for the 24 h time point; and ±24 h for the subsequent time points.

[l]At early discontinuation visit only.

[m]Joint assessment includes determination of tender joints and swollen joints. At screening, counts of tender and swollen joints out of 28 selected joints will be performed (for the 2010 ACR and EULAR classification criteria). At all subsequent visits, counts of tender and swollen joints out of 68 and 66 selected joints, respectively, will be performed (for the ACR core set criteria and the DAS28).

[n]At screening, prior medications will also be reviewed.

[o]Record height at screening only.

*Initial blinded randomization is to be performed after all inclusion/exclusion criteria are reconfirmed at Week 0.

**Blinded re-randomization. At Week 22, the original Remicade-US group is to be randomized 1:1 to a Switch group and a Remicade-US group. The Remicade-US group will continue on Remicade-US from Week 22 through Week 54 every 8 weeks. At Week 22, the Switch group will receive NI-071; at Week 30, this group will receive Remicade-US; and at Weeks 38, 46, and 54, this group will receive NI-071. The original NI-071 group will continue on NI-071 from Week 22 through Week 54 every 8 weeks.

9.1 Patient Informed Consent

Prior to performing any study-related procedures, the Investigator (or his/her designated staff member) will obtain written informed consent from the patient.

9.2 Patient Re-Screening

A patient who is screened and does not meet the study entry criteria may be re-screened once only. Investigator discretion should be exercised in determining who may be re-screened. Patients who otherwise meet entry criteria but require a longer washout period for a DMARD, antibiotics, or vaccination; or require time for stabilization of the MTX regimen; or require time for starting prophylaxis treatment for latent TB (see Section 12.3) will be able to re-screen. All patients who are eligible to be re-screened must be fully consented a second time before the second set of screening assessments take place, and they will keep their original patient numbers. The re-screening process to follow in the IVRS/IVWS will be detailed in the study manual.

In the case of doubt about the accuracy of screening laboratory value(s), the laboratory test(s) may be repeated provided that this can be done within the 4-week screening period without the need to repeat all other screening procedures (i.e., no re-screening).

9.3 Procedures by Week

Assessments are to be performed as outlined in the following subsections. For visits at Weeks 2 through 62, there will be a window of ±3 days, except for the blood draw visits during the full PK sampling interval following the Week 46 dose. Sampling windows for these blood draw time points are ±15 minutes for 1 h after start of infusion, +15 minutes for the end of infusion (EOI), ±15 minutes for 4 h after start of infusion, ±2 h for 24 h after start of infusion, and ±24 h for the subsequent time points.

9.3.1 Screening

The screening visit will occur within Day -28 to Day -7 prior to the Week 0 visit. If needed, patients may be re-screened once (see Section 9.2). The following procedures will be performed during screening:

- Obtain written informed consent.
- Obtain demographic data.
- Record medical history and current conditions, including an evaluation of the risk of TB infection (e.g., prior history of active or latent TB, possible exposure to individuals with active TB) and smoking history.
- Record prior and concomitant medications for RA and other indications.
- Measure vital signs (blood pressure, pulse, oral/tympanic body temperature) and weight. Record height at screening only.
- Perform a 12-lead electrocardiogram (ECG).
- Perform a physical examination.

- Assess the NYHA classification.
- Collect a blood sample for a QuantiFERON TB test.
- Perform chest x-rays (anterior-posterior and lateral views) if the QuantiFERON TB test is positive, unless there are recent x-rays available (done within 12 weeks prior to screening).
- Collect blood and urine samples for standard clinical laboratory tests (including HbA1C at screening).
- Collect blood for a serum pregnancy test (females of childbearing potential only).
- Collect blood for screening serum immunology tests, rheumatoid factor (RF) test, and anti-citrullinated protein antibody (ACPA) test.
- Collect blood for CRP.
- Collect blood to perform ESR locally (site personnel must enter the ESR result for each patient into the eCRF).
- Administer the patient global assessment of disease activity on a visual analog scale (VAS).
- Assess 28 joints for tenderness and swelling and ask the patient about the duration of synovitis (pain, swelling, tenderness) in the joints that are tender/swollen (for use in the 2010 ACR RA classification).
- Ascertain patient eligibility by evaluating patient results against the inclusion/exclusion criteria.
- Ask patients to avoid taking analgesics during the 24 h prior to a clinic visit.
- Remind patients that they are required to stay on their stable regimens of MTX and folic/folinic acid throughout the study.

9.3.2 Week 0 (Baseline)

Patients who meet the inclusion/exclusion criteria at screening will continue to the Week 0 visit (baseline). The following procedures will be performed:

- Measure vital signs and weight, and perform a limited physical examination.
- Record concomitant medications.
- Administer the patient pain assessment, the patient global assessment of disease activity, the Health Assessment Questionnaire Disability Index (HAQ-DI), the RAPID3, and the SF-36.
- Assess 68 joints for tenderness and 66 for swelling (for use in the ACR core set and DAS28).
- Perform the physician global assessment of disease activity (VAS).
- Reconfirm eligibility.
- Randomize the patient using IVRS/IWRS.

- Collect blood and urine samples for standard clinical laboratory tests.
- Collect urine to perform pregnancy test locally (females of childbearing potential only).
- Collect blood for CRP.
- Collect blood to perform ESR locally.
- Collect blood for trough PK and ADA assessments.
- Obtain the blinded study drug number from IVRS/IWRS for the unblinded pharmacist or designee to prepare the study treatment.
- Prior to administration of the study drug, patients may be given antihistamines and/or acetaminophen (paracetamol) per standard care.
- Administer study treatment.
- Monitor for AEs. Observe the patient for at least 30 minutes after dosing for symptoms of infusion-related reactions and allergic reactions, including anaphylaxis (see Section 16, Appendix 3).
- Instruct the patient on recognition of delayed serious allergic reactions, including anaphylaxis. Advise the patient to seek immediate medical attention if he or she experiences any symptoms of severe allergic reactions.
- Remind patients to avoid taking analgesics during the 24 h prior to a clinic visit.
- Remind patients that they are required to stay on their stable regimens of MTX and folic/folinic acid throughout the study.

9.3.3 Weeks 2, 6, and 14

The following procedures will be performed at Weeks 2, 6, and 14:

- Measure vital signs and weight, and perform a limited physical examination.
- Record concomitant medications.
- Administer the patient pain assessment, the patient global assessment of disease activity, the HAQ-DI, and the RAPID3.
- At Week 14 only, administer the SF-36.
- Assess 68 joints for tenderness and 66 for swelling (for use in the ACR core set and DAS28).
- Perform the physician global assessment of disease activity (VAS).
- Collect blood and urine samples for standard clinical laboratory tests.
- Collect urine to perform pregnancy test locally (females of childbearing potential only).
- Collect blood for CRP.
- Collect blood to perform ESR locally.

- Collect blood for trough PK and ADA assessments.
- Obtain the blinded study drug number from IVRS/IWRS for the unblinded pharmacist or designee to prepare the study treatment.
- Prior to administration of the study drug, patients may be given antihistamines and/or acetaminophen (paracetamol) per standard care.
- Administer study treatment.
- Monitor for AEs. Observe the patient for at least 30 minutes after dosing for symptoms of infusion-related reactions and allergic reactions, including anaphylaxis (see Section 16, Appendix 3).
- Remind the patient on recognition of delayed serious allergic reactions, including anaphylaxis. Advise the patient to seek immediate medical attention if he or she experiences any symptoms of severe allergic reactions.
- Remind patients to avoid taking analgesics during the 24 h prior to a clinic visit.
- Remind patients that they are required to stay on their stable regimens of MTX and folic/folinic acid throughout the study.

9.3.4 Week 18

At Week 18, the following procedures will be performed:

- Measure vital signs and weight, and perform a limited physical examination.
- Record concomitant medications.
- Administer the patient pain assessment, the patient global assessment of disease activity, the HAQ-DI, and the RAPID3.
- Assess 68 joints for tenderness and 66 for swelling (for use in the ACR core set and DAS28).
- Perform the physician global assessment of disease activity (VAS).
- Collect blood and urine samples for standard clinical laboratory tests.
- Collect blood for CRP.
- Collect blood to perform ESR locally.
- Monitor for AEs.
- Remind patients to avoid taking analgesics during the 24 h prior to a clinic visit.
- Remind patients that they are required to stay on their stable regimens of MTX and folic/folinic acid throughout the study.

