1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E6011-J081-201
Study Protocol Title:	A Dose Response Study of E6011 in Subjects With Rheumatoid Arthritis Inadequately Responding to Methotrexate
Sponsor:	Eisai Co., Ltd. 4-6-10 Koishikawa, Bunkyo-Ku, Tokyo 112-8088, Japan
Investigational Product Name:	E6011
Indication:	Rheumatoid arthritis (RA) patients inadequately responding to methotrexate (MTX)
Phase:	2
Approval Date:	V1.0 31 Aug 2016 V2.0 13 Oct 2016 V3.0 23 Feb 2017 V4.0 24 Apr 2017 V5.0 31 Aug 2018 V6.0 25 Mar 2019
GCP Statement:	This study is to be performed in full compliance with Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E6011

Name of Active Ingredient: To be determined

Study Protocol Title

A Dose Response Study of E6011 in Subjects With Rheumatoid Arthritis Inadequately Responding to Methotrexate

Study Regions (Countries) or Sites

Japan

Study Period and Phase of Development

October 2016 to February 2020 (planned)
Phase 2

Objectives

To conduct the following assessments on repeated subcutaneous administrations of E6011 in rheumatoid arthritis (RA) patients inadequately responding to methotrexate (MTX):

<Primary objectives>

- To evaluate the efficacy of E6011 compared with placebo by using ACR20 response rate at Week 12 as a primary endpoint
- To evaluate the safety and tolerability of E6011

<Secondary objectives>

- To evaluate the effect of E6011 on suppressing radiographic progression of joint destruction at Week 24
- To evaluate the pharmacokinetics (PK) and immunogenicity of E6011

<Exploratory objective>

- To explore the PK/pharmacodynamics (PD) and biomarkers of E6011

Study Design

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study. The following 4 treatment groups are selected for the study: E6011 100 mg, 200 mg, 400 mg, and placebo. In the E6011 100 mg, 200 mg, and placebo groups, subjects will receive the study treatment (100 mg, 200 mg, or placebo, respectively) at Weeks 0, 1, 2, and then every 2 weeks. In the E6011 400 mg group, subjects will receive 400 mg at Weeks 0, 1, 2, 4, 6, 8, 10 and then 200 mg every 2 weeks.

The study consists of Screening, Observation, Treatment, Extension, and Follow-up Phases.

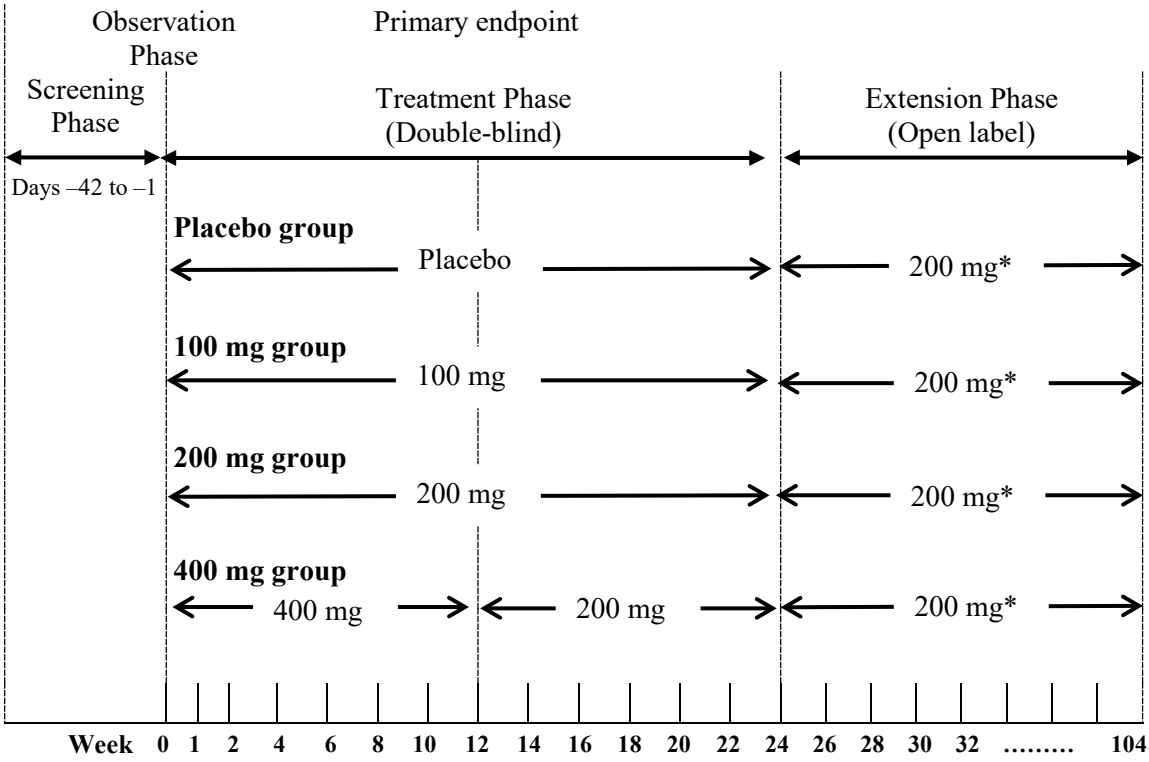
After undergoing screening assessments within 42 days prior to the study treatment, subjects with the certain eligibility confirmed in the Observation Phase will be allocated to any of the E6011 100 mg, 200 mg, 400 mg, or placebo groups at a 1:2:2:2 ratio through dynamic allocation using the following factors: C-reactive protein (CRP) level at the Screening Phase, disease duration, and history of biologics treatment.

In the Treatment Phase (24 weeks), subjects will receive either E6011 or placebo at Weeks 0, 1, 2, and every 2 weeks until Week 22 in a double-blind manner.

Subjects who complete evaluations at Week 24 of the Treatment Phase will enter the Extension Phase. The Extension Phase is up to 104 weeks after the start of the study treatment, and subjects will receive an open-label E6011 200 mg every 2 weeks until Week 102. If the investigator or subinvestigator judges that the response to treatment is insufficient in the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed (reduction of the dose back to 200 mg after an increase to 400 mg will also be allowed).

If subjects complete or discontinue the study, a follow-up visit should be conducted 28 days after the completion or discontinuation of the study, and a follow-up visit or telephone interview should be conducted 70 days after the last dosing.

An overview of the study design is presented below.



*: If the investigator or subinvestigator judges that response to treatment is insufficient during the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed.

In addition, if subjects complete or discontinue the study, a follow-up visit should be conducted 28 days after the completion or discontinuation of the study, and a follow-up visit or telephone interview should be conducted 70 days after the last dosing.

Number of Subjects

A total of 175 subjects (25 for the 100 mg group, 50 for the 200 mg group, 50 for the 400 mg group, and 50 for the placebo group)

Inclusion Criteria

Subjects must meet all of the following criteria to participate in this study:

1. Aged ≥18 and <75 years old at the time of written informed consent
2. RA patients who meet the 1987 ACR criteria or 2010 ACR/EULAR criteria ≥12 weeks before written informed consent
3. Received MTX treatment at 6 to 16 mg/week for ≥12 weeks before screening and presented ≥6 tender joints (out of 68 joints) and ≥6 swollen joints (out of 66 joints) in the Screening and Observation Phases
4. Able to continue a stable dose regimen of MTX at 6 to 16 mg/week from 4 weeks or more before starting the study treatment until completion of the Extension Phase (or until study discontinuation)
5. For patients with a history of biologics treatment for RA [Note], the following criteria should be fulfilled.
   (Note: This includes those treated in clinical studies)
   - The history of biologics treatment for RA with any of adalimumab, infliximab, golimumab, certolizumab pegol, etanercept, tocilizumab, and abatacept (including biosimilars).
   - No biologics treatment for RA within 12 weeks prior to the study treatment
6. CRP level ≥0.6 mg/dL or erythrocyte sedimentation rate (ESR) ≥28 mm/hr in the Screening Phase
7. Erosions at ≥3 sites in radiographic joint image in the Screening Phase, or those with erosions at ≥1 site and either positive for rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibody in the Screening Phase
8. Weighs ≥30 kg and ≤100 kg in the Screening Phase
9. Has voluntarily consented, in writing, to participate in this study. If a subject is below the age of 20, written consent should be obtained from a legally acceptable representative.
10. Has been thoroughly briefed on the requirements of the study, can understand, and is willing and able to comply with all aspects of the protocol

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any history or complication of inflammatory arthritic disorder [Note] other than RA and Sjogren's syndrome
   (Note: Such as arthritis associated with viral infection, systemic lupus erythematosus, mixed connective tissue disease, dermatomyositis/polymyositis, scleroderma, rheumatic polymyalgia, psoriatic arthritis, and arthritis occurring in patients under 16 years of age)
2. Class IV in the Criteria for Functional Status in RA (the ACR 1991 Revised Criteria) in the Screening Phase
3. Received biologics treatment for RA but discontinued it because of inadequate response
4. Received disease-modifying antirheumatic drugs (DMARDs) other than MTX within 4 weeks before staring the study treatment
5. Received reflunomid or tofacitinib within 12 weeks before starting the study treatment
6. Received corticosteroids equivalent to >10 mg/day of prednisolone within 4 weeks before starting the study treatment
7. Received corticosteroids (intraarticular, intramuscular, or intravenous), intraarticular injection of sodium hyaluronate (including sodium hyaluronate crosslinked polymer and sodium hyaluronate crosslinked polymer crosslinked with vinylsulfone), intraarticular injection of local anesthesia

agent, or an analgesic other than NSAIDs (oral, suppository, and topical) within 4 weeks before starting the study treatment

8. Treatment with MTX, folic acid, corticosteroids (equivalent to ≤10 mg/day of prednisolone, taken orally or by suppository) or herbal medicine indicated for RA was started, or dose regimen was modified within 4 weeks before starting the study treatment (however, if MTX dose was increased or decreased beyond 4 mg at one time, MTX should be used at a stable regimen for 8 weeks before starting the study treatment).
9. Underwent arthrocentesis/drainage within 4 weeks before starting the study treatment or cytapheresis therapy within 8 weeks before starting the study treatment
10. Underwent surgical operation on the joint (including synovectomy and repair of tendon rupture) which is evaluated in this study within 8 weeks before informed consent
11. Received cyclophosphamide, cyclosporin (except for eye drop solution), azathioprine, or denosumab within 52 weeks before starting the study treatment
12. Received immunoglobulin preparations or blood products within 24 weeks before starting the study treatment
13. Received a live vaccine within 12 weeks before starting the study treatment, or is planning to receive one
14. Any current clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, or renal disease) that could affect the subject's safety or interfere with the conduct of study in the opinion of the investigator or subinvestigator
15. Any current uncontrolled disorders such as acute cardiac infarction, unstable angina, brain infarct, or symptomatic intracerebral hemorrhage
16. Severe or uncontrolled diabetes
17. History of severe allergy (shock or anaphylactoid symptoms)
18. History or current clinical condition of malignant tumor, lymphoma, leukemia, or lymphoproliferative disease, except for skin carcinoma (epithelial carcinoma or basal cell carcinoma) and cervix carcinoma which have been completely excised and without metastasis or recurrence for more than 5 years before informed consent
19. Immunodeficiency or history of human immunodeficiency virus (HIV) infection
20. Infection requiring hospitalization or intravenous administration of antibiotics within 4 weeks before starting the study treatment or disease requiring administration of antivirus drugs (e.g., herpes zoster) within 4 weeks before starting the study treatment
21. History of tuberculosis or current active tuberculosis
22. History of clinically important vasculitis
23. Tested positive for any of the following in the Screening Phase: HIV, hepatitis B virus surface antigen (HBs antigen), hepatitis B virus surface antibody (HBs antibody), hepatitis B virus core antibody (HBc antibody), hepatitis B virus DNA (HBV DNA), hepatitis C virus antibody (HCV antibody), human T-lymphotrophic virus type I antibody (HTLV-1 antibody), or syphilis (except if positive for the HBs antibody only, and it is clear that this is due to hepatitis B vaccination. In case of positive RPR and negative TP antibody results in the syphilis tests, the positive result is not considered valid if a false positivity is confirmed by repeated TP antibody negative results of other syphilis tests performed 21 days or more later). For subjects who are negative for both HBs antigen and HBV-DNA quantitative test and positive for either or both of anti-HBc antibody and anti-HBs antibody, their study participation is allowed if the investigator or subinvestigator takes a proper measure such as HBV-DNA monitoring based on the "Guideline for measures against hepatitis B caused by immunosuppression and chemotherapy."

24. Positive in tuberculosis test (QuantiFERON®TB Gold Test or T-SPOT®.TB Test) in the Screening Phase. For those whose results are "hold" (indeterminable) in repeated tests, their study participation is only allowed if they start receiving a prophylactic treatment with isoniazid (in principle, 300 mg/day [5 mg/kg/day in case of low weight] for approximately 9 months) ≥21 days before starting the study treatment.
25. Findings indicating a history of tuberculosis on chest x-ray in the Screening Phase
26. Neurological findings such as motor paralysis, visual impairment, or language disorder in the Screening Phase
27. Blood CD4-positive cell count <200 /μL or white blood cell count <3,000 /μL in the Screening Phase
28. Any of the following laboratory abnormalities in the Screening Phase
    - Hemoglobin: <8.0 g/dL
    - Neutrophil count: <1,500/μL
    - Platelet: <100,000/μL
    - AST or ALT: >3× the upper limit of normal (ULN)
    - Serum creatinine: >1.5 mg/dL
    - Serum KL-6: >ULN
    - β-D glucan: >ULN
29. Demonstrated prolonged QTcF interval (>450 ms) in repeated ECG examinations
30. Women of childbearing potential who have a positive pregnancy test in the Screening or Observation Phase or of breastfeeding
31. Women of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device [IUD], a double-barrier method [such as condom plus diaphragm with spermicide], an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 70 days after the last dosing.
    - Are currently abstinent, and do not agree to use a double-barrier method (condom plus diaphragm with spermicide) during the study period or for 70 days after the last dosing.
    - Are using oral contraceptives but are not on a stable dose of the same oral contraceptives for at least 4 weeks before study treatment, or who do not agree to use the same oral contraceptives during the study or for 70 days after the last dosing.

- All women will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [i.e., either of bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy was performed at least 1 month before study treatment]).

32. Men who have not had a successful vasectomy (without confirmed azoospermia) and their female partners do not meet any of the criteria above (however, study entry is allowed if the female partner is not of childbearing potential or practicing highly effective contraception throughout the study period or for 70 days after the last dosing). No sperm donation is allowed during the study period or for 70 days after the last dosing.
33. Scheduled for surgery during the study
34. Currently enrolled in another clinical study, or used any investigational drug or device within 28 days (or 5× the half-life, whichever is longer) before informed consent

35. Has been treated with E6011 or any unapproved biologics for RA
36. Use of a psychotropic agent as recreational purpose other than therapeutic purpose
37. Any history of a medical condition or a concomitant medical condition that in the opinion of the investigator or subinvestigator would compromise the subject's ability to safely complete the study

Study Treatments

Treatment Phase: In the E6011 100 mg, 200 mg, or placebo group, subjects will receive each dose at Weeks 0, 1, 2 and then every 2 weeks up to Week 22 by repeated subcutaneous administration. In the E6011 400 mg group, subjects will receive 400 mg at Weeks 0, 1, 2, 4, 6, 8, 10 and then 200 mg every 2 weeks up to Week 22 by repeated subcutaneous administration.

Extension Phase: E6011 200 mg will be subcutaneously administered every 2 weeks until Week 102. When subjects insufficiently respond to the treatment, repeated subcutaneous administration (400 mg of E6011 every 2 weeks) will be allowed.

The study drug containing E6011 50 mg, 100 mg, or placebo in 1 vial (1 mL) will be used in the study. In the Treatment Phase, 4 mL will be subcutaneously administered in Weeks 0 to 10, and 2 mL will be subcutaneously administered in Weeks 12 to 22. In the Extension Phase, 2 mL will be administered subcutaneously for the 200 mg dosing and 4 mL will be administered subcutaneously for the 400 mg dosing.

In the 2 mL administration, subjects will receive study drug subcutaneously in 2 separate sites, 1 mL each, from the following sites: right or left upper arm, right or left abdomen, or right or left thigh. In the 4 mL administration, subjects will receive study drug subcutaneously in 4 separate sites, 1 mL each. However, 2 mL of the study drug may be given subcutaneously in 1 site only if the investigator or subinvestigator judges that the study drug can be administered properly.

Duration of Treatment

Treatment Phase: 24 weeks

Extension Phase: 80 weeks

Concomitant Drug/Therapy

<Prohibited Concomitant Drugs and Therapies>

The concomitant use of the following drugs or therapies is prohibited until completion of the Extension Phase (or until study discontinuation).

- DMARDs (except MTX)
- Biologics (adalimumab, infliximab, golimumab, certolizumab pegol, etanercept, tocilizumab, abatacept, etc.), including biosimilars
- Intraarterial, intramuscular, or intravenous injection of corticosteroids
- Intraarticular injection of sodium hyaluronate (including sodium hyaluronate crosslinked polymer and sodium hyaluronate crosslinked polymer crosslinked with vinylsulfone) or local anesthetic agent
- Arthrocentesis/drainage
- Cytapheresis
- Any analgesic other than NSAIDs (oral, suppository, or topical)
- Cyclophosphamide, cyclosporin (with the exception of eye drops), azathioprine, or denosumab
- Immunoglobulin preparations or blood products

- Live vaccines
- Activated form folic acid, over-the-counter medications containing folic acid as main component
- Other investigational drugs or investigational devices
- Surgical operations on arthritic disorder

< Restricted Concomitant Drugs >

- MTX and folic acid should be continued at a stable dose regimen up to completion of the Extension Phase (or until study discontinuation). However, if an adverse event associated with MTX is noted during the Extension Phase, dose reduction or interruption is permitted. If the event disappears after dose reduction or interruption, the dose can be increased to the previous level.
- Corticosteroids (equivalent to ≤10 mg/day of prednisolone, taken orally or by suppository) and herbal medicine indicated for RA are allowed under restricted conditions, but the dose regimen should not to be modified up to Week 24 (or until study discontinuation). Between Week 24 and Week104, the regimen should not be modified except for the following cases: dose reduction, dose interruption, dose increase following the dose reduction (up to the initial dose level), and restarting administration after interruption.
- NSAIDs (oral, suppository, or topical) may be taken concomitantly but are prohibited between the night before the day of efficacy assessments and the end of the assessments.
- After the date Version 6 of the protocol is approved by IRB, dose reduction, dose interruption, dose increase following the dose reduction (up to the initial dose level), and restarting administration after interruption will be allowed for MTX, folic acid, corticosteroids, or herbal medicine indicated for RA). There will be no restrictions in using NSAIDs (oral, suppository, or topical).

Assessments

After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct assessments other than <safety>.

< Efficacy >
Number of tender joints, number of swollen joints, visual analog scale (VAS; patient's pain assessment and patient's disease activity global assessment, and physician's disease activity global assessment), patient's physical function assessment (health assessment questionnaire [HAQ]), CRP, ESR, and joint x-ray

< Safety >
Safety will be assessed based on all adverse events (AEs) observed, regular monitoring of clinical laboratory tests (including vasculitis marker tests), vital signs, chest x-ray, standard 12-lead electrocardiograms, physical findings, injection site findings, and neurological findings.

< Pharmacokinetics >
Serum E6011 concentration

< Biomarkers >
Serum total fractalkine (FKN) concentration, serum RF concentration, serum anti-CCP antibody concentration, serum matrix metalloproteinase (MMP)-3 concentration, serum tartrate resistant acid phosphatase (TRACP) -5b concentration, serum cytokine concentration (granulocyte macrophage colony-stimulating factor [GM-CSF], interferon-γ [IFN-γ], interleukin [IL]-1β, IL-6, TNFα, etc.),

serum leucine-rich alpha-2 glycoprotein 1 (LRG1) concentration, serum angiopoietin 2 (Ang2) concentration, Vectra™ DA, immunocytes such as blood CX3CR1-positive cells

< Immunogenicity >
Serum anti-E6011 antibody

Bioanalytical Methods

Serum E6011 concentration, serum total FKN concentration, serum RF concentration, serum anti-CCP antibody concentration, serum MMP-3 concentration, serum TRACP-5b concentration, serum cytokine concentration, serum LRG1 concentration, serum Ang2 concentration, Vectra™ DA, and serum anti-E6011 antibody will be determined using validated assay methods. Immunocytes such as blood CX3CR1-positive cells will be analyzed.

Statistical Methods

The statistical analyses in the Treatment Phase will be performed after the database in the Treatment Phase is locked and the treatment is unblinded, and then final statistical analyses will be performed by using all data after the database throughout the study period is locked.

The details will be described separately in the Statistical Analysis Plans. The Statistical Analysis Plans for the Treatment Phase and the entire study (the Treatment and Extension Phases) will be finalized before each database lock.

< Primary Endpoint >

- ACR20 response rate at Week 12

< Secondary Endpoints >

- ACR20, ACR50, and ACR70 response rates at each evaluation time point (excluding ACR20 response rate at Week12)
- Values and changes from baseline in ACR components (number of tender joints, number of swollen joints, VAS [patient's pain assessment and patient's disease activity global assessment, and physician's disease activity global assessment], patient's physical function assessment [HAQ], and CRP/ESR), DAS28-ESR, DAS28-CRP, simple disease activity index (SDAI), and clinical disease activity index (CDAI) at each evaluation time point
- EULAR response classification and disease activity classification based on DAS28-ESR and DAS28-CRP at each evaluation time point
- Remission rates calculated based on remission criteria (DAS28-ESR, DAS28-CRP, SDAI, CDAI, and Boolean) at each evaluation time point
- Values and changes from baseline in modified total sharp score (mTSS) at each evaluation time point

< Analysis Sets >

- The Full Analysis Set (FAS) is the group of randomized subjects who received the study drug and had at least 1 evaluable postdose primary efficacy data.
- The Per Protocol Set (PPS) is the group of subjects who sufficiently complied with the protocol. Details of the PPS criteria will be determined before database lock and treatment unblinding and will be specified in the Statistical Analysis Plan.
- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 evaluable postdose safety data.

< Efficacy Analyses >

The primary efficacy analysis set is FAS.

Analyses for the Primary Endpoint

ACR20 response rate at Week 12 will be analyzed using a logistic regression model with CRP level at the Screening Phase, disease duration and history of biologics treatment as covariates, for the comparison between placebo and either E6011 200 mg or 400 mg. Overall significance level is α=0.025 (one-sided). The Hochberg method will be used to adjust the multiplicity. Subjects with missing primary efficacy endpoint due to early discontinuation or other reasons will be considered nonresponders. In case that the number of subjects in each category of covariates is very small, integration of the categories will be planned. ACR20 response rate and its 2-sided 95% confidence interval for each treatment group will be calculated. The difference in ACR20 response rate between each of E6011 doses and placebo and its 2-sided 95% confidence interval will also be calculated. Subgroup analyses or sensitivity analyses will be conducted as needed.

In addition, the following analyses will be conducted for ACR20 response rate at Week 12.

- To compare ACR20 response between E6011 100 mg and placebo by using a logistic regression model (CRP level at the Screening Phase, disease duration and history of biologics treatment as covariates). The difference in ACR20 response rate between E6011 100 mg and placebo and its 2-sided 95% confidence interval will also be calculated.
- To estimate the dose-response relationship using a statistical model, such as E_{max} model, if appropriate

Analyses for the Secondary Endpoints

The multiplicity adjustment will not be considered for secondary efficacy analyses.

For ACR20 (excluding Week 12), ACR50, and ACR70 response rates at each evaluation time point, similar analyses to primary analyses will be conducted.

For each component of ACR (number of tender joints, number of swollen joints, VAS [patient's pain assessment and patient's disease activity global assessment, and physician's disease activity global assessment], patient's physical function assessment [HAQ], and CRP/ESR), DAS28-ESR, DAS28-CRP, SDAI, and CDAI, summary statistics (mean, standard deviation, median, and range) for values and changes from the baseline will be calculated by treatment group and evaluation point. The changes from baseline will also be analyzed by using ANCOVA with baseline value, CRP level at the Screening Phase, disease duration and history of biologics treatment as covariates. The significance level for comparisons between placebo and each treatment group with E6011 (100 mg, 200 mg, and 400 mg) is α=0.05 (2-sided).