9.3.5 Week 22

The Week 22 visit is the primary efficacy time point for assessing biosimilarity (the last visit in Stage 1) and the first dosing visit for Stage 2. As the blinded re-randomization will occur within the IVRS/IWRS, the clinical procedure for handling study treatment will remain unchanged throughout the study.

The following procedures will be performed at Week 22:

- Measure vital signs and weight, and perform a limited physical examination.
- Record concomitant medications.
- Administer the patient pain assessment, the patient global assessment of disease activity, the HAQ-DI, the RAPID3, and the SF-36.
- Assess 68 joints for tenderness and 66 for swelling (for use in the ACR core set and DAS28).
- Perform the physician global assessment of disease activity (VAS).
- Collect blood and urine samples for standard clinical laboratory tests.
- Collect urine to perform pregnancy test locally (females of childbearing potential only).
- Collect blood for CRP.
- Collect blood to perform ESR locally.
- Collect blood for trough PK and ADA assessments.
- Obtain the blinded study drug number from IVRS/IWRS for the unblinded pharmacist or designee to prepare the study treatment.
- Prior to administration of the study drug, patients may be given antihistamines and/or acetaminophen (paracetamol) per standard care.
- Administer study treatment.
- Monitor for AEs. Observe the patient for at least 30 minutes after dosing for symptoms of infusion-related reactions and allergic reactions, including anaphylaxis (see Section 16, Appendix 3).
- Remind the patient on recognition of delayed serious allergic reactions, including anaphylaxis. Advise the patient to seek immediate medical attention if he or she experiences any symptoms of severe allergic reactions.
- Remind patients to avoid taking analgesics during the 24 h prior to a clinic visit.
- Remind patients that they are required to stay on their stable regimens of MTX and folic/folinic acid throughout the study.

9.3.6 Weeks 26, 30, 34, 38, and 42

Visits at Weeks 26, 30, 34, 38, and 42 will have the following safety and efficacy assessments. In addition, at Weeks 30 and 38, pre-dose PK and ADA assessments will be

done, and study treatment will be administered (see below). At Week 30, there will also be additional safety assessments (see below).

- Measure vital signs and weight, and perform a limited physical examination.
- Record concomitant medications.
- Administer the patient pain assessment, the patient global assessment of disease activity, the HAQ-DI, and the RAPID3.
- At Week 38 only, administer the SF-36.
- Assess 68 joints for tenderness and 66 for swelling (for use in the ACR core set and DAS28).
- Perform the physician global assessment of disease activity (VAS).
- Collect blood and urine samples for standard clinical laboratory tests.
- Collect blood for CRP.
- Collect blood to perform ESR locally.
- Monitor for AEs.
- Remind patients to avoid taking analgesics during the 24 h prior to a clinic visit.
- Remind patients that they are required to stay on their stable regimens of MTX and folic/folinic acid throughout the study.

At Weeks 30 and 38 only:

- Collect urine to perform pregnancy test locally (females of childbearing potential only).
- Collect blood for trough PK and ADA assessments.
- Obtain the blinded study drug number from IVRS/IWRS for the unblinded pharmacist or designee to prepare the study treatment.
- Prior to administration of the study drug, patients may be given antihistamines and/or acetaminophen (paracetamol) per standard care.
- Administer study treatment.
- Monitor for AEs. Observe the patient for at least 30 minutes after dosing for symptoms of infusion-related reactions and allergic reactions, including anaphylaxis (see Section 16, Appendix 3).
- Remind the patient on recognition of delayed serious allergic reactions, including anaphylaxis. Advise the patient to seek immediate medical attention if he or she experiences any symptoms of severe allergic reactions.

At Week 30 only:

- Collect a blood sample for a QuantiFERON TB test.

- Perform chest x-rays (anterior-posterior and lateral views) if the QuantiFERON TB test is positive.

9.3.7 Weeks 46, 50, 54, and 58

At the Week 46 visit, the dosing interval begins for assessing the full PK profile (Week 46 to Week 54). In addition to the pre-dose trough sample, blood draws will be required at the following time points: 1 h after infusion start, at the EOI, at 4 h and 24 h after infusion start, and at 4 days, 7 days (Week 47), 14 days (Week 48), 28 days (Week 50), 42 days (Week 52), and 56 days (Week 54) post-dose. Sampling windows for the blood draws are ±15 minutes for the 1 h time point, +15 minutes for the EOI, and ±15 minutes for the 4 h time point; ±2 h for the 24 h time point; and ±24 h for the subsequent time points. The clinic will need to schedule patients to return to the clinic on these days.

Visits at Weeks 46, 50, 54, and 58 will have the following safety and efficacy assessments. In addition, at Weeks 46 and 54, pre-dose PK and ADA assessments will be done, and study treatment will be administered (see below). At Week 46, there will also be the additional post-dose blood draws for PK assessments (see below).

- Measure vital signs and weight, and perform a limited physical examination.
- Record concomitant medications.
- Administer the patient pain assessment, the patient global assessment of disease activity, the HAQ-DI, and the RAPID3.
- Assess 68 joints for tenderness and 66 for swelling (for use in the ACR core set and DAS28).
- Perform the physician global assessment of disease activity (VAS).
- Collect blood and urine samples for standard clinical laboratory tests.
- Collect blood for CRP.
- Collect blood to perform ESR locally.
- Monitor for AEs.
- Remind patients to avoid taking analgesics during the 24 h prior to a clinic visit.
- Remind patients that they are required to stay on their stable regimens of MTX and folic/folinic acid throughout the study.

At Weeks 46 and 54 only:

- Collect urine to perform pregnancy test locally (females of childbearing potential only).
- Collect blood for trough PK and ADA assessments.
- Obtain the blinded study drug number from IVRS/IWRS for the unblinded pharmacist or designee to prepare the study treatment.
- Prior to administration of the study drug, patients may be given antihistamines and/or acetaminophen (paracetamol) per standard care.

- Administer study treatment.
- Monitor for AEs. Observe the patient for at least 30 minutes after dosing for symptoms of infusion-related reactions and allergic reactions, including anaphylaxis (see Section 16, Appendix 3).
- Remind the patient on recognition of delayed serious allergic reactions, including anaphylaxis. Advise the patient to seek immediate medical attention if he or she experiences any symptoms of severe allergic reactions.

At Week 46 only:

- Perform blood draws at 1 h after infusion start, at the EOI, and at 4 h after infusion start.
- Schedule patients for returning to the clinic at the following post-dose time points: 24 h, 4 days, 7 days (Week 47), 14 days (Week 48), 28 days (Week 50), 42 days (Week 52), and 56 days (Week 54).

9.3.8 Week 62 (End of Study Visit or Early Discontinuation Visit)

The following procedures will be done at the end of study (Week 62) visit, or if a patient is prematurely withdrawn from the study, at the early discontinuation visit:

- Measure vital signs and weight, and perform a limited physical examination.
- Perform a 12-lead ECG (early discontinuation visit only).
- Record concomitant medications.
- Administer the patient pain assessment, the patient global assessment of disease activity, the HAQ-DI, the RAPID3, and the SF-36.
- Assess 68 joints for tenderness and 66 for swelling (for use in the ACR core set and DAS28).
- Perform the physician global assessment of disease activity (VAS).
- Collect blood and urine samples for standard clinical laboratory tests.
- Collect blood for CRP.
- Collect blood to perform ESR locally.
- Collect blood for trough PK and ADA assessments.
- Collect urine to perform pregnancy test locally (females of childbearing potential only).
- Collect a blood sample for a QuantiFERON TB test.
- Perform a chest x-ray if the QuantiFERON TB test is positive.
- Monitor for AEs.

Patients who prematurely withdraw from the study for any reason should complete the early discontinuation visit requirements. If the early discontinuation visit is not done, the reason(s) will be recorded in the eCRF.

9.3.9 Unscheduled Visits

The Investigator may at his/her discretion arrange for a patient to have an unscheduled assessment, especially in the case of adverse events (AEs) that require follow-up or an AE considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

10 EFFICACY ASSESSMENTS

10.1 Primary Efficacy Variable

The primary efficacy variable, the ACR20-CRP response rate at Week 22, is based on a 20% improvement from baseline (Week 0) in specific elements of the ACR core set criteria.[9,10] The core set criteria consist of 7 elements:

1. Tender joint count (out of 68 joints)
2. Swollen joint count (out of 66 joints)
3. Patient pain assessment (VAS/100 mm)
4. Patient global assessment of disease activity (VAS/100 mm)
5. Physician global assessment of disease activity (VAS/100 mm)
6. Patient-completed HAQ-DI
7. Acute-phase reactant (CRP or ESR; CRP will be evaluated for the primary endpoint)

Achieving ACR20 is defined by a 20% improvement in tender and swollen joint counts, plus a 20% improvement in 3 out of the remaining 5 items.

ACR core set criteria will be measured at the time points indicated in the schedule of assessments in Table 2. The following subsections describe these criteria.

10.1.1 Tender and Swollen Joint Counts

At screening, counts of tender and swollen joints out of 28 selected joints will be performed (for the 2010 ACR and EULAR classification criteria). At all subsequent visits, counts of tender and swollen joints out of 68 and 66 selected joints, respectively, will be performed (for the ACR core set criteria and the DAS28). Counts will be performed by a trained and qualified joint assessor using standardized techniques recommended by EULAR.[11] Results will be recorded immediately on a tablet device provided (constituting source data). For each patient, efforts will be made to use the same blinded joint evaluator at all visits. The blinded joint evaluator will perform only the joint counts and will **not** perform other assessments in the study. To maintain consistency, 2 or 3 joint evaluators per site will be trained on how to assess joints for the purpose of the study using a number of training opportunities. The training opportunities may include, but not be limited to, attendance at the Investigators' Meeting, the site initiation visit, a video, and a written manual detailing how to perform the joint assessment. Training will be documented by certificates kept in the site file.

If a joint is unevaluable for any reason, the joint will be recorded as such on the tablet device. If this is due to amputation, the joint will automatically be recorded as unevaluable for the remainder of the study. If a joint is unevaluable for any other reason (such as infection,

injury, or surgery), the joint should be re-assessed for evaluability at each visit by the joint examiner. Criteria for excluding such joints from the joint count used to calculate the ACR20/50/70 and the DAS28 will be detailed in the Statistical Analysis Plan (SAP).

10.1.2 Assessments Using Visual Analog Scales

Patient pain assessment VAS (ranging from no pain to pain as bad as it can be), patient global assessment of disease activity VAS (ranging from very well to very poor), and physician global assessment of disease activity VAS (ranging from none to extremely active) will be assessed on 100-mm scales at the visits specified in the schedule of assessments.[36,37] All of these assessments are part of the ACR core set criteria. In addition, the patient global assessment of disease activity with the 100-mm scale is used to calculate the DAS28-CRP and DAS28-ESR scores.

VAS data will be recorded on a tablet device and will be regarded as source data.

10.1.3 HAQ-DI

The HAQ-DI to be used for the ACR core set criteria is the version without questions concerning the use of aids or assistance from others. The questionnaire is a 20-question, self-administered instrument that measures the patient's functional ability on a 4-level difficulty scale (0 to 3, with 0 representing normal or no difficulty, and 3 representing inability to perform). Eight categories of functioning are included: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and usual activities.[12,13]

The HAQ-DI questionnaire will be completed by the patient on the tablet device at the visits indicated in the schedule of assessments.

10.1.4 Acute-Phase Reactants

Serum CRP levels analyzed by the central laboratory and ESR analyzed locally are the acute-phase reactants included in the ACR core set criteria; CRP is used to determine the ACR 20/50/70-CRP response rates, and ESR is used to determine the ACR 20/50/70-ESR response rates. These levels are also used in calculating the DAS28-CRP and the DAS28-ESR.

10.2 Secondary Efficacy Variables

Secondary efficacy variables include the ACR20-CRP response rate at time points other than Week 22; the ACR50-CRP, ACR50-ESR, ACR70-CRP, and ACR70-ESR response rates (50% and 70% improvements calculated in the same way as the ACR20), and change from baseline in each of the ACR core set criteria (see ACR variables described in Section 10.1). Other secondary efficacy variables include the DAS28-CRP and DAS28-ESR, the RAPID3 score, and the SF-36.

10.2.1 DAS28-CRP and DAS28-ESR

The DAS28 scores are based on the extent of pain and swelling of 28 specific joints, including the shoulders, elbows, wrists, metacarpophalangeal joints, proximal carpal joints, and knees.[7] In addition, the score includes the patient global assessment of disease activity VAS and the CRP or ESR value. In this study, both DAS28-CRP and DAS28-ESR scores will be calculated for each patient. The greater the numerical score, the higher the disease activity. A score of <2.6 indicates minimum disease activity (remission), a score of ≥2.6 to

<3.2 indicates low activity, a score of ≥3.2 to ≤5.1 indicates moderate activity, and a score of >5.1 indicates highly active RA.[1]

10.2.2 RAPID3

The RAPID3 is an increasingly used assessment in both RA clinical trials and clinical practice. The RAPID3 has recently been used in clinical trials with methotrexate, leflunomide, adalimumab, and abatacept.[29,30,31] In clinical practice, the ease of use and the short time (<30 seconds) for patient completion of the RAPID3 are key advantages over other indices.[32,33] RAPID3 scores have been shown to correlate well with DAS28 scores in clinical trials and clinical care.[34]

The RAPID3 score is a composite disease activity index consisting of 3 patient-reported outcomes: disability, pain, and global assessment of disease activity. For the RAPID3, disability is measured using the first 10 questions of the physical function section of the multidimensional HAQ (MD-HAQ), with each question about physical tasks performed over the past week scored from 0 (without any difficulty) to 3 (unable to do); the total score from the 10 questions is divided by 10, then multiplied by 3.33 to obtain the weighted disability score in the range of 0-10 for the RAPID3. The pain intensity score for the RAPID3 is based on the following question: How much pain have you had because of your condition over the past week? The numerical scale with 0.5 increments ranges from 0 (no pain) to 10 (pain as bad as it could be). The patient global assessment of disease activity score for the RAPID3 is based on the following statement: Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing. The numerical scale with 0.5 increments ranges from 0 (very well) to 10 (very poorly).[35]

For the calculation of the RAPID3 score, the results from the 3 parts are summed: MD-HAQ physical function (range 0–10), pain intensity score (range 0–10), and patient global assessment of disease activity score (range 0–10). Thus, the range of the RAPID3 score is 0-30, and disease activity categories are as follows: remission 0 to 3, low >3.1 to 6, moderate >6.1 to 12, and high >12.[34]

The RAPID3 will be completed by the patient on the tablet device at the visits indicated in the schedule of assessments.

10.2.3 SF-36

The SF-36 is a 36-item, short-form health survey that has 8 subscales divided across physical and psychological health-related quality of life domains: physical function, role physical, bodily pain, global health, vitality, social function, role emotional, and mental health. Scores on these subscales can be combined to form 2 higher-order summary scores, the physical component summary and the mental component summary. As the SF-36 is a generic tool instead of one that targets a specific disease or population, it can be used to compare the quality of life between diseases and in comparison to healthy populations. The SF-36 has been found to be a valid and reliable measure in RA, correlating well with the HAQ-DI.[19,20]

The SF-36 will be completed by the patient on the tablet device at the visits indicated in the schedule of assessments.

10.3 Other Disease Assessments (at Screening)

Two classifications used to assess the RA of each patient at screening include (1) the 2010 ACR and EULAR classification criteria used to confirm that a patient has definite RA,[8] and (2) the 1991 ACR revised criteria for classification of global functional status (see Section 16, Appendix 1).[14]

11 PHARMACOKINETIC ASSESSMENTS

Interchangeability will be assessed from the analysis (specifically AUC_{tau} and C_{max}) of blood samples collected during the dosing interval of Week 46 to Week 54. The specific time points for collecting these PK samples are presented in Table 2.