For mTSS, summary statistics for values and change from baseline will be calculated by treatment group and evaluation time point. The changes from baseline will be analyzed by using ANCOVA in the same manner as above.

For EULAR response classification and disease activity classification based on DAS28-ESR and DAS28-CRP, shift tables will be created by treatment group and evaluation time point.

For remission rates in DAS28-ESR, DAS28-CRP, SDAI, CDAI, and Boolean, similar analyses to primary analyses will be conducted.

< Pharmacokinetic Analyses >

For the Treatment Phase, summary statistics for serum E6011 concentrations at each specified time point will be calculated by treatment group. Serum E6011 concentration-time profiles will be plotted.

Population pharmacokinetic analyses will be conducted. Data from other studies will be integrated as necessary. E6011 concentration data will be used to build PK models. The models may be used to explore the relationship between PK and covariates. The relationship between serum E6011

concentrations and biomarkers and/or efficacy will also be explored through population PK/PD modeling. For population PK analyses, the details will be described in the separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

< Biomarkers >

For the Treatment Phase, summary statistics for values, and changes and percent changes from baseline of serum RF concentration, serum anti-CCP antibody concentration, and serum MMP-3 concentration, serum TRACP-5b concentration, serum cytokine concentration, serum LRG1 concentration, serum Ang2 concentration, Vectra™ DA and its components (VCAM-1, epidermal growth factor [EGF], vascular endothelial growth factor [VEGF]-A, IL-6, tumor necrosis factor receptor-I [TNF-RI], MMP-1, MMP-3, YKL-40, leptin, resistin, serum amyloid A [SAA], and CRP), by treatment group and evaluation time point, will be calculated. Exploratory investigations of the relationship between efficacy and biomarkers will be conducted. Details and results of analyses of immunocytes such as blood CX3CR1-positive cells will be provided in a separate report, and will not be included in the clinical study report.

< Immunogenicity >

All immunogenicity analyses will be performed using the Safety Analysis Set. The percentage and frequency of occurrences will be calculated for serum anti-E6011 antibodies by treatment group and evaluation time point. If anti-E6011 antibody develops, the frequency and percentage of any anti-E6011 antibody neutralization activity and isotypes will be calculated.

< Safety Analyses >

All safety analyses will be performed on the Safety Analysis Set. For the Treatment Phase, summary statistics for safety data, presented by treatment group, will be calculated on an "as treated" basis (n, mean, standard deviation, median, minimum, maximum for continuous variables; n and percentage for categorical variables). Safety variables include adverse events, clinical laboratory parameters, vital signs, standard 12-lead ECG results, chest x-ray, neurological findings, and blood CD4-positive cell count.

- Incidence (%) of adverse events occurring postdose will be calculated by treatment group
- For clinical laboratory parameters, vital signs, and blood CD4-positive cell counts, summary statistics for each value and change from baseline will be calculated by treatment group
- For standard 12-lead ECG, chest x-ray, and neurological findings, the frequency and percentage of abnormal findings will also be calculated by treatment group

As to the Extension Phase, similar analyses to those described above in the Treatment Phase will be conducted for efficacy, pharmacokinetics (except for population PK and PK/PD analyses), biomarker, immunogenicity, and safety endpoints by treatment group of the Treatment Phase.

Interim Analyses

No interim analysis is planned for this study.

Sample Size Rationale

ACR20 response rate at Week 12 was assumed to be 30% in the placebo group and at least 60% in both of the E6011 200 mg and 400 mg groups, on the basis of the previous E6011-J081-103 study and the results from other drugs for treatment of RA. Although multiplicity will be considered by using the Hochberg method in the primary analysis, sample size was conservatively calculated at a 1-sided significance level of α=0.0125 (α=0.025/2). The sample sizes of 50 for the E6011 200 mg, 400 mg, and placebo groups will have 91% power to detect a difference in response rate of 35% between placebo and each E6011 group and will have 79% power to detect a difference in response

rate of 30% based on a chi-square test. The sample size of 25 for the E6011 100 mg group was determined for the purpose of estimating the dose-response curve.

3 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACR	American College of Rheumatology
ADL	activities of daily living
ANCOVA	analysis of covariance
Ang2	angiopoietin 2
ALP	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
AST	aspartate aminotransferase (SGOT)
ATC	anatomical therapeutic chemical
BUN	blood urea nitrogen
CCP	cyclic citrullinated peptide
CDAI	clinical disease activity index
CH50	50% hemolytic unit of complement
CRA	clinical research associate
CRO	contract research organization
CRP	C-reactive protein
CTCAE	common terminology criteria for adverse events
CX3CR1	CX3C motif chemokine receptor 1 (receptor of fractalkine)
DAS	disease activity score
DNA	deoxyribonucleic acid
DMARDs	disease-modifying antirheumatic drugs
EGF	epidermal growth factor
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	full analysis set
FKN	fractalkine
γ-GTP	γ-glutamine transpeptidase
GCP	good clinical practice
GM-CSF	granulocyte macrophage colony-stimulating factor
HAQ	health assessment questionnaire
HbA1c	hemoglobin A1c
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTLV-1	human T cell lymphotropic virus-1
ICAM-1	intercellular adhesion molecule-1
ICH	International Conference on Harmonisation

Abbreviation	Term
IFN-γ	interferon-γ
IgG	immunoglobulin G
IL	interleukin
IVRS/IWRS	interactive voice/web response systems
LDH	lactate dehydrogenase
LRG1	leucine-rich alpha-2 glycoprotein 1
MedDRA	Medical Dictionary for Regulatory Activities
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging system
mTSS	modified total sharp score
MTX	methotrexate
NSAIDs	nonsteroidal antiinflammatory drug
PD	pharmacodynamics
PK	pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PPS	per protocol set
PT	preferred term
QOL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RA	rheumatoid arthritis
RF	rheumatoid factor
SAA	serum amyloid A
SDAI	simple disease activity index
SOC	system organ class
SOP	standard operating procedures
TEAE	treatment emergent adverse events
TNFα	tumor necrosis factor α
TNF-RI	tumor necrosis factor receptor-I
TRACP-5b	tartrate resistant acid phosphatase 5b
VAS	visual analog scale
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) constituted and functioning in accordance with Good Clinical Practice (GCP). Any protocol amendment or revision to the ICF will be resubmitted to the IRB for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in CRA[s], change of telephone number[s]). Documentation of IRB compliance with the GCP regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB chairman must be sent to the head of the medical institution before study start and such documents must be sent to the sponsor before the release of any study drug to the site by the sponsor or its designee. If the IRB decides to suspend or terminate the study, the head of the medical institution will immediately send the notice of study suspension or termination to the sponsor.

In accordance with GCP, study progress is to be reported to IRB annually (or as required) by the investigator via the head of the medical institution. The sponsor will submit periodic reports and inform the IRB via the investigator and the head of the medical institution of any reportable adverse events (AEs) per GCP and local IRB standard operating procedures. Upon completion of the study, the investigator will provide the IRB and the sponsor with a brief report of the outcome of the study via the head of the medical institution.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to the following:

- Principles of the World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects)
- GCP
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960)

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator or subinvestigator must explain to each subject (or guardian/legally acceptable representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential clinical risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may reject the participation or withdraw from the study at any time, and that the rejection or withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject (or the subject's legally acceptable representative) should understand the statement before signing and dating it and will be given a copy of the signed document. The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB-approved ICF must be prepared in accordance with GCP and all applicable local regulations. Each subject must sign an approved ICF before study participation. The form must be signed and dated by the investigator or subinvestigator (and clinical research coordinator, if required). The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site. The subject (or the subject's legally acceptable representative) should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators selected by the sponsor (Eisai) at approximately 100 investigational sites in Japan.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor are listed in Appendix 2.

7 INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease characterized by the inflammation of synovium in a joint. Its major clinical symptoms are pain and swelling of joints of limbs. Progressed inflammation of synovium causes joint destruction, which leads to impaired activity of daily living (ADL) and eventually lowers quality of life (QOL). Joint dysfunction may be reversible after treatment in many cases at the onset, but it often becomes irreversible after the development of joint destruction. In addition, prolonged disease increases the incidence of complications such as interstitial pneumonia and secondary amyloidosis. As a result, RA patients are considered to have a shorter life expectancy than healthy adult people by approximately 10 years due to events including cardiovascular system associated with infection and inflammation as well as dysfunction caused by joint destruction (Tanaka Y, 2011; Miyasaka N, 2013).

Estimated prevalence of RA is approximately 1% of the world population, of which 600,000 to 700,000 are Japanese. Patients most commonly affected are women in their 40s to 50s, who are in their most productive years. This causes significant psychological, social, and financial burdens to their family in addition to their own physical difficulties (Ochi T, et al., 2004).

Disease-modifying antirheumatic drugs (DMARDs) have been mainly used to treat RA patients, with methotrexate (MTX) being the standard medication. However, some patients

do not sufficiently benefit from DMARD therapy as they experience adverse reactions, or do not adequately respond to DMARDs (Kremer JM, 2001).

There are several reports indicate that the emergence of biologics such as anti-TNF agents can improve clinical symptoms, prevent joint destruction progression, and improve impaired physical function in patients who do not adequately respond to DMARD therapy (Maini R, et al., 1999; Nishimoto N, et al., 2007; Takeuchi T, et al., 2013). Meanwhile, the remission rate is approximately 20% to 40% after biologics treatment (Takeuchi T, 2010) and there are patients who are unable to continue the treatment due to the adverse reactions. Thus, medical needs are not fully satisfied and development of highly effective and safer drugs with a new mechanism of action is eagerly anticipated.

E6011 is the world's first humanized fractalkine (FKN) monoclonal antibody (mAb). The antibody was created in KAN Research Institute, Inc., a research subsidiary of Eisai Co., Ltd. FKN is thought to have both chemotaxis and adhesive effects to leukocytes and to play an important role on cell invasions in inflamed tissues (Imai T, et al., 2005). E6011 inhibited human FKN-induced chemotaxis of human fractalkine receptor (CX3CR1) expressing mouse B lymphocyte precursor cells, in vitro. In a collagen-induced arthritis (CIA) model in mice, a widely used animal model for RA, administrations of FKN monoclonal antibodies against mouse FKN showed amelioration of the status of RA. CX3CR1 and FKN are reported to be strongly expressed in the synovium of patients with RA (Nanki T, et al., 2002) and the relationship with RA is suggested. FKN is reported to be involved in the differentiation of osteoclast (Koizumi K, et al., 2009); thus, E6011 is also expected to have an inhibitory effect against the structural damage of joints through inhibition of bone absorption in RA.

A Phase 1 clinical study of single intravenous (IV) administration of E6011 in healthy adults (E6011-J081-001, hereinafter called Study 001) and a Phase 1 clinical study of single subcutaneous (SC) administration of E6011 in healthy adults (E6011-J081-002, hereinafter called Study 002) have been completed. In Study 001 (IV: 0.0006 to 10 mg/kg) and Study 002 (SC: 50 to 400 mg), adverse events which could affect safety and tolerability have not been observed in any dose group.

In a Phase 1/2 clinical study of repeated subcutaneous administrations of E6011 in RA subjects (E6011-J081-103, hereinafter called Study 103), we evaluated the safety and tolerability of E6011 at repeated subcutaneous administrations of 100 mg, 200 mg, and 400 mg as primary objective. Analysis of 12-week dosing presented no concerns about the safety and tolerability in RA subjects who repeatedly received E6011 at 100 to 400 mg and the clinical symptoms of RA tended to be improved in exploratory efficacy evaluations. In consideration of current situation where an RA medication with novel mechanism of action in terms of safety and efficacy is desired and E6011 is highly expected to provide benefits to RA patients as a novel therapeutic agent, a double-blind, placebo-controlled, parallel-group comparison study was planned to assess the dose response of the efficacy and safety of E6011.

The last subject entered the Extension Phase (open-label) in March 2018, and all subjects had completed 52 weeks of treatment with E6011 by March 2019. Consequently, it was

considered unnecessary to conduct any non-safety assessments after March 2019, and the protocol will be revised to Version 6.

8 STUDY OBJECTIVES

The following assessments will be conducted on repeated subcutaneous administrations of E6011 in RA patients inadequately responding to MTX.