Trough sampling will be done at the visits specified in Table 2. In addition, if a patient discontinues from the study at any time, he/she will need to provide a blood sample for trough analysis at the early discontinuation visit.

The actual date and time of each blood sample collection will be recorded in the eCRF. The timing of PK samples may be altered and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

A laboratory manual that contains detailed information on sample collection and handling/shipping of the samples will be provided to the sites.

12 SAFETY ASSESSMENTS

Safety assessments (vital signs, weight, physical examinations, ECG recordings, AEs, routine clinical laboratory tests (hematology, blood chemistry, and urinalysis), pregnancy tests, antibody assays, and QuantiFERON TB tests (and chest x-rays, if applicable) are to be performed at the visits specified in the schedule of assessments in Table 2.

12.1 Vital Signs, Height, and Weight

Vital signs (oral/tympanic body temperature, pulse, systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the schedule of assessments. All vital signs will be measured after the patient has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) will be recorded whenever vital signs are recorded, and height (without shoes) will be recorded at screening only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure and pulse measurements will be repeated at the Investigator's discretion. Any confirmed, clinically significant vital sign measurements must be recorded as AEs.

12.2 Physical Examination

A complete physical examination (head, eyes, ears, nose, throat, heart, lungs, abdomen, skin, cervical and axillary lymph nodes, neurological, and musculoskeletal systems) will be performed at screening. In addition, medical history (including smoking history) will be recorded at screening.

A limited physical examination to verify continued patient eligibility and to follow up any change in medical history will be performed at the visits indicated in the schedule of assessments. Symptom-driven physical examinations will be performed as clinically indicated at any study visit. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

12.3 Tuberculosis Screening

At screening, a QuantiFERON test will be done to screen for latent TB. If the test is positive, a chest x-ray is to be performed at screening unless a recent x-ray is available (done within 12 weeks prior to screening).

A patient who tests positive for latent TB (with a positive or indeterminate QuantiFERON test, plus a chest x-ray negative for active TB) will be allowed to enroll if prior prophylactic treatment was documented or if prophylactic treatment for TB was initiated at least 4 weeks prior to baseline (first dose of study drug). If the result is indeterminate, the test may first be repeated, or purified protein derivative (PPD) testing may be done. If confirmed indeterminate, the patient should be managed as though they have a positive test result or excluded from the study.

If necessary, a patient may be re-screened once to allow for this prophylactic treatment period. Prophylactic treatment should be according to local guidelines, which may vary depending upon the sensitivity of strains of *M. tuberculosis* present locally. As a guide, the US Centers for Disease Control and Prevention recommendations are available online.[15] Patients with latent TB should receive appropriate treatment for at least 4 weeks prior to baseline and should be committed to completing the course of antimycobacterial therapy during the study.

In case of any doubt as to the diagnosis of latent TB and the appropriate course of antimycobacterial therapy, it is advised that a local physician with expertise in the treatment of TB is consulted.

All patients will be retested at Week 30 and Week 62 (or at the early discontinuation visit).

For further information about TB screening, see Section 16, Appendix 4.

12.4 Electrocardiogram

A 12-lead resting ECG will be obtained at screening and at the early discontinuation visit, if applicable. At screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded and if the ECG is considered abnormal, the abnormality will be documented in the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present.

12.5 New York Heart Association Classification

Patients will be evaluated at screening for cardiac disease by means of the NYHA functional classification (see Table 3). If patients have Class III or IV cardiac disease, they will be excluded from the study.

Table 3 New York Heart Association Classification

Class	New York Heart Association Classification
I	Patients have cardiac disease but without the resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients have cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: Raphael C, Briscoe C, Davies J, et al.[16]

12.6 Clinical Laboratory Parameters

Samples for assessing clinical laboratory parameters (Table 4) are to be obtained at the visits designated in the schedule of assessments.

Table 4 Clinical Laboratory Parameters

Hematology	Serum chemistry	Urine analysis (dipstick)
Full and differential blood count Hematocrit (Hct) Hemoglobin (Hb) 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 Glycated hemoglobin (HbA1C) (at screening only)	Albumin Alanine aminotransferase (ALT) Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Blood urea nitrogen (BUN) or urea Creatinine Electrolytes (Na, K, Cl, Ca, P) Gamma-glutamyl transpeptidase (GGT) Glucose Lactate dehydrogenase (LDH) Total bilirubin Direct bilirubin	Appearance pH Protein Glucose Ketone bodies Indicators of blood and WBCs Urobilinogen
Serum immunology tests: At screening, HBsAg, HBsAb, HBcAb, HCV Ab, HIV Ab, anti-dsDNA, and β-D-glucan (using the Fungitell® assay) will be measured.		
RA tests: Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) tests will be done at screening.		
Pregnancy test: For women of childbearing potential, a serum pregnancy test will be done at screening, and urine dipstick tests will be done at all dosing visits and at Week 62 (or the early discontinuation visit).		
QuantiFERON TB test: This test will be performed for all patients at screening, Week 30, and Week 62 (or the early discontinuation visit). A dedicated incubator must be available at the site for storing samples at 37ºC prior to shipping them to the central laboratory (at room temperature or refrigerated) within 3 days.		
C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests: CRP and ESR levels will be analyzed at every visit. CRP will be analyzed by the central laboratory, and ESR will be analyzed locally.		

Blood and urine samples will be analyzed at a central laboratory facility, unless indicated otherwise. Urine samples will be analyzed by dipstick, and a microscopic analysis will be performed if the results of the dipstick indicate abnormalities to be further investigated.

The Investigator must review all laboratory reports and document the review. Any laboratory test result or change considered by the Investigator to be clinically significant should be considered an AE and recorded in the AE eCRF. Clinically significant abnormal values occurring during the study will be followed until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.7 Immunogenicity Assessments

The detection and characterization of antibodies to study drug (Remicade-US and NI-071) will be performed using a validated immunoassay method. Positive immunogenicity samples

will be further examined to confirm the specificity of binding. If the sample is confirmed to be positive for specific ADAs, the neutralizing capacity of these antibodies will be investigated.

Blood samples will be collected at the time points indicated in the schedule of assessments (pre-dose at dosing visits). In addition, if a patient discontinues from the study at any time, he/she will need to provide a sample at the early discontinuation visit. A laboratory manual that contains detailed information on sample collection and handling/shipping of the samples will be provided to the sites.

12.8 Adverse Events

12.8.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs. Surgical procedures that were planned before the patient enrolled in the study are not considered AEs if the conditions were known before study inclusion; the medical condition should be reported in the patient's medical history.

Additionally, anticipated AEs for this study population are reported in Table 5 and are based on AEs reported with Remicade from the premarketing clinical studies as well as from post-marketing experience. Anticipated AEs must be reported by Investigators to the Sponsor but will not necessarily be expedited on an individual basis. Instead these AEs will be reviewed in aggregate every month by the medical monitor. This aggregate review may result in an expedited safety report.

Adverse events of special interest include serious infections, malignancies, hepatotoxicity, heart failure, cytopenias, and infusion-related reactions (any AE reported during an infusion or within 1 h after an infusion). As anaphylaxis may occur at any time during or after infusion, Investigators are to observe patients during and after infusions for anaphylactic reactions as defined by the criteria in Section 16, Appendix 3.[17]

Table 5 List of Anticipated AEs with Study Drug (AEs Reported with Remicade)

System Organ Class	Frequency[a]	Adverse Reaction
Infections and infestations	Very common	Viral infections (e.g., influenza, herpes virus)
	Common	Bacterial infections (e.g., sepsis, cellulitis, abscess)
	Uncommon	Tuberculosis, fungal infections (e.g., candidiasis)
	Rare	Meningitis, opportunistic infections (such as invasive fungal infections, bacterial infections, and viral infections), parasitic infections, hepatitis B reactivation
	Not known	Vaccine breakthrough infection
Neoplasms benign, malignant, and unspecified	Rare	Lymphoma, non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, melanoma, cervical cancer
	Not known	Hepatosplenic T-cell lymphoma, Merkel cell carcinoma
Blood and lymphatic system disorders	Common	Neutropenia, leucopenia, anemia, lymphadenopathy,
	Uncommon	Thrombocytopenia, lymphopenia, lymphocytosis
	Rare	Agranulocytosis, thrombotic thrombocytopenic purpura, pancytopenia, hemolytic anemia, idiopathic thrombocytopenic purpura
Immune system disorder	Common	Allergic respiratory symptom
	Uncommon	Anaphylactic reaction, lupus-like syndrome, serum sickness or serum sickness-like reaction
	Rare	Anaphylactic shock, vasculitis, sarcoid-like reaction
Psychiatric disorders	Common	Depression, insomnia
	Uncommon	Amnesia, agitation, confusion, somnolence, nervousness
	Rare	Apathy
Nervous system disorders	Very common	Headache
	Common	Vertigo, dizziness, hypoesthesia, paresthesia
	Uncommon	Seizure, neuropathy
	Rare	Transverse myelitis, central nervous system demyelinating disorders, peripheral demyelinating disorders
Eye disorders	Common	Conjunctivitis
	Uncommon	Keratitis, periorbital edema, hordeolum
	Rare	Endophthalmitis

System Organ Class	Frequency[a]	Adverse Reaction
	Not known	Transient visual loss occurring during or within 2 h of infusion
Cardiac disorders	Common	Tachycardia, palpitation
	Uncommon	Cardiac failure (new onset or worsening), arrhythmia, syncope, bradycardia
	Rare	Cyanosis, pericardial effusion
	Not known	Myocardial ischemia/myocardial infarction occurring during or within 2 h of infusion
Vascular disorders	Common	Hypotension, hypertension, ecchymosis, hot flush, flushing
	Uncommon	Peripheral ischemia, thrombophlebitis, hematoma
	Rare	Circulatory failure, petechia, vasospasm
Respiratory, thoracic, and mediastinal disorders	Very common	Upper respiratory tract infection, sinusitis
	Common	Lower respiratory tract infection (e.g., bronchitis, pneumonia), dyspnea, epistaxis
	Uncommon	Pulmonary edema, bronchospasm, pleurisy, pleural effusion
	Rare	Interstitial lung disease (including rapidly progressive disease, lung fibrosis, and pneumonitis)
Gastrointestinal disorders	Very common	Abdominal pain, nausea
	Common	Gastrointestinal hemorrhage, diarrhea, dyspepsia, gastroesophageal reflux, constipation
	Uncommon	Intestinal perforation, intestinal stenosis, diverticulitis, pancreatitis, cheilitis
Hepatobiliary disorders	Common	Hepatic function abnormal, transaminases increased
	Uncommon	Hepatitis, hepatocellular damage, cholecystitis
	Rare	Autoimmune hepatitis, jaundice
	Not known	Liver failure
Skin and subcutaneous tissue disorders	Common	New onset or worsening psoriasis including pustular psoriasis (primarily palm and soles), urticarial, rash, pruritus, hyperhidrosis, dry skin, fungal dermatitis, eczema, alopecia
	Uncommon	Bullous eruption, onychomycosis, seborrhea, rosacea, skin papilloma, hyper keratosis, abnormal skin pigmentation
	Rare	Toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, furunculosis
	Not known	Worsening of symptoms of dermatomyositis

System Organ Class	Frequency[a]	Adverse Reaction
Musculoskeletal and connective tissue disorders	Common	Arthralgia, myalgia, back pain
Renal and urinary disorders	Common	Urinary tract infection
	Uncommon	Pyelonephritis
Reproductive system and breast disorders	Uncommon	Vaginitis
General disorders and administration site conditions	Very common	Infusion-related reaction, pain
	Common	Chest pain, fatigue, fever, injection site reaction, chills, edema
	Uncommon	Impaired healing
	Rare	Granulomatous lesion
Investigations	Uncommon	Autoantibody positive
	Rare	Complement factor abnormal

[a]Very common: ≥10%; Common: ≥1% and <10%; Uncommon: ≥0.1% to <1%; Rare:≥0.01% to <0.1%; Very Rare: <0.01%; Not known: cannot be determined from the available data. Within each frequency group, adverse reactions are presented in order of decreasing seriousness.
Source: Remicade EMA EPAR Product Information[4]

All SAEs must be reported to the Sponsor or Sponsor designee immediately after the Investigator becomes aware of the event, along with a determination as to whether it is associated with the study drug.

Patients will be instructed to report AEs at each study visit. All AEs are to be followed until resolution or until a stable clinical endpoint is reached.

Each AE is to be documented in the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or non-serious. Changes in AEs and resolution dates are to be documented in the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent through Week 54 (or early discontinuation visit). Follow-up of the AE is required until the event resolves or stabilizes at a level acceptable to the Investigator.

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 6 and Table 7.

Table 6 Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 7 Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the study drug, but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the study drug; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the study drug; or (4) it does not reappear or worsen when the drug is re-administered.
POSSIBLY: This category applies to those AEs for which a connection with the study drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the study drug.
PROBABLY: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the study drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the study drug.
DEFINITELY: This category applies to those AEs that the Investigator feels are incontrovertibly related to study drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the study drug.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

12.8.2 Serious Adverse Events

An AE is considered serious if in the view of either the Investigator or Sponsor, it meets 1 or more of the following criteria:

- Is fatal
- Is life-threatening
- Results in inpatient hospitalization or prolongation of existing hospitalization
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. Since SAEs are critically important for the identification of significant safety problems, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.8.3 Serious Adverse Event Reporting

An SAE occurring during the study or within 8 weeks after stopping the treatment must be reported to the inVentiv Health Pharmacovigilance Group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made with the SAE reporting form by using the dedicated fax line or by scanning and emailing to the safety mailbox for the inVentiv Health Pharmacovigilance Group:

inVentiv Health Pharmacovigilance Fax Numbers:

North America: +1-866-880-9343

All other countries: +44-1628-461184

inVentiv Health Pharmacovigilance Email: SafetyPV@inventivhealth.com

If notification cannot be made via these means due to technical delivery problems, initial notification may be made by telephone, using the SAE Hotline number:

inVentiv Health Pharmacovigilance Hotline: +1-888-750-8020

A telephone call to the SAE Hotline does not substitute for the site's responsibility to submit a written SAE reporting form to inVentiv Health. If the Investigator makes initial contact by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed by detailed descriptions later on, including clear and anonymized

photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the inVentiv Health Pharmacovigilance Group within 10 calendar days. All SAEs will be followed until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.8.4 Suspected Unexpected Serious Adverse Reactions

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and will be reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- Serious
- Unexpected (i.e., the event is not consistent with the safety information in the IB)
- There is at least a reasonable possibility that there is a causal relationship between the event and the study treatment.

The Investigator will assess whether an event is causally related to study treatment. The Sponsor (or inVentiv Health) will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the IEC/IRBs (where required) within 7 days after the Sponsor (or inVentiv Health) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or inVentiv Health) has first knowledge of them.

The Sponsor (or inVentiv Health) is responsible for reporting SUSARs to the regulatory authorities and for informing Investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

12.8.5 Pregnancy

Female patients of childbearing potential must have a negative serum pregnancy test at screening. Following administration of study drug, any known cases of pregnancy in female patients will be reported until the patient completes or withdraws from the study. The pregnancy will be reported immediately by phone and by faxing/emailing a completed Pregnancy Report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however the Investigator will follow the

patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up Pregnancy Report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., spontaneous or therapeutic abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator will report the event by phone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

12.8.6 Overdose

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug. The patient will be monitored for any signs or symptoms of adverse reactions or effects, and appropriate symptomatic treatment will be given.

13 STATISTICAL ANALYSIS

A SAP will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will supersede planned analyses in the protocol in the case of any differences.

The statistical evaluation will be performed using SAS® Version 9.3 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group according to study stage. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of patients for each category by treatment group according to study stage.

The treatment groups according to study stages are as follows: 2 treatment groups in Stage 1 (i.e., Remicade-US and NI-071) and 3 treatment groups in Stage 2 (i.e., NI-071 throughout the study, Remicade-US throughout the study, and the Switch group [patients who were originally allocated to Remicade-US during Stage 1, then were re-randomized to alternate between treatments with NI-071 and Remicade-US in Stage 2]). In addition, a combined group will be displayed.