8.1 Primary Objectives

- To evaluate the efficacy of E6011 compared with placebo by ACR20 response rate at Week 12 as a primary endpoint
- To evaluate the safety and tolerability of E6011

8.2 Secondary Objectives

- To evaluate the effect of E6011 on suppressing radiographic progression of joint destruction at Week 24
- To evaluate the PK and immunogenicity of E6011

8.3 Exploratory Objective

- To explore the PK/pharmacodynamics (PD) and biomarkers of E6011

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study. The following 4 treatment groups are selected for the study: E6011 100 mg, 200 mg, 400 mg, and placebo. In the E6011 100 mg, 200 mg, and placebo groups, subjects will receive the study treatment (100 mg, 200 mg, or placebo, respectively) at Weeks 0, 1, 2, and then every 2 weeks. In the E6011 400 mg group, subjects will receive 400 mg at Weeks 0, 1, 2, 4, 6, 8, 10 and then 200 mg every 2 weeks.

The study consists of Screening, Observation, Treatment, Extension, and Follow-up Phases.

Screening assessments will be performed within 42 days prior to the study treatment, and subjects with the certain eligibility confirmed in the Observation Phase will be allocated to any of the E6011 100 mg, 200 mg, 400 mg, or placebo groups at a 1:2:2:2 ratio through dynamic allocation using the following factors: C-reactive protein (CRP) level at the Screening Phase, disease duration and history of biologics treatment.

In the Treatment Phase (24 weeks), subjects will receive either E6011 or placebo at Weeks 0, 1, 2, and every 2 weeks until Week 22 in a double-blind manner.

Subjects who complete evaluations at Week 24 of the Treatment Phase will enter the Extension Phase. The Extension Phase is up to 104 weeks after the start of the study treatment, and subjects will receive an open-label E6011 200 mg every 2 weeks until Week 102. If the investigator or subinvestigator judges that the response to treatment is insufficient in the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed (reduction of the dose back to 200 mg after an increase to 400 mg will also be allowed).

If subjects complete or discontinue the study, a follow-up visit should be conducted 28 days after the completion or discontinuation of the study, and a follow-up visit or telephone interview should be conducted 70 days after the last dosing.

An overview of the study design is presented in Figure 1.

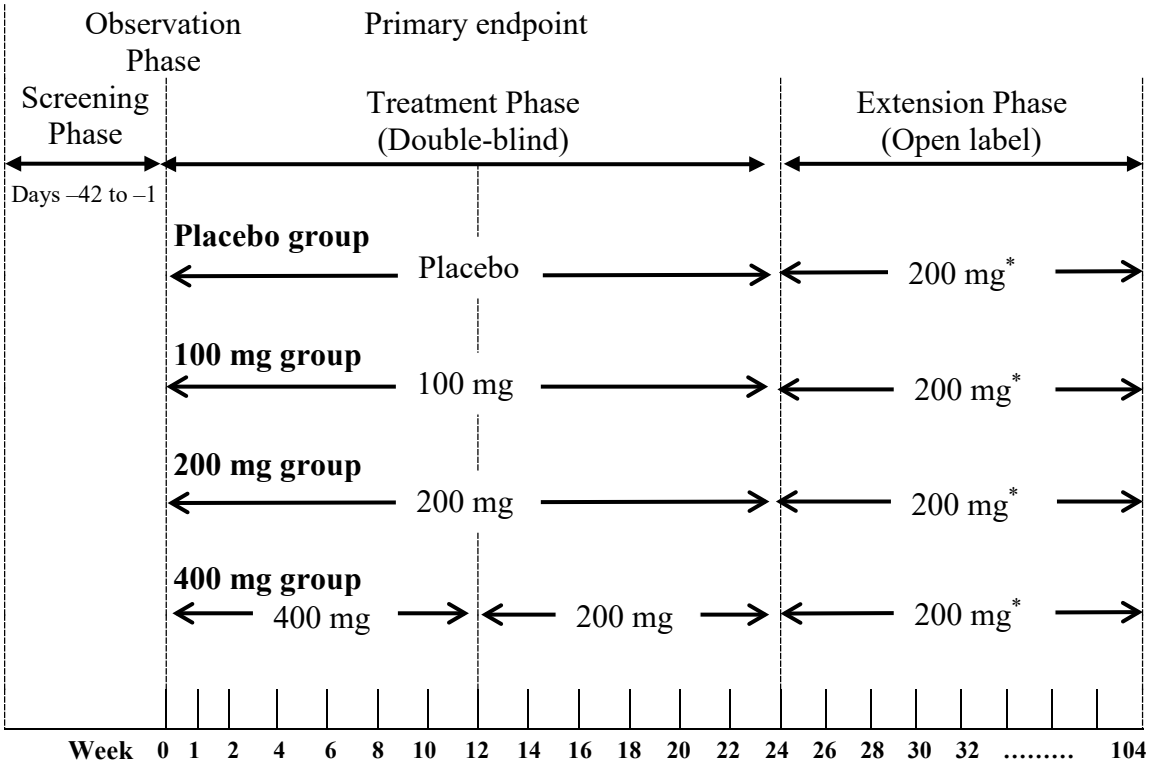


Figure 1 Study Design

*: If the investigator or subinvestigator judges that response to treatment is insufficient during the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed.

In addition, if subjects complete or discontinue the study, a follow-up visit should be conducted 28 days after the completion or discontinuation of the study, and a follow-up visit or telephone interview should be conducted 70 days after the last dosing.

9.1.1 Screening Phase

Subjects must be fully informed of the nature of the study and written informed consent must be obtained prior to the start of any assessment/evaluation for this study. The procedure for obtaining informed consent is described in Section 5.3.

Subjects who submitted informed consent will undergo screening evaluations between Day –42 and Day –1 to confirm that each subject meets all the inclusion criteria and none of the exclusion criteria.

Results of the screening assessments will be recorded in the CRF. If a subject is judged ineligible to enroll the study, the reason should also be recorded in the CRF.

For subjects who require prophylactic treatments with isoniazid based on the results of the tuberculosis test at the Screening Phase, the prophylactic treatments are needed for at least 21 days before starting the study treatment, so the duration of the Screening Phase may be extended until 21 days from the start of isoniazid administrations. If a patient requires another syphilis test based on the result in the Screening Phase, reexamination has to be performed after an interval of 21 days or longer during the Screening Phase. The Screening Phase can be extended until the reexamination result is obtained.

9.1.2 Observation Phase (Day 1: Predose)

Subjects who complete the assessments in the Screening and Observation Phases and meet the criteria for inclusion/exclusion (Sections 9.3.1 and 9.3.2) will start the Treatment Phase.

9.1.3 Treatment Phase

Subjects with confirmed eligibility in the Observation Phase to enter the study will be randomized to E6011 100 mg, 200 mg, 400 mg, or placebo group at a 1:2:2:2 ratio through dynamic allocation using the following factors: CRP level at the Screening Phase, disease duration and history of biologics treatment. Subjects will receive either E6011 or placebo at Weeks 0, 1, 2, and then every 2 weeks until Week 22 in a double-blind manner.

9.1.4 Extension Phase

Subjects who complete evaluations at Week 24 of the Treatment Phase will enter the Extension Phase. The investigator or subinvestigator must confirm that all data through Week 24 of the Treatment Phase (the double-blind part) are completely entered into CRFs by Week 26, when the initial assessments in the Extension Phase will be performed. Each subject's assigned treatment group will be blinded until the database of the Treatment Phase is fixed.

The Extension Phase is up to 104 weeks after the start of the study treatment, and subjects will receive an open-label E6011 200 mg every 2 weeks until Week 102. If the investigator or subinvestigator judges that the response to treatment is insufficient in the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed (reduction of the dose back to 200 mg after an increase to 400 mg will also be allowed).

9.1.5 Follow-up Phase

If subjects complete or discontinue the study, a follow-up visit should be conducted 28 days after the completion or discontinuation of the study, and a follow-up visit or telephone interview should be conducted 70 days after the last dosing.

9.2 Discussion of Study Design, Including Choice of Control Groups

This is a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison, dose-response study with a primary objective to evaluate the efficacy and safety of repeated subcutaneous administrations of E6011 in RA subjects who inadequately respond to a treatment with MTX.

In all of the recommendations of the European League Against Rheumatism (EULAR) (Josef SS, et al., 2013), the guideline of the American College of Rheumatology (ACR) (Singh JA, et al., 2016), and "the guideline for the use of TNF inhibitors" of the Japan College of Rheumatology, a basic treatment for RA is the one with low molecular weight DMARDs, particularly MTX, a standard therapeutic drug, and biologics are considered as a secondary option when patients inadequately respond to MTX. For a clinical study of E6011, we consider it appropriate to target those who inadequately respond to MTX (a standard therapeutic drug for RA) as subjects.

Randomization will be used for avoiding bias in assigning subjects to treatment groups, and making the distributions of subject characteristics (such as demographics and other baseline characteristics), known and unknown, of treatment groups be similar, as well as improving the validity of statistical comparison among groups. Blinding will be also employed to avoid the occurrence of bias in data collections or evaluation of endpoints. In this study, placebo will be used as a comparator drug and subjects will be randomized to treatment groups through dynamic allocation using the following factors with a potential impact on efficacy evaluations: CRP level at the Screening Phase, disease duration and history of biologics treatment.

All of the EULAR recommendations (Josef SS, et al., 2013), the ACR guideline (Singh JA, et al., 2016), and the guideline for the use of TNF inhibitors of the Japan College of Rheumatology indicate that drug therapies for RA should be reviewed every 3 or 6 months. "The Guideline for the clinical evaluation of antirheumatic drugs" also describes that "the duration of Phase 3 study should be determined according to the properties of an investigational drug and should be approximately 12 weeks in general or up to 6 months as needed". In fact, many clinical studies in RA patients are designed to have a primary evaluation time point at Week 12 or 24.

Since the result from Study 103 suggested the efficacy of E6011 in its 12-week treatment period, the primary endpoint of this study is determined to be ACR20 response rate at Week 12. E6011 is expected to have an inhibitory effect against the structural damage of joints through inhibition of bone absorption in RA. Therefore, modified Total Sharp Score (mTSS), a measure for joint destruction progression, is also evaluated in this study. "The Guideline for the clinical evaluation of antirheumatic drugs" and clinical study data of

similar drugs to E6011 indicate that at least 24 weeks is required for mTSS evaluation; thus, the double-blind part of this study is designed to be 24 weeks.

Subjects who complete the double-blind part for 24 weeks will be able to proceed to the Extension Phase, where E6011 200 mg may be administered every 2 weeks up to Week 104 in an open-label manner. Our target is patients who inadequately respond to MTX, a standard therapeutic agent for RA. Therefore, we consider that the study design where subjects can continue E6011 treatment is useful from the perspective of patient benefit.

Furthermore, if the subjects insufficiently respond to the treatment in the Extension Phase, the design also allows for administration of E6011 400 mg every 2 weeks

The Follow-up Phase was set to be 70 days after the last dose of the study drug, which is approximately 5 times of the longest half-life of E6011 in the previous clinical data.