An interim analysis is planned in order to decide if the study should continue or be stopped for futility after Stage 1 (see Section 13.8).

13.1 Determination of Sample Size

The sample size required to be randomized in Stage 1 was derived with consideration of the required sample size needed for PK analysis at the end of Stage 2 and assumes a 25% drop-out of patients during Stages 1 and 2. Stage 3 will follow patients for safety after the final dose and does not have sample size requirements.

To show PK similarity, the 90% geometric CIs of the ratio (Switch/Remicade-US) of the least squares means from the analysis of variance (ANOVA) of the ln-transformed AUC_{tau} and C_{max} must be within 80.00% and 125.00%. For the PK interchangeability analysis at the end of Stage 2, assuming coefficients of variation (CVs) of 49% and 33% for AUC_{tau} and

C_{max}, respectively, and CIs of the ratios between 95% and 105%, at least 109 patients per treatment group are required for an 80% powered trial. (**Note:** The CV assumptions for the PK sample size estimations were derived from a multiple-dose PK study conducted in ankylosing spondylitis patients for the Remsima™ infliximab biosimilar.[18] In the Phase 1 single-dose PK study of NI-071 and Remicade-US in 96 healthy Japanese male volunteers, the CVs were quite low, about 24% for AUC and 15% for C_{max}, possibly due to the homogeneity of the healthy population and to no or little impact from ADA formation after a single dose. Using the data from the multiple-dose Remsima study in 222 patients with ankylosing spondylitis provides a more appropriate basis for this planned multiple-dose study in patients with RA.)

In order to meet this Stage 2 requirement, in Stage 1 (at Week 0), approximately 585 patients are expected to be randomized in a ratio of 2:1 to Remicade-US (390 patients) and NI-071 (195 patients). This sample size will provide over 90% power to test for equivalence, using an asymmetric margin (-12%, 15%) and a two 1-sided test (TOST) analysis with α=0.05 for each 1-sided statistical test. Greater than 90% power is achieved when the ACR20-CRP response rate for Remicade-US at Week 22 is assumed to be 79.4% (the Remicade-US ACR20-CRP result at Week 22 from Study NI071F1 using the study's modified intent-to-treat population).

Assuming a 25% drop-out rate during Stage 1, at least 292 patients in the Remicade-US group and 146 patients in the NI-071 group are expected to complete Stage 1 of the study. In Stage 2 (at Week 22), patients in the original Remicade-US group (about 292 patients) will be re-randomized in a 1:1 ratio to a Remicade-US group (146 patients) and a Switch group (146 patients). Assuming a 25% drop-out rate during Stage 2, approximately 109 patients per treatment group will be available for the PK analysis at the end of Stage 2.

The asymmetric margins (-12%, 15%) were selected based on the following justifications.

The lower -12% margin is justified for the following reasons:

- Combest et al. (2014) indicated "From a clinical perspective, an equivalence margin of [±]15% or less is not a clinically meaningful difference based on a meta-analysis of both infliximab and adalimumab trials with a focus on Phase III trials."[25]
- Smolen et al. (2014), in a review that considered the ACR20 and other responses across a broad range of therapies, suggested that when comparing treatment effects between products, any differences in the effects of one RA treatment on the ACR20 endpoint that are -12% or less (i.e., -12% to -1%) then effects seen with the comparator product would not be considered to represent clinical meaningful differences in effects.[27]
- A lower margin of -12% is more conservative than a -15% lower margin, which was used to test equivalence between a study product and infliximab in patients with RA, as reported by Yoo et al. (2013),[28] and more conservative than a -18% lower margin, which was used to test noninferiority in patients with RA, as reported by Ogata et al. (2014).[26]

The upper 15% margin is justified for the following reasons:

- Combest et al. (2014) indicated "From a clinical perspective, an equivalence margin of [±]15% or less is not a clinically meaningful difference based on a meta-analysis of both infliximab and adalimumab trials with a focus on Phase III trials."[25]
- Van Vollenhoven et al. (2012) reported results from testing a product against a placebo looking for 20% improvement in ACR20.[21] This suggests that differences in ACR20 that are not at least 20% or more should not be considered to be clinically meaningful. Therefore, a product having a treatment effect that is not more than 15% greater than that observed with a reference comparator product could be considered to be equivalent with the comparator product.

Of note, the power analysis for equivalence was performed using PASS v13.0 and performed using all enrollees; enrollment sample sizes have not been reduced for considerations of loss to follow-up or protocol deviations because the primary evaluation of efficacy is planned using the intent-to-treat (ITT) population, defined as all randomized and treated patients, regardless of loss to follow-up. This is consistent with van Vollenhoven (2012) and Schiff (2008).[21,22]

13.2 Analysis Populations

Five analysis populations are being defined for this study, as follows.

Intent-To-Treat Population

The ITT population will include all patients who are randomized, irrespective of any deviation from the protocol or premature discontinuation. Patients will be analyzed according to the treatment group assigned at the Stage 1 randomization. The ITT population will serve as the basis for the primary efficacy analysis in Stage 1.

Safety Population

The safety population will include all ITT patients who receive at least 1 dose of study drug. Patients will be analyzed according to the actual treatment they receive rather than as randomized. This population will be used for the analysis of safety.

Full Analysis Set

The full analysis set (FAS) will include all patients in the safety population with at least 1 post-baseline ACR20 efficacy assessment. Patients will be analyzed according to the treatment group assigned at the most recent randomization. This population will be used for the secondary efficacy analyses, as well as a sensitivity analysis for the primary efficacy endpoint.

Per-Protocol Population

The per-protocol (PP) population will include all patients in the FAS with no major protocol deviations in Stage 1, and sufficient time in the study. Sufficient time will be defined as having at least the Week 22 ACR20-CRP efficacy assessment and all study drug administrations up to and including the Week 14 study drug administration. Since this population excludes patients with major protocol deviations, patients will be analyzed according to the treatment they were randomized to and received during Stage 1. This population will be used for a sensitivity analysis of the primary efficacy analysis.

Pharmacokinetic Population

The PK population will include all patients in the FAS population in Stage 1 who have valid PK assessments through Stage 2. This includes only patients who have received all and complete treatments required per protocol through Stage 2. This population will be used for the analysis of interchangeability in Stage 2.

13.3 Demographic and Baseline Characteristics

Demographic variables to be recorded include age, gender, race, ethnicity, body height, and body weight.

Demographic information will be presented in listings, and summarized in tables using descriptive statistics or counts and percentages.

13.4 Efficacy Analysis

The efficacy analyses will focus on the ACR core set criteria, the ACR20/50/70-CRP and ACR20/50/70-ESR (20%/50%/70% improvements from baseline in the ACR core set criteria using CRP and ESR, respectively) response rates, and DAS28 (both DAS28-CRP and DAS28-ESR) scores recorded throughout the study. In addition, the SF-36 scores will be analyzed to evaluate health-related quality of life.

13.4.1 Analysis of Primary Efficacy Endpoint

The primary clinical efficacy endpoint for biosimilarity, the ACR20-CRP response rate at Week 22, will be analyzed using the ITT population. Patients who do not have an ACR20-CRP assessment at Week 22, as well as patients who do not receive study drug up to and including the Week 14 administration, will be considered to have not achieved ACR20-CRP. Because these patients are considered non-responders for this analysis, the primary analysis is considered an analysis on the composite endpoint of both ACR20-CRP response and adherence to study drug treatment.

To determine biosimilarity, two standard 1-sided asymptotic Wald tests of the difference between NI-071 and Remicade-US response rates will be performed. If the null hypotheses of both tests are rejected at α=0.05, the equivalence in efficacy is achieved. The hypotheses that will be evaluated are stated, as follows, where P_{NI-071} is the response rate in the NI-071 arm and $P_{Remicade-US}$ is the response rate in the Remicade-US arm:

Ho: $P_{NI-071} - P_{Remicade-US} \leq -12\%$
Ho: $P_{NI-071} - P_{Remicade-US} \geq 15\%$
Ha: $-12\% < (P_{NI-071} - P_{Remicade-US}) < 15\%$

13.4.1.1 Sensitivity Analyses of the Primary Efficacy Endpoint

Five types of sensitivity analyses will be performed for the primary efficacy endpoint. These analyses are outlined in Table 8 and described in detail in the SAP.

Table 8 Sensitivity Analyses of the Primary Efficacy Endpoint

Description	Purpose	Population
Repeat of the primary analysis (Wald-test)	Rather than applying the non-responder imputation (NRI) for patients who did not receive all treatments through Week 14, the data actually collected will be used to determine response status at Week 22. This sensitivity analysis addresses the composite nature of the primary endpoint.	ITT
Repeat of the primary analysis (Wald-test)	The primary analysis will be performed for different populations. For the FAS, 2 analyses will be done: with and without NRI for patients who discontinue study drug.	FAS, PP
Repeat of the primary analysis (Wald-test)	The primary analysis will be performed using a different imputation method. Rather than not allowing for imputation of missing ACR20 components, the mixed component last observation carried forward (LOCF) method for calculating ACR20 response status will be employed.	ITT, FAS, PP
Logistic regression model of the primary endpoint	Modeling will be performed to evaluate if there is any impact on the primary analysis from baseline disease status or geographical region. The model will use ACR20-CRP at Week 22 as a dependent variable, and treatment group, baseline CRP values, and region as covariates.	ITT, FAS, PP
Tipping point analysis of the primary endpoint	A tipping point analysis will be performed if the primary analysis for the ITT population concludes similarity. The purpose is to identify the hypothetical response rates required among the patients with missing data in order to produce statistics that no longer support similarity. To start, instead of assuming a 0% response rate for patients with missing data, the observed response rate for the Remicade-US arm in the PP population will be assumed for both treatment groups. Through iterative steps of increasing the number of non-responders in the NI-071 group, the analysis will assess where the response conclusion switches direction.	ITT

Abbreviations: ACR20-CRP=20% improvement from baseline in the American College of Rheumatology core set criteria using C-reactive protein as the acute-phase reactant; FAS=full analysis set; ITT=intent-to-treat; LOCF=last observation carried forward; NRI=Non-responder imputation; PP=per protocol.

13.4.2 Analysis of Secondary Efficacy Endpoints

Secondary clinical efficacy endpoints include ACR20-CRP (at time points other than Week 22), ACR20-ESR, ACR50-CRP, ACR50-ESR, ACR70-CRP, ACR70-ESR, ACR core set items, DAS28-CRP, and DAS28-ESR. Summary statistics (including number of patients, mean, standard deviation, minimum, median, maximum) of numerical endpoints for DAS28-CRP and DAS28-ESR (value and change from baseline for visit) will be calculated and presented by visit and treatment group. Point estimate and 95% CI of differences between NI-071 and Remicade-US for DAS28-CRP and DAS28-ESR will also be presented. Frequency tables of the number and percentage of patients achieving ACR20-CRP, ACR20-ESR, ACR50-CRP, ACR50-ESR, ACR70-CRP, and ACR70-ESR will be calculated and presented by visit and treatment group. ACR core set items will be summarized (value and change from baseline for visit) descriptively. RAPID3 scores will be summarized (value and change from baseline for visit) descriptively. SF-36 domain subscores and summary scores will be summarized (value and change from baseline for visit) descriptively.

These secondary analyses are considered exploratory, as the power of the trial, designed for the primary endpoint, is not sufficient for the secondary endpoints.

13.5 Pharmacokinetic Analysis

To determine PK similarity, using the GLM procedure in SAS, the 90% CIs of the ratios (Switch/Remicade-US) of least squares means from the ANOVA of the ln-transformed AUC_{tau} and C_{max} will be evaluated at the alpha level of 0.05 for the PK population during the dosing interval of Weeks 46 to 54. If the CI is within the range of 80.00% to 125.00%, PK similarity is achieved. Secondary PK parameters include C_{min} and t_{max} during this dosing interval. Wilcoxon's test will be performed on t_{max}, and C_{min} will be summarized descriptively. Additional PK analyses may be performed.

A complete description of the PK statistical analyses to be performed will be presented in the SAP.

13.6 Accounting for Multiplicity

To maintain the overall significance level of 0.05 for this study, a hierarchical test procedure is applied, where the results of the interchangeability assessment performed at Stage 2 by the PK analysis will be regarded as confirmatory in nature only if the results of the biosimilarity assessment at Stage 1 have shown significant results. By this hierarchical approach, the significance level of the PK analysis does not need further adjustments to account for multiplicity.

No adjustments for multiplicity are necessary following the interim analysis because the interim analysis will be checking for a stop for futility reasons only. Further, the PK analysis for the interchangeability assessment in Stage 2 is based solely on objective variables (plasma concentration data); hence, the introduction of additional bias can be excluded.

13.7 Safety Analysis

13.7.1 Adverse Events

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs (events with onset dates on or after the start of the study drug) and treatment-related TEAEs will be summarized by system organ class (SOC) and preferred term (PT). Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. SAEs and AEs that result in treatment discontinuation will be summarized. AEs of special interest will be summarized by SOC and PT; categories of AEs of special interest include serious infections, malignancies, infusion-related reactions, hepatotoxicity, heart failure, and cytopenias. In addition, CIs will be calculated for the difference in incidence of these AEs of special interest to determine the risk difference between the NI-071 and Remicade-US groups.

All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

13.7.2 Vital Signs, Weight, Physical Examination, and ECG

Vital signs and weight will be summarized using descriptive statistics including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each time point.

Physical examination results at screening will be listed, and changes from screening values will be documented at each time point.

ECG parameters (heart rate and cardiac intervals) at screening and early discontinuation will be listed.

13.7.3 Clinical Laboratory Parameters

Clinical laboratory data will be summarized using descriptive statistics including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each time point.

13.7.4 Anti-drug Antibodies and Neutralizing Antibodies

Positive immunogenicity results will be listed. The incidence of circulating ADAs and the incidence of neutralizing antibodies will be summarized, and the titer of ADA will be summarized over time by treatment group.

13.7.5 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary. Summary tables will be provided for prior medications recorded at screening and concomitant medications continued and/or initiated during the study period.

13.8 Interim Analysis

This study was designed using a hierarchical approach, where the results of the interchangeability assessment (PK analysis) performed at the end of Stage 2 will be regarded as confirmatory in nature only if the results of the biosimilarity assessment at the end of Stage 1 have shown significant results. An interim analysis is planned in order to decide if the study should continue or be stopped for futility after Stage 1.

The interim analysis of the primary clinical efficacy endpoint, the ACR20-CRP response rate, will be performed after the last patient has completed the last visit in Stage 1, the Week 22 visit (the visit of the assessments for the primary efficacy endpoint). This analysis will be performed by an unblinded statistician not otherwise affiliated with the study. An independent data monitoring committee (IDMC) will be established to assess the results and determine whether the study should continue or be stopped for futility. An IDMC charter will be prepared to describe the details of the outputs available to the IDMC as well as to describe the decision tree for the IDMC meeting.

13.9 Independent Data Monitoring Committee

An IDMC will be established by the Sponsor or its designee to evaluate the results of a formal interim efficacy analysis. Members will include experts in RA and biostatistics who are not participating in this study and do not have affiliation with the Investigators or the Sponsor. The IDMC can recommend in writing to the Sponsor whether to continue or stop the clinical study on the basis of the results of the interim analysis. The IDMC's specific duties as well as statistical monitoring guidelines and procedures will be fully described in an IDMC charter.

14 STUDY MANAGEMENT

14.1 Approval and Consent

14.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US Code of Federal Regulations (CFR), and in compliance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

14.1.2 Institutional Review Board/Independent Ethics Committee

The conduct of the study must be approved the Regulatory Authorities and by an appropriately constituted Institutional Review Board (IRB)/ Independent Ethics Committee (IEC). Approval is required for the study protocol, investigational drug brochure, protocol amendments, ICFs, and patient information sheets.

14.1.3 Informed Consent

For each study patient, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the Investigator or one of his/her associates must explain orally and in writing the nature, duration, and purpose of the study, and the action of the drug in such a manner that the patient is aware of the potential risks,

inconveniences, or adverse effects that may occur. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and ICH guidelines. The Investigator will provide the Sponsor or its representative with a copy of the IRB/IEC-approved ICF prior to the start of the study.