9.3 Selection of Study Population

Subjects who meet all of the inclusion criteria and do not meet any of the exclusion criteria will be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to participate in this study:

1. Aged ≥18 and <75 years old at the time of written informed consent
2. RA patients who meet the 1987 ACR criteria or 2010 ACR/EULAR criteria ≥12 weeks before written informed consent
3. Received MTX treatment at 6 to 16 mg/week for ≥12 weeks before screening and presented ≥6 tender joints (out of 68 joints) and ≥6 swollen joints (out of 66 joints) in the Screening and Observation Phases
4. Able to continue a stable dose regimen of MTX at 6 to 16 mg/week from 4 weeks or more before starting the study treatment until completion of the Extension Phase (or until study discontinuation)
5. For patients with a history of biologics treatment for RA[Note], the following criteria should be fulfilled.
   (Note: This includes those treated in clinical studies)
   - The history of biologics treatment for RA with any of adalimumab, infliximab, golimumab, certolizumab pegol, etanercept, tocilizumab, and abatacept (including biosimilars).
   - No biologics treatment for RA within 12 weeks prior to the study treatment
6. CRP level ≥0.6 mg/dL or erythrocyte sedimentation rate (ESR) ≥28 mm/hr in the Screening Phase
7. Erosions at ≥3 sites in radiographic joint image in the Screening Phase, or those with erosions at ≥1 site and either positive for rheumatoid factor (RF) or anti-cyclic citrullinated peptide (CCP) antibody in the Screening Phase

8. Weighs ≥30 kg and ≤100 kg in the Screening Phase
9. Has voluntarily consented, in writing, to participate in this study. If a subject is below the age of 20, a legally acceptable representative should provide written consent
10. Has been thoroughly briefed on the requirements of the study, can understand, and is willing and able to comply with all aspects of the protocol

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Any history or complication of inflammatory arthritic disorder[Note] other than RA and Sjogren's syndrome
   (Note: This includes arthritis associated with viral infection, systemic lupus erythematosus, mixed connective tissue disease, dermatomyositis/polymyositis, scleroderma, rheumatic polymyalgia, psoriatic arthritis, and arthritis occurring under 16 years of age)
2. Class IV in the Criteria for Functional Status in RA (the ACR 1991 Revised Criteria) in the Screening Phase
3. Received biologics treatment for RA but discontinued it because of inadequate response
4. Received disease-modifying antirheumatic drugs (DMARDs) other than MTX within 4 weeks before staring the study treatment
5. Received reflunomid or tofacitinib within 12 weeks before starting the study treatment
6. Received corticosteroids equivalent to >10 mg/day of prednisolone within 4 weeks before starting the study treatment
7. Received corticosteroids (intraarticular, intramuscular, or intravenous), intraarticular injection of sodium hyaluronate (including sodium hyaluronate crosslinked polymer and sodium hyaluronate crosslinked polymer crosslinked with vinylsulfone), intraarticular injection of local anesthesia agent, or an analgesic other than NSAIDs (oral, suppository, and topical) within 4 weeks before starting the study treatment
8. Treatment with MTX, folic acid, corticosteroids (equivalent to ≤10 mg/day of prednisolone, taken orally or by suppository) or herbal medicine indicated for RA was started, or dose regimen was modified within 4 weeks before starting the study treatment (however, if MTX dose was increased or decreased beyond 4 mg at one time, MTX should be used at a stable regimen for 8 weeks before starting the study treatment).
9. Underwent arthrocentesis/drainage within 4 weeks before starting the study treatment or cytapheresis therapy within 8 weeks before starting the study treatment
10. Underwent surgical operation on the joint (including synovectomy and repair of tendon rupture) which is evaluated in this study within 8 weeks before informed consent
11. Received cyclophosphamide, cyclosporin (except for eye drop solution), azathioprine, or denosumab within 52 weeks before starting the study treatment
12. Received immunoglobulin preparations or blood products within 24 weeks before starting the study treatment
13. Received a live vaccine within 12 weeks before starting the study treatment, or is planning to receive one

14. Any current clinically significant disease (e.g., cardiac, respiratory, gastrointestinal, or renal disease) that could affect the subject's safety or interfere with the conduct of study in the opinion of the investigator or subinvestigator
15. Any current uncontrolled disorders such as acute cardiac infarction, unstable angina, brain infarct, or symptomatic intracerebral hemorrhage
16. Severe or uncontrolled diabetes
17. History of severe allergy (shock or anaphylactoid symptoms)
18. History or current clinical condition of malignant tumor, lymphoma, leukemia, or lymphoproliferative disease, except for skin carcinoma (epithelial carcinoma or basal cell carcinoma) and cervix carcinoma which have been completely excised and without metastasis or recurrence for more than 5 years before informed consent
19. Immunodeficiency or history of human immunodeficiency virus (HIV) infection
20. Infection requiring hospitalization or intravenous administration of antibiotics within 4 weeks before starting the study treatment or disease requiring administration of antivirus drugs (e.g., herpes zoster) within 4 weeks before starting the study treatment
21. History of tuberculosis or current active tuberculosis
22. History of clinically important vasculitis
23. Tested positive for any of the following in the Screening Phase: HIV, hepatitis B virus surface antigen (HBs antigen), hepatitis B virus surface antibody (HBs antibody), hepatitis B virus core antibody (HBc antibody), hepatitis B virus DNA (HBV DNA), hepatitis C virus antibody (HCV antibody), human T-lymphotrophic virus type I antibody (HTLV-1 antibody), or syphilis (except if positive for the HBs antibody only, and it is clear that this is due to hepatitis B vaccination. In case of positive RPR and negative TP antibody results in the syphilis test, the positive result is not considered valid if a false positivity is confirmed by repeated TP antibody negative results of other syphilis tests performed 21 days or more later). For subjects who are negative for both HBs antigen and HBV-DNA quantitative test and positive for either or both of anti-HBc antibody and anti-HBs antibody, their study participation is allowed if the investigator or subinvestigator takes a proper measure such as HBV-DNA monitoring based on the "Guideline for measures against hepatitis B caused by immunosuppression and chemotherapy."
24. Positive in tuberculosis test (QuantiFERON®TB Gold Test or T-SPOT®.TB Test) in the Screening Phase. For those whose results are "hold" (indeterminable) in repeated tests, their study participation is only allowed if they start receiving a prophylactic treatment with isoniazid (in principle, 300 mg/day [5 mg/kg/day in case of low weight] for approximately 9 months) ≥21 days before starting the study treatment.
25. Findings indicating a history of tuberculosis on chest x-ray in the Screening Phase
26. Neurological findings such as motor paralysis, visual impairment, or language disorder in the Screening Phase
27. Blood CD4-positive cell count <200 /μL or white blood cell count <3,000 /μL in the Screening Phase
28. Any of the following laboratory abnormalities in the Screening Phase
    - Hemoglobin: <8.0 g/dL

- Neutrophil count: <1,500 /μL
- Platelet: <100,000 /μL
- AST or ALT: >3× the upper limit of normal (ULN)
- Serum creatinine: >1.5 mg/dL
- Serum KL-6: >ULN
- β-D glucan: >ULN

29. Demonstrated prolonged QTcF interval (>450 ms) in repeated ECG examinations
30. Women of childbearing potential who have a positive pregnancy test in the Screening or Observation Phase or of breastfeeding
31. Women of childbearing potential who:
    - Had unprotected sexual intercourse within 30 days before study entry and who do not agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device [IUD], a double-barrier method [such as condom plus diaphragm with spermicide], an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period or for 70 days after the last dosing.
    - Are currently abstinent, and do not agree to use a double-barrier method (condom plus diaphragm with spermicide) during the study period or for 70 days after the last dosing.
    - Are using oral contraceptives but are not on a stable dose of the same oral contraceptives for at least 4 weeks before study treatment, or who do not agree to use the same oral contraceptives during the study or for 70 days after the last dosing.
    - All women will be considered to be of childbearing potential unless they are postmenopausal [amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause] or have been sterilized surgically [i.e., either of bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy was performed at least 1 month before dosing of study drug]).
32. Men who have not had a successful vasectomy (without confirmed azoospermia) and their female partners do not meet any of the criteria above (however, study entry is allowed if the female partner is not of childbearing potential or practicing highly effective contraception throughout the study period or for 70 days after the last dosing). No sperm donation is allowed during the study period or for 70 days after the last dosing.
33. Scheduled for surgery during the study
34. Currently enrolled in another clinical study or used any investigational drug or device within 28 days (or 5× the half-life, whichever is longer) before informed consent
35. Has been treated with E6011 or any unapproved biologics for RA.
36. Use of a psychotropic agent as recreational purpose other than therapeutic purpose
37. Any history of a medical condition or a concomitant medical condition that in the opinion of the investigator or subinvestigator would compromise the subject's ability to safely complete the study

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator or subinvestigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

All subjects who discontinue the study should be followed for procedures/assessments at discontinuation as specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4; also see Section 9.5.5 "Completion/Discontinuation of Subjects" for more information).

A subject will be withdrawn from the study under any of the following circumstances.

1. Occurrence of AE that made it difficult to continue the study
2. Subject is pregnant.
3. Subject's ineligibility is confirmed.
4. Concomitant medication or therapy cannot be continued in accordance with the protocol.
5. Required surgical operation on arthritic disorder
6. Diagnosed with malignant tumor
7. Tested positive in tuberculosis test (QuantiFERON TB® Gold Test or T-SPOT®.TB Test)
8. Tested positive for any of the following: HIV, HBs antigen, HBV DNA, HCV antibody, HTLV-1 antibody, or syphilis (except if false positive for the syphilis test)
9. When the investigator or subinvestigator judges that efficacy of E6011 is insufficient, after the date Version 6 of the protocol was approved by IRB
10. When the investigator or subinvestigator judges that there are other effective treatment options available besides continuing this study, after the date Version 6 of the protocol was approved by IRB

Withdrawal from the study will be considered if a subject skips 3 consecutive administrations.

9.4 Treatments

9.4.1 Treatments Administered

Treatment Phase: In the E6011 100 mg, 200 mg, or placebo groups, subjects will receive each dose at Weeks 0, 1, 2 and then every 2 weeks up to Week 22 by repeated subcutaneous administration. In the E6011 400 mg group, subjects will receive 400 mg at Weeks 0, 1, 2, 4, 6, 8, 10 and then 200 mg every 2 weeks up to Week 22 by repeated subcutaneous administration.

Extension Phase: Subjects will receive E6011 200 mg every 2 weeks from Week 24 to Week 102 by repeated subcutaneous administration. When subjects

insufficiently respond to the treatment, repeated subcutaneous administration (400 mg of E6011 every 2 weeks) will be allowed.

The study drug contains E6011 50 mg, 100 mg, or placebo in 1 vial (1 mL). In the Treatment Phase, 4 mL will be subcutaneously administered in Weeks 0 to 10, and 2 mL will be subcutaneously administered in Weeks 12 to 22. In the Extension Phase, 2 mL will be subcutaneously administered for the 200 mg dosing and 4 mL will be subcutaneously administered for the 400 mg dosing.

In the 2 mL administration, subjects will receive study drug subcutaneously in 2 separate sites, 1 mL each, from the following sites: right or left upper arm, right or left abdomen, or right or left thigh. In the 4 mL administration, subjects will receive study drug subcutaneously in 4 separate sites, 1 mL each. However, 2 mL of the study drug may be given subcutaneously in 1 site only if the investigator or subinvestigator judges that the study drug can be administered properly.

The dose and administration method for the study drug is described in Table 1.

Study drug will be administered upon completion of all the planned assessments (except for findings on injection sites) on the day of study drug administration. On the first and second administrations of the study drug in both the Treatment and Extension Phases (i.e., Weeks 0, 1, 24, and 26), subjects are required to stay at the site for at least 60 minutes after dosing to confirm its safety before being discharged.

Table 1 Dose and Administration of the Study Drug

Phase	Dose	Dosage Volume	Dosage and Injection Site
Treatment Phase: Weeks 0 to 10 (Double-blind)	100 mg 200 mg 400 mg or placebo	4 mL (4 vials[b])	Study drug will be given subcutaneously in 4 separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh. (The study drug may be given subcutaneously in 2 separate sites, 2 mL each, only if the investigator or subinvestigator judges that the study drug can be administered properly.)
Treatment Phase: Weeks 12 to 22 (Double-blind)	100 mg 200 mg or placebo	2 mL (2 vials[c])	Study drug will be given subcutaneously in 2 separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh.
Extension Phase: Weeks 24 to 102 (Open label)	200 mg	2 mL (2 vials[d])	Study drug will be given subcutaneously in 2 separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh. (2 mL of the study drug may be given subcutaneously in 1 site only if the investigator or subinvestigator judges that the study drug can be administered properly.)
	400 mg[a]	4 mL (4 vials[e])	Study drug will be given subcutaneously in 4 separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh. (The study drug may be given subcutaneously in 2 separate sites, 2 mL each, only if the investigator or subinvestigator judges that the study drug can be administered properly.)

a: When subjects insufficiently respond to the treatment, repeated subcutaneous administration (400 mg of E6011 every 2 weeks) will be allowed.

b: 2×50 mg/mL vial and 2×0 mg/mL vial for 100 mg administration, 4×50 mg/mL vial for 200 mg administration, 4×100 mg/mL vial for 400 mg administration, and 4×0 mg/mL vial for placebo

c: 2×50 mg/mL vial for 100 mg administration, 2×100 mg/mL vial for 200 mg administration, and 2×0 mg/mL vial for placebo

d: 2×100 mg/mL vial for 200 mg administration

e: 4×100 mg/mL vial for 400 mg administration

9.4.2 Identity of Investigational Products

The study drugs for this study are provided in Table 2.