14.2 Data Handling

Any data to be recorded directly in the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. Source data should be recorded contemporaneously with the activities performed.

Clinical data will be entered on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must carry only coded identifiers such that personally identifying information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by inVentiv Health. Access to the EDC system is available to authorized users via the study's Internet web site, where an assigned username and password are required for access. Any changes made to data after collection will be made through the use of data clarification forms. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

All study data are to be captured in the eCRF with the exception of clinical laboratory, PK, and immunogenicity data, which will be provided electronically by the laboratories, and data recorded on tablet devices provided to the sites. Reports received by the site from the central laboratory should be printed, retained as source documentation and signed by a medically qualified Investigator, indicating which values are considered clinically significant and to be reported as AEs. All data recorded on the tablet devices will be regarded as source data.

14.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study.

14.4 Record Retention

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a patient's identification number or coded number. All study records, source medical records, and code sheets or logs linking a patient's name to an identification number will be kept in a secure location. Study records such as eCRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission

of the patient/legal representative, except as specified in the ICF (e.g., necessary for monitoring by regulatory authorities or the Sponsor of the clinical study). The Investigator must also comply with all applicable privacy regulations (e.g., US Health Insurance Portability Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

The study site (and the Investigator) will retain the essential documents specified in the ICH GCP (e.g., source document such as medical records, contract, signed ICF). Essential documents should be retained at the study site for at least 15 years following completion of the study, or per regulatory obligations if longer, and thereafter destroyed only after agreement with the Sponsor. However, this is not always applied to those that are not preserveable such as blood samples. In the event of any inconsistency between the above mentioned contents and the contract with the study site, the contract shall prevail. These documents should be retained for a longer period, however, if needed by the Sponsor, and the specific period and method of retention will be separately discussed between the study site and the Sponsor. The Sponsor should notify the head of the study site in writing when the study-related records are no longer needed. The records should be managed by a responsible person appointed by the head of the study site.

14.5 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

On-site monitoring visits will be made at appropriate times during the study. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor source documents and medical records necessary to complete eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the conduct of the study is being done in accordance with applicable regulations and ICH GCP guidelines.

14.6 Definition of the End of Trial

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and have completed the study as stated in the regulatory application (i.e., clinical trial application) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the clinical trial application) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

End of Trial in all other participating countries is defined as Last Patient Last Visit.

14.7 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor will arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating

procedures, ICH GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

14.8 Protocol Amendment and Protocol Deviation

14.8.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no impact on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB/IEC for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate Regulatory Authorities and the IRBs/IECs for approval.

14.8.2 Protocol Deviations

Should a protocol deviation occur, inVentiv Health will inform the Sponsor as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB/IEC and in accordance with applicable Regulatory Authority mandates is an Investigator responsibility. Prospective protocol waivers are strictly prohibited.

14.9 Ethical Considerations

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant US federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US CFR, the EU Directive 2001/20/EC, all other applicable country regulations, and in compliance with ICH GCP guidelines.

IRBs/IECs will review and approve this protocol and the ICF. All patients are required to give written informed consent prior to participation in the study.

14.10 Financing and Insurance

Prior to the study commencing, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide insurance coverage for the clinical study as required by national regulations.

14.11 Publication Policy / Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study

agreement that will be agreed between the Institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their Institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

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16 APPENDICES

Appendix 1: American College of Rheumatology Revised Criteria for the Classification of Functional Status in Rheumatoid Arthritis

Class I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)[a]
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 ability to perform usual self-care, vocational, and avocational activities

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

Source: Hochberg MC, Chang RW, Dwosh I, et al.[14]

Appendix 2: Prohibited DMARDs

Treatment with DMARDs (other than MTX), including traditional non-biologic drugs, biologic drugs, and protein kinase inhibitors, is prohibited during the study and within a period prior to screening (a washout period) appropriate to the pharmacodynamic profile of the specific drug. The following table is a list of these prohibited drugs and the appropriate washout periods.[23]

Traditional Non-biologic DMARDs Prohibited during the Study		
Drug	**Washout Period Prior to Screening**	
Azathioprine	4 weeks	
Chlorambucil	12 weeks	
Chloroquine	4 weeks	
Cyclosporine	8 weeks	
Gold (oral or injectable)	6 months	
Hydroxychloroquine	4 weeks	
Leflunomide	12 weeks or 4 weeks with 11 days standard cholestyramine washout	
Mycophenolate mofetil	12 weeks	
Penicillamine	6 months	
Sulfasalazine	4 weeks	
Tacrolimus	12 weeks	
Marketed Biologic DMARDs Prohibited during the Study		
Drug	**Target**	**Washout Period Prior to Screening**
Abatacept	CTLA-4	12 weeks
Adalimumab	TNF-α	12 weeks
Anakinra	IL-1	1 month
Certolizumab pegol	TNF-α	12 weeks
Etanercept	TNF-α	4 weeks
Golimumab	TNF-α	12 weeks
Infliximab	TNF-α	no prior use allowed
Rituximab	CD20	12 months
Tocilizumab	IL6	12 weeks

Marketed Protein Kinase Inhibitors		
Drug	**Target**	**Washout Period Prior to Screening**
Tofacitinib	PKI	12 weeks

Appendix 3: Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is defined as a serious allergic reaction that is rapid in onset and may cause death. The following criteria were outlined by Sampson et al from the Second Symposium on the Definition and Management of Anaphylaxis (a 2005 meeting of the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network).[17]

Anaphylaxis is highly likely when any 1 of the following 3 criteria are met:

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 1 of the following:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
    b. Reduced blood pressure (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 peak expiratory flow, hypoxemia)
    c. Reduced BP or associated symptoms of end-organ dysfunction (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. Low systolic BP for children is defined as less than 70 mmHg from 1 month to 1 year, less than (70 mmHg + [2 x age]) from 1 to

10 years, and less than 90 mmHg from 11 to 17 years.

b. Adults: systolic BP of less than 90 mmHg or greater than 30% decrease from that person's baseline

Appendix 4: TB Screening Information

Immunosuppressant biologic treatments have been shown to increase the risk of TB infection or to cause conversion from latent to active TB in some circumstances. Because of this, and in accordance with the approved prescribing instructions for Remicade, patients must be screened for active or latent TB prior to entry into this study.

Definitions

Active TB is a disease caused by *M. tuberculosis* in any part of the body and that is in an active state as determined by either a smear or culture taken from any source in the person's body which tests positive for TB or by radiographic evidence. Individuals with active TB are symptomatic, depending upon the location of the disease (most commonly in the lungs but also possibly in the brain, kidneys, spine, or elsewhere), and can spread the infection to others.

Latent TB is said to exist when an individual is infected with *M. tuberculosis*, as evidenced by a positive Interferon Gamma Release Assay (IGRA), such as QuantiFERON-TB Gold, or by a positive purified protein derivative (PPD) skin test, but is asymptomatic and has no evidence of active infection on screening pathology or radiographic tests. Such individuals do not pass the disease to others and should commence a course of prophylactic antimycobacterial treatment to eliminate the infection at least 4 weeks prior to randomization (or longer, if local guidelines specify) and commit to completing the course of treatment.

TB Screening

Ideally, as part of the medical history, the patient should be asked if they have presented with active or latent TB in the past and whether they have received a Bacillus Calmette-Guérin (BCG) vaccination. They should also be asked if they have been in contact with any individuals known to have active TB, or been placed in any circumstances that may have exposed them to an increased risk of TB infection, such as travels to TB endemic regions, close contact with persons with active TB, or workplace risk (e.g., prison, hospitals).

In this study, a patient who tests positive for latent TB (with a positive or indeterminate QuantiFERON test, plus a chest x-ray negative for active TB) will be allowed to enroll if prior prophylactic treatment was documented or if prophylactic treatment for TB was initiated at least 4 weeks prior to baseline (first dose of study drug). If the result is

indeterminate, the test may first be repeated, or PPD testing may be done if the patient has not received a BCG vaccination. If confirmed indeterminate, the patient should be managed as though they have a positive test result or excluded from the study.

Updated Guidelines for Using IGRA[38]

https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5905a1.htm