Study drugs will be packed as per the study design and provided by the sponsor. Details of labeling and package of the study drugs are shown in Appendix 5.

Table 2 Study Drugs

Study Drug	Dosage Form and Strength
E6011	Aqueous solution containing 50 mg or 100 mg E6011 in a vial (1 mL)
Placebo	Aqueous solution containing no E6011 in a vial (1 mL)

Storage Condition: 2 to 8 °C, protected from light.
Manufacturer: Eisai Co., Ltd.

The study drugs for the Treatment Phase (double-blind) will be provided in small boxes packed in 2 large boxes, one containing small boxes for 5 administrations (Weeks 0 to 6) and the other containing small boxes for 8 administrations (Weeks 8 to 22).

The study drugs for the Extension Phase (100 mg E6011 in 1 mL vial) will be provided in boxes containing 10 vials each.

9.4.2.1 Chemical Name and Structural Formula of E6011

- Test drug code: E6011
- Generic name: To be determined
- Chemical name: IgG2
- Molecular weight: 147 kDa
- Structural formula: glycoprotein with immunoglobulin structure having 2 heavy chains (445 amino acids/chain)
  linked by disulfide bonds to 2 light chains (214 amino acids/chain)

9.4.2.2 Comparator Drug

Placebo

9.4.2.3 Labeling for Study Drug

The following information has to be provided:

- Statement to the effect “For clinical study use only”
- Name and address of the sponsor
- Chemical name and Identification number
- Manufacturing number or symbol
- Storage conditions

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the specified storage conditions. The study drug manager (or designee) will monitor the temperature at the storage location to ensure that

the study drug is maintained within an established temperature range. The study drug manager (or designee) is responsible for ensuring that the temperature is monitored throughout the study period and that records are maintained; the temperature should be monitored continuously by using an in-house validated data acquisition system, by using an automatic temperature recording device or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatment groups through dynamic allocation algorithm that will be prepared by an independent enrollment center.

After screening assessments are performed within 42 days before starting the study treatment, eligible subjects will be randomized to E6011 100 mg, 200 mg, 400 mg, or placebo at a 1:2:2:2 ratio through dynamic allocation using the following factors: CRP level at the Screening Phase, disease duration and history of biologics treatment.

Randomization will be performed centrally by an interactive web response system (IWRS). The person responsible for randomization will generate the list of randomized drug numbers. At screening, the investigator or designee will access the IWRS to register the subject information. The independent enrollment center will confirm the eligibility of the subject, assign each subject to a treatment group by using dynamic allocation algorithm, and inform the drug number to the investigator or subinvestigator via email. Upon completing all the planned assessments at the Observation Phase, the investigator or subinvestigator will prescribe the study drug for the eligible subject based on the drug number specified by the independent enrollment center.

9.4.4 Selection of Doses in the Study

In the Treatment Phase (12 weeks) of Study 103, 21 of 37 subjects (56.8%) experienced adverse events (AEs). AEs occurring in 2 or more subjects were injection site erythema, nasopharyngitis, headache, and oropharyngeal pain. As a dose-dependent increase in the incidence of adverse reactions or occurrence of events to be concerned related to E6011 were not observed in Study 103, we consider that subcutaneous administration of E6011 is generally safe and tolerated in RA subjects at a dose up to 400 mg every 2 weeks. Regarding the efficacy, although Study 103 was an open-label study without a placebo control, the clinical symptoms of RA tended to improve in all of the E6011 100 mg, 200 mg, and 400 mg groups in evaluations up to Week 12.

The relationship between E6011 and its target membrane-bound FKN was investigated based on PK/PD analysis using serum E6011 and total FKN concentrations (sum of free FKN and E6011-FKN complex) in Study 001 and Study 002. Based on the result, the share of membrane-bound FKN for E6011 at Week 12 was estimated to be 98.9% and 99.6% in the E6011 100 mg and 200 mg groups in Study 103, respectively. It is reported that the share of membrane-bound FKN for biologics commercially available as RA drugs and given at clinically recommended dose was estimated to be approximately 99.5% (Tani K, et al, 2013).

Thus sufficient share of membrane-bound FKN and improvement of clinical symptoms can be expected with E6011 200 mg, and we determined that the administration of 200 mg every 2 weeks is appropriate as a central dose. We also set the dose of 400 mg as a high-dose level, since earlier achievement of sufficient share of membrane-bound FKN and improvement of clinical symptoms may be expected in that dose. However, since 400 mg administration requires 4 subcutaneous administrations (or 2 subcutaneous administrations of 2 mL each), evaluations with 400 mg administrations are limited to 12 weeks (for the primary evaluation period) to reduce the burden on the subjects (particularly those who are given placebo for 24 weeks) and the subjects will receive 200 mg (central dose) subcutaneously in 2 separate sites from Week 12 onward.

"The guideline for the clinical evaluation of antirheumatic drugs" recommends a Phase 2b study include placebo and 3 doses of active drug. To collect data on the dose response and safety of E6011 with the widest possible dose range, we consider it appropriate to set the following 3 active drug groups: E6011 200 mg as a central dose group; E6011 100 mg as a low-dose group; and E6011 400 mg as initial dose administered until Week 10 and 200 mg after Week 12 as a high-dose group. E6011 100 mg is only set as a dose for evaluation of the dose response and not for evaluation of the efficacy compared with placebo.

In the Extension Phase, subjects will receive 200 mg administrations of E6011 (central dose) every 2 weeks. However, when subjects insufficiently respond to the treatment (E6011 200 mg every 2 weeks), dose escalation will be allowed (E6011 400 mg every 2 weeks).

E6011 is to be administered at Weeks 0, 1, 2, and then every 2 weeks because a loading administration 1 week after the first administration led to the prompt achievement of steady state in PK in Study 103.

9.4.5 Selection and Timing of Dose for Each Subject

Please refer to Section 9.4.1 "Treatments Administered".

Study drugs can be administered regardless of the meal time. Study drugs must be administered upon completion of all the planned assessments (except for findings on injection site) on the day.

9.4.6 Blinding

During the double-blind part, subjects and all personnel involved in the conduct of study and evaluations, including investigators, subinvestigators, and clinical research associates (CRAs), will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by the sponsor or CRO and accessible only to authorized persons (e.g., Eisai Global Safety) until the time of unblinding, per standard operating procedures (SOP).

Although the Extension Phase is an open-label part, each subject's assigned treatment group will be blinded to subjects and any personnel involved in the conduct of study or evaluations, including investigators, subinvestigators, and CRAs, until the database of the Treatment Phase is fixed.

The bioanalytical laboratory and the immunogenicity assay laboratory will report the results to the sponsor after unblinding.

Joint x-ray images will be directly sent to the institute of joint x-ray central evaluation and evaluated in a blinded manner so as to maintain the blindness. After unblinding, the sponsor will obtain the evaluation results of those joint x-ray images captured by Week 24.

- Key code and emergency key code

After study drug randomization (and prior to delivering the assigned study drug to the site), the person responsible for randomization will immediately seal the key codes and keep them until unblinding. The emergency key code will be prepared to assure the subjects' safety. After study drug randomization (and prior to delivering the assigned study drug to the site), the person responsible for randomization will immediately seal the emergency key code for each subject (per drug number) and the emergency key code center will store them until unblinding. Only in the case of a medical emergency where information about the assigned study drug is needed (including regulatory requirements) for appropriate treatment of the subject or ensuring the subject's safety, the emergency key code for the subject may be broken (opened).

At unblinding, the person responsible for randomization will verify that all the emergency key codes are maintained for blinding, except those broken (opened) according to the prescribed procedure.

- Sealing boxes of study drugs at collection by the sponsor

The study drug manager (or designee) must check the number of all opened and unused study drugs and seal (stamp or sign) the opened box containing unused study drugs at collection by the sponsor.

- Procedures for unblinding

After database lock, the sponsor will ask the person responsible for randomization for unblinding, and the person responsible for randomization will break (open) the key code.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject between the date of informed consent (12 weeks prior to the consent for DMARDs) and the follow-up assessments (28 days after discontinuation or completion of study) will be recorded in the CRF. All prior biologics for RA will be recorded regardless of the timing of dosing. The investigator or subinvestigator will record any concomitant medication/therapy associated with the occurrence of AEs in the CRF. However, medications, test agents, solvents or fluid infusions used as pretreatment for surgery, examination, or drug administration will not be considered concomitant drugs.

For prior and concomitant medications indicated above, the name, administration route, dose (medications for RA and folic acid only [not for NSAIDs]), treatment start date (or timing of treatment initiation), treatment end date, reason for use, and reason for withdrawal (biologics for RA only) will be recorded in the CRF. For concomitant therapy, the name, treatment

start date (or timing of treatment initiation) and treatment end date, and reason for concomitant use will be recorded in the CRF.

9.4.7.1 Prohibited Concomitant Therapies and Drugs

9.4.7.1.1 PROHIBITED CONCOMITANT THERAPIES AND DRUGS

The concomitant use of the following drugs or therapies is prohibited until completion of the Extension Phase (or until study discontinuation).

- DMARDs (except MTX)
- Biologics (adalimumab, infliximab, golimumab, certolizumab pegol, etanercept, tocilizumab, abatacept, etc.), including biosimilars
- Intraarticular, intramuscular, or intravenous injection of corticosteroids
- Intraarticular injection of sodium hyaluronate (including sodium hyaluronate crosslinked polymer and sodium hyaluronate crosslinked polymer crosslinked with vinylsulfone) or intraarticular injection of local anesthetic agent
- Arthrocentesis/drainage
- Cytapheresis
- Any analgesics other than NSAIDs (oral, suppository, or topical)
- Cyclophosphamide, cyclosporin (with the exception of eye-drops), azathioprine, or denosumab
- Immunoglobulin preparations or blood products
- Live vaccines
- Folic acid preparation or over-the-counter medications containing folic acid as main component
- Other investigational drugs or medical devices
- Surgical operations on arthritic disorder

9.4.7.1.2 RESTRICTED CONCOMITANT THERAPIES AND DRUGS

- MTX and folic acid should be used as a stable dose regimen up to completion of the Extension Phase (or until study discontinuation). However, if an adverse event associated with MTX is noted, dose reduction or interruption is permitted. If the event disappears after dose reduction or interruption, the dose can be increased to the previous level.
- Corticosteroids (equivalent to ≤10 mg/day of prednisolone, taken orally or by suppository) and herbal medicine indicated for RA are allowed under restricted conditions, but the dose regimen should not to be modified up to Week 24 (or until study discontinuation). Between Week 24 and Week 104, the regimen should not be modified except for the following cases: dose reduction, dose interruption, dose increase following the dose reduction (up to the initial dose level), and restarting administration after interruption.

- NSAIDs (oral, suppository, or topical) may be taken concomitantly but are prohibited between the night before the day of efficacy assessments and the end of the assessments.

- After the date Version 6 of the protocol is approved by IRB, it is unnecessary to record concomitant medications/therapies in the CRF.

9.4.8 Treatment Compliance

The investigator, subinvestigator, or clinical research coordinator will record the time and status of study drug administrations in the CRF throughout the study period. If a subject cannot complete the entire dose, the reason for incomplete dosing will be recorded in the CRF. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

The study drug manager (or designee) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the instructions for handling of study drugs provided by the sponsor and adherence to GCP guidelines as well as other regulatory requirements.

Under no circumstances will the investigator or subinvestigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The study drug manager (or designee) must keep accurate and timely records of the number of all study drugs received, the number of study drugs prescribed, the number of study prescribed to subject but not used (unused drug 1), the number of study drugs dispensed to investigational site but not prescribed to subject (unused drug 2) and the number of study drugs returned to the sponsor (total of unused drugs 1 and 2), and where applicable (if study drugs are discarded at the site). This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log per subject, (c) drug accountability log, (d) documentation of returns to the sponsor, and (e) certificates of destruction for any destruction of study drugs that occurs at the site.

The drug accountability logs must be made available, upon request, for review by a CRA or inspection by a representative of a health authority. The study drug manager (or designee) must check the quantity of all unused study drugs, exchange the study drug return form for the study drug recovery form with the sponsor, and return all unused study drugs to the sponsor. Unused study drugs that are to be returned from the site will be collected directly by CRA and will be returned to the sponsor’s designated depot(s).

Drug accountability will be reviewed by CRA throughout the study period (during site visits, at the completion of the study, etc.).

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Demographic information of subjects will be collected during the Screening Phase. Demographic information includes date of birth, sex, and race/ethnicity. In addition to these, subject identification code and date of obtaining written informed consent will be also documented in the CRF.

9.5.1.2 Assessments in the Screening and Observation Phases

9.5.1.2.1 Smoking History, Medical History/Complications, and Physical Examinations

Smoking history, medical history (including surgeries), and comorbidities will be assessed during the Screening Phase, and smoking history, surgical history for RA or comorbidities, and medical history concerning the exclusion criteria 15, 16, 18, 20, and 26 will be recorded in the CRF.

Physical examinations will be performed at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). The results of the physical examination will be recorded in the medical chart at the site. If changes in physical findings from screening meet the definition of an AE, the AE will be recorded in the CRF.

9.5.1.2.2 Prior Medications

For treatment drugs for RA and folic acid, all biologics for RA and medications other than biologics for RA administered after informed consent (12 weeks prior to the enrollment for DMARDs) should be recorded in the CRF, with the name, administration route, dose (only treatment drugs for RA and folic acid except for NSAIDs), treatment start date (or timing of treatment initiation), treatment end date, and reason for discontinuation (biologics for RA only) detailed.

9.5.1.2.3 Disease Characteristics of RA

- Time of Diagnosis
- Classification of Functional Status in RA (ACR 1991 Revised Criteria)
- Number of tender joints and number of swollen joints
- CRP and ESR
- Joint x-ray image (number of bone erosions)
- RF or anticyclic citrullinated peptide (anti-CCP) antibody (positive/negative)

9.5.1.2.4 Other Assessments

- Height and weight

- Virus tests: HIV, HBs antigen, HBs antibody, HBc antibody, HBV-DNA, HCV antibody, and HTLV-1 antibody
- Syphilis testing
- Tuberculosis test (QuantiFERON TB® Gold Test or T-SPOT®.TB Test)

Assays will be performed at the same laboratory where clinical laboratory tests are conducted (except for QuantiFERON TB® Gold Test or when T-SPOT®.TB Test is performed at the study institution), and test results will be recorded as a source document at the investigational site. Samples will be handled according to the separately prescribed procedures.

9.5.1.3 Efficacy Assessments

After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct assessments for efficacy.

9.5.1.3.1 Assessment of Tender and Swollen Joint Counts

The number of tender joints and the number of swollen joints will be evaluated during the Screening and Observation Phases, Treatment Phase (Weeks 2, 4, 8, 12, 16, 20, and 24), Extension Phase (up to Week 104, every 4 weeks), and at discontinuation. As a general rule, assessments will be performed by the same investigator or subinvestigator at each site.

A total of 68 joints will be examined for tenderness by applying pressure to the joint or by moving joints. Tender joints will be marked with tick or cross in corresponding frames of the Assessment Sheet for Tender and Swollen Joint Counts (Appendix 7). A total of 66 joints (minus 2 hip joints) will be examined for swollen joints. Swollen joints will be marked with open circles in corresponding frames of the Assessment Sheet for Tender and Swollen Joint Counts (Appendix 7). If assessment cannot be made because the subject had a joint replacement procedure or due to any other reasons, a filled square will be entered.

9.5.1.3.2 Assessment Using Visual Analog Scale (VAS)

Subjects will be evaluated using a visual analog scale (VAS) during the Observation Phase, Treatment Phase (Weeks 2, 4, 8, 12, 16, 20, and 24), Extension Phase (every 4 weeks up to Week 104), and at discontinuation. As a general rule, assessments will be performed by the same investigator or subinvestigator at each site.

For physician's disease activity assessment, disease activity of the subject will be evaluated and the result will be entered by the physician on a score sheet, "Physician's disease activity assessment form" (Appendix 8), by placing a mark on a 100 mm analog scale.

For patient's pain assessment, the degree of pain associated with RA will be indicated by the subject on a score sheet, "Patient's pain/disease activity assessment form patient" (Appendix 9), by placing a mark on a 100 mm analog scale.

For patient's disease activity assessment, the degree of disease activity of RA will be indicated by the subject on a score sheet, "Patient's pain/disease activity assessment form (Appendix 9), by placing a mark on a 100 mm analog scale.

Patient's pain/disease activity assessments (except for those at discontinuation) must be performed prior to any evaluations and tests by the investigator or subinvestigator at the time point, so that any influence on the subject's evaluation can be avoided.

The investigator, subinvestigator, or clinical research coordinator will read the scale on the assessment form and enter the result on the assessment form and the CRF.

9.5.1.3.3 Assessment Using Health Assessment Questionnaire (HAQ)

Subjects will be evaluated using the health assessment questionnaire (HAQ) during the Observation Phase, Treatment Phase (Weeks 2, 4, 8, 12, 16, 20, and 24), Extension Phase (up to Week 104, every 4 weeks), and at discontinuation.

Physical function will be self-evaluated by the subject using a Health assessment questionnaire (HAQ) (Appendix 10). The assessment will be made based on the activities capable without any aids or devices. The assessments (except for that at discontinuation) must be performed prior to any evaluations and tests by the investigator or subinvestigator at the time point, so that any influence on the subject's evaluation can be avoided. The investigator or subinvestigator will verify the report by the subject for its accuracy and consistency before releasing the subject. The result of the completed HAQ will be documented in the CRF by the investigator, subinvestigator, or clinical research coordinator. This assessment is made based on the activities at each evaluation time point, and the results will not be compared with previous data.

9.5.1.3.4 Assessment of Erythrocyte Sedimentation Rate (ESR)

Erythrocyte sedimentation rate (ESR) of each subject will be measured during the Screening Phase, Observation Phase, Treatment Phase (Weeks 2, 4, 8, 12, 16, 20, and 24), Extension Phase (up to Week 104, every 4 weeks), and at discontinuation, and the result will be recorded in the CRF.

9.5.1.3.5 Assessment of C-reactive protein (CRP)

CRP of each subject will be measured as part of blood biochemical tests during the Screening Phase, Observation Phase, Treatment Phase (Weeks 2, 4, 8, 12, 16, 20, and 24), Extension Phase (every 4 weeks up to Week 104), and at discontinuation.

9.5.1.3.6 Assessment of Joint X-ray

Joint x-ray images will be captured in the Screening Phase, Treatment Phase (Week 24), Extension Phase (Weeks 52, 76, and 104), and at discontinuation.

Joint x-ray images will be sent to the institute of joint x-ray central evaluation with subject identification number. The institute will evaluate the images, and the evaluation results of joint x-ray images captured by Week 24 will be submitted to the sponsor after unblinding. Joint x-ray images will be evaluated according to the separately prescribed procedures.

9.5.1.4 Pharmacokinetic, Pharmacogenomic, Biomarker, and Immunogenicity Assessments

After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct assessments for pharmacokinetic, pharmacogenomic, biomarker, and immunogenicity. However, pharmacokinetic and immunogenicity assessments will be conducted at discontinuation.

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Serum E6011 Concentration

Blood samples will be collected for measuring serum E6011 concentrations at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Serum E6011 concentrations will be measured at the bioanalytical laboratory using a validated, specific, and selective analytical method. Planned blood volume for these measurements is provided in Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures.

9.5.1.4.2 PHARMACOGENOMIC ASSESSMENTS

Not applicable.

9.5.1.4.3 ASSESSMENTS OF BIOMARKERS

Serum Total FKN Concentration

Blood samples will be collected for measuring serum total FKN concentrations at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Planned blood volume for these analyses is provided in Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures. Measurements will be conducted at the biomarker assay laboratory.

Serum Concentrations of RF, Anti-CCP, and MMP-3

Blood samples will be collected for measuring serum concentrations of rheumatoid factor (RF), anticyclic citrullinated peptide (anti-CCP) antibody, and matrix metalloproteinase (MMP)-3 at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Planned blood volume for these measurements is provided in Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures. Measurements will be conducted at the biomarker assay laboratory.

Serum Concentrations of Cytokines, LRG1, and Ang2

Blood samples will be collected for measuring serum concentrations of cytokines (granulocyte macrophage colony-stimulating factor [GM-CSF], interferon-γ [IFN-γ], interleukin [IL]-1β, IL-6, TNFα, etc.), leucine-rich alpha-2 glycoprotein 1 (LRG1), and angiopoietin 2 (Ang2) at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Planned blood volume for these measurements is provided in

Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures. Measurements will be conducted at the biomarker assay laboratory.

Serum TRACP-5b Concentration

Blood samples will be collected for measuring serum concentrations of tartrate resistant acid phosphatase (TRACP)-5b at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Planned blood volume for these measurements is provided in Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures. Measurements will be conducted at the biomarker assay laboratory.

Measurement of Immunocytes Such as Blood CX3CR1-positive Cells

Blood samples will be collected for measuring immunocytes such as blood CX3CR1-positive cells at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Planned blood volume for these measurements is provided in Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures. Measurements will be conducted at the biomarker assay laboratory.

Vectra™ DA

Blood samples will be collected for Vectra™ DA, assay kit for biomarkers including VCAM-1, epidermal growth factor [EGF], vascular endothelial growth factor [VEGF]-A, IL-6, tumor necrosis factor receptor-I [TNF-RI], MMP-1, MMP-3, YKL-40, leptin, resistin, serum amyloid A [SAA], and CRP at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Planned blood volume for these measurements is provided in Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures. Measurements will be conducted at the biomarker assay laboratory.

9.5.1.4.4 IMMUNOGENICITY ASSESSMENTS

Serum Anti-E6011 Antibody

Blood samples will be collected for measuring of serum anti-E6011 antibodies at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). The presence or absence of serum anti-E6011 antibody will be assessed at the immunogenicity assay laboratory using a validated, specific, and selective analytical method. When anti-E6011 antibodies are observed, the neutralization activity and isotypes of the anti-E6011 antibody will be evaluated. Planned blood volume for these measurements is provided in Table 5 (Section 9.5.2.2). Samples will be handled according to the separately prescribed procedures.

9.5.1.5 Safety Assessments

Safety assessments will consist of the following, as specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4).

All AEs observed; regular monitoring of clinical laboratory tests (including vasculitis marker tests), vital signs, chest x-ray, standard 12-lead electrocardiograms, physical findings, injection site findings, and neurological findings.

9.5.1.5.1 Adverse Events and Events Associated with Special Situations

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drugs are E6011 and placebo.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not

However, worsening of the primary disease (RA) is not considered an AE unless the symptom aggravated unexpectedly (slight change of RA condition is captured under efficacy assessments as disease progression rather than as an AE).

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE.

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, must be collected during the time the subject signed the informed consent and 70 days after the subject's last dose. Subjects who failed screening in Screening or Observation Phase primarily due to AE(s), such AE(s) and seriousness must be recorded in the CRF.

Any laboratory abnormality considered to constitute an AE will be reported on the CRF. Abnormal laboratory values are listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Medical and scientific judgment is exercised in deciding whether an isolated laboratory abnormality is classified as an AE.

All AEs must be followed for 70 days after the subject's last dose, or until resolution, whichever comes first. However, all SAEs must be followed until resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of Adverse Events

Adverse events will be graded on a 5-point scale according to Common Terminology Criteria for Adverse Event (CTCAE v4.0). Investigators will report CTCAE grades for all AEs for increasing severity.

As to ALP and γ-GTP, criteria for Grade 2 will be changed from ULN×2.5 (in the CTCAE) to ULN×3.0.

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

Not related	A causal relationship between the study drug and the AE is not a reasonable possibility.
Related	A causal relationship between the study drug and the AE is a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures (see Section 9.5.4.2 and Section 9.5.4.3) but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that is in place before study entry

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 3. The Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4) shows the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	WBC count, RBC count, hemoglobin, hematocrit, platelets, and differential of WBC (basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Blood chemistry	
Liver function tests	Total bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase
Renal function tests	Blood urea nitrogen, creatinine
Other	Glucose, HbA1c, albumin, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, amylase, inorganic phosphorus, LDH, creatine kinase, total protein, uric acid, sodium, potassium, chloride, calcium, CRP, KL-6, β-D-glucan
Urinalysis	pH, protein, glucose, urobilinogen, ketones, occult blood, specific gravity, amylase
Other	
Vasculitis marker	Serum complement titer (CH50), soluble intercellular adhesion molecule (ICAM)-1, soluble vascular cell adhesion molecule (VCAM)-1, soluble E-selectin, thrombomodulin, D-dimer
Autoantibody	Antinuclear antibody, anti-DNA antibody

CRP = C-reactive protein, HDL cholesterol = high-density lipoprotein cholesterol, LDH = lactate dehydrogenase, LDL cholesterol = low-density lipoprotein cholesterol, RBC = red blood cell, WBC = white blood cell

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded in the CRF.

9.5.1.5.4 Vital Signs and Weight Measurements

Measurement of vital signs (i.e., systolic and diastolic blood pressure [mmHg], pulse [beats per minute], body temperature [in centigrade], and weight [kg]) will be performed at the visits specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4) by using prespecified methods and recorded in the CRF. Blood pressure and pulse will be measured in the sitting or supine position after a rest for 5 minutes. All blood pressure measurements should be performed on the same arm, and body temperature should be measured by axillary thermometer.

If blood sampling is planned at the same timeframe and vital signs are measured after blood collection, measurement of vital signs must be carried out after sufficient time to avoid potential influence of blood collection on vital signs.

9.5.1.5.5 Physical Examinations

Physical examinations will be performed at the visits specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Physical examination results will be

recorded in the medical chart at the site. Changes from screening physical examination findings that meet the definition of an AE will be recorded in the CRF.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained at the visits specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Standard 12-lead ECG recordings will be used. Subjects must be in the supine position for 5 minutes prior to ECG. The investigator or subinvestigator records the results (abnormal or normal) in the CRF. If blood sampling is planned at the same timeframe and ECG is performed after blood collection, ECG must be carried out after sufficient time to avoid potential influence of blood collection on ECG.

An ECG abnormality may meet the criteria of an AE as described in this protocol (Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the ECG abnormality will be recorded as an AE in the CRF.

For ECG abnormalities meeting the criteria of an SAE (Section 9.5.1.5.2), the investigator must report the sponsor using the SAE form (with the ECG report) via fax, or other means of transmission (see “Reporting of Serious Adverse Events”).

9.5.1.5.7 OTHER SAFETY ASSESSMENTS

Chest x-ray

Chest x-rays (frontal view and lateral view) will be assessed at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). The investigator or subinvestigator will determine whether findings are normal or abnormal, and record the results in the CRF. For any abnormalities meeting the criteria of an AE as defined in this protocol (Section 9.5.1.5.1), they should be recorded as an AE in the CRF.

When a subject who was previously ineligible for this study is enrolled after obtaining informed consent again, chest x-ray results which were assessed within 12 weeks before the start of study drug administration can be used as screening data, only if the chest x-ray was examined for the purpose of this study following the previous informed consent.

Pregnancy test

For female subjects of childbearing potential, blood test (quantitative, the central laboratory) will be performed at the Screening Phase, Weeks 12, 24, 52, 76, 104, and at discontinuation, and on-site test will be performed during the Observation Phase. All the test results will be recorded in the medical chart at the site.

Injection site findings

Drug injection sites will be examined on each subject at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). The results will be recorded

in the medical chart at the site. Any abnormal findings should be recorded as an AE in the CRF.

Neurological findings

Subjects will be examined for the presence or absence of neurological findings at time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4), by using the Neurological finding checklist (see Appendix 11), and the results will be recorded in the CRF. If any abnormal neurological findings are suspected anytime at the scheduled or unscheduled time points, the subject must be examined by using the Neurological finding checklist. If any abnormal findings appear after administration of the study drug, the sponsor must be notified immediately using the Neurological finding report form (Appendix 12) sent by fax, etc. and the subject must be examined by a neurologist. Head MRI (T1-weighted image, FLAIR image and diffusion-weighted image) must be performed within 2 weeks and the copies of the images must be submitted to the sponsor. The sponsor must immediately transmit any pertinent information to the progressive multifocal leukoencephalopathy (PML) evaluation expert, who will advise on whether the treatment should be continued on the subject or not. The study drug administration must be suspended until the evaluation by the PML evaluation expert is completed. Such events should be recorded in the CRF as AEs.

Blood CD4-positive cell counts

Blood samples will be collected to measure blood CD4-positive cell counts at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Planned blood volume for these measurements is provided in Table 5 (Section 9.5.2.2).

The clinical laboratory facility will report the results to the investigational site and the sponsor, and the results will be stored as source document at the site. Samples will be handled according to the separately prescribed procedures.

9.5.1.6 Other Assessments

Anti-JC virus antibody test

Anti-JC virus (JCV) antibody test will be performed at the time points specified in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4). Samples will be handled according to the separately prescribed procedures.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Study Schedule

Table 4 presents the schedule of procedures/assessments for this study.

Each assessment will be performed within 3 days before or after the scheduled date during Weeks 1 to 12 or within 7 days before or after the scheduled date after Week 14 using Week 0 as a reference point. In the Follow-up Phase, each assessment will be performed within 7 days before or after the scheduled date ("within 7 days after the scheduled date" for

the assessments at “70 days after the last dosing”). However, the interval between study treatments should be at least 3 days until 2 weeks after the start of study treatment, and at least 6 days after 4 weeks have elapsed since the start of study treatment. If any scheduled assessment or administration of the study drug cannot perform within the above period, each assessment will still be performed, but administration of the study drug will be skipped.

After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct "tender and swollen joint counts/ESR", "VAS/HAQ", "RF/anti-CCP antibody/MMP-3", "serum E6011 concentration", "serum anti-E6011 antibody", "serum total FKN concentration", "cytokines/LRG1/Ang2", "TRACP-5b", "CX3CR1-positive cell count", or "Vectra™ DA". However, assessments of "serum E6011 concentration" and "serum anti-E6011 antibody" will be conducted at discontinuation.

Table 4 Schedule of Procedures/Assessments in Study E6011-J081-201

Phase	Screen-ing	Obser-vation	Treatment							
Time postdose / Assessment	Day –42 to Day –1	W0 Day 1 Pre	W0 Day 1 Dosing	W1 Day 8 ±3 days	W2 Day 15 ±3 days	W4 Day 29 ±3 days	W6 Day 43 ±3 days	W8 Day 57 ±3 days	W10 Day 71 ±3 days	W12 Day 85 ±3 days
Informed consent	X									
Demographics, medical history, complication	X									
Inclusion/exclusion criteria	X	X								
Study drug administration[a]			X	X	X	X	X	X	X	X
Prior treatment / concomitant medication or therapy	◄									►
Vital signs	X	X		X	X	X		X		X
Height / body weight[b]	X[b]									X
Physical findings, injection site finding[c]	X	X		X	X	X		X		X
Standard 12-lead ECG	X									X
Chest x-ray	X									X
Pregnancy test[d]	X	X[d]								X
Neurological findings[e]	X									X
Anti-JCV antibody test	X									
Blood CD4-positive cells	X									X
Viral test, syphilis test, TB test	X									
Number of tender / swollen joints, ESR	X	X			X	X		X		X
VAS, HAQ		X			X	X		X		X
Joint x-ray	X									
Hematology, blood chemistry, urinalysis, RF, anti-CCP antibody, MMP-3	X	X			X	X		X		X
Autoantibody		X								X
serum KL-6, β-D glucan	X									X
Vasculitis marker tests		X								X
Adverse events	◄									►
Serum E6011 concentration		X		X	X	X		X		X
Serum anti-E6011 antibody		X				X		X		X
Serum total FKN		X								
Serum cytokine concentration, LRG1, Ang2		X				X				X
Serum TRACP-5b concentration		X								X
Immunocytes such as blood CX3CR1-positive cells		X			X	X				X
Vectra™ DA		X								X

Table 4 Schedule of Procedures/Assessments in Study E6011-J081-201 (continued)

Phase	Treatment					
Time postdose / Assessment	W14 ±7 days	W16 ±7 days	W18 ±7 days	W20 ±7 days	W22 ±7 days	W24 ±7 days
Informed consent						
Demographics, medical history, complication						
Inclusion/exclusion criteria						
Study drug administration[a,f]	X	X	X	X	X	X[g]
Prior treatment / concomitant medication or therapy	◄	—	—	—	—	►
Vital signs		X		X		X
Height / body weight[b]						X
Physical findings, injection site finding[c]						X
Standard 12-lead ECG						X
Chest x-ray						X
Pregnancy test[d]						X
Neurological findings[e]						X
Anti-JCV antibody test						X
Blood CD4-positive cells						X
Viral test, syphilis test, TB test						
Number of tender / swollen joints, ESR		X		X		X
VAS, HAQ		X		X		X
Joint x-ray						X
Hematology, blood chemistry, urinalysis, RF, anti-CCP antibody, MMP-3		X		X		X
Autoantibody						X
Serum KL-6, β-D glucan						X
Vasculitis marker tests						X
Adverse events	◄	—	—	—	—	►
Serum E6011 concentration		X		X		X
Serum anti-E6011 antibody		X		X		X
Serum total FKN						
Serum cytokine concentration, LRG1, Ang2						X
Serum TRACP-5b concentration						X
Immunocytes such as blood CX3CR1-positive cells						X
Vectra™ DA						X

Table 4 Schedule of Procedures/Assessments in Study E6011-J081-201 (continued)

Phase	Extension													
Time postdose / Assessment	W26 ±7 days	W28 ±7 days	W30 ±7 days	W32 ±7 days	W34 ±7 days	W36 ±7 days	W38 ±7 days	W40 ±7 days	W42 ±7 days	W44 ±7 days	W46 ±7 days	W48 ±7 days	W50 ±7 days	W52 ±7 days
Informed consent														
Demographics, medical history, complication														
Inclusion/exclusion criteria														
Study drug administration[a,f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior treatment / concomitant medication or therapy	◄													►
Vital signs		X		X		X		X		X		X		X
Height / body weight[b]						X								X[b]
Physical findings, injection site finding[c]						X								X
Standard 12-lead ECG														X
Chest x-ray														X
Pregnancy test[d]														X
Neurological findings[e]						X								X
Anti-JCV antibody test														X
Blood CD4-positive cells														X
Viral test, syphilis test, TB test														X
Number of tender / swollen joints, ESR		X		X		X		X		X		X		X
VAS, HAQ		X		X		X		X		X		X		X
Joint x-ray														X
Hematology, blood chemistry, urinalysis, RF, anti-CCP antibody, MMP-3		X		X		X		X		X		X		X
Autoantibody						X								X
Serum KL-6, β-D glucan														X
Vasculitis marker tests						X								X
Adverse events	◄													►
Serum E6011 concentration		X		X		X		X		X		X		X
Serum anti-E6011 antibody		X		X		X		X		X		X		X
Serum total FKN														
Serum cytokine concentration, LRG1, Ang2														X
Serum TRACP-5b concentration														X
Immunocytes such as blood CX3CR1-positive cells														X
Vectra™ DA														X

Table 4 Schedule of Procedures/Assessments in Study E6011-J081-201 (continued)

Phase	Extension						Treatment/ Extension	Follow-up	
Time postdose / Assessment	W52+2n[h] ±7 days	W52+4n[i] ±7 days	W64 W88 ±7 days	W76 ±7 days	W100 ±7 days	W104 ±7 days	Discont.	28 days after completion or discount.	70 days after the last dosing
Informed consent									
Demographics, medical history, complication									
Inclusion/exclusion criteria									
Study drug administration[a,f]	X	X	X	X	X				
Prior treatment / concomitant medication or therapy	◄	———	———	———	———	———	———	►	
Vital signs		X	X	X	X	X	X	X	
Height / body weight[b]						X	X	X	
Physical findings, injection site finding[c]			X	X		X	X	X	
Standard 12-lead ECG				X		X	X		
Chest x-ray				X		X	X		
Pregnancy test[d]				X		X	X		
Neurological findings[e]			X	X		X	X		
Anti-JCV antibody test				X		X	X		
Blood CD4-positive cells				X		X	X		
Viral test, syphilis test, TB test						X	X		
Number of tender / swollen joints[l], ESR[l]		X	X	X	X	X	X		
VAS[l], HAQ[l]		X	X	X	X	X	X		
Joint x-ray[l]				X		X	X		
Hematology, blood chemistry, urinalysis, RF[l], anti-CCP antibody[l], MMP-3[l]		X	X	X	X	X	X	X	
Autoantibody						X	X		
Serum KL-6, β-D glucan						X	X		
Vasculitis marker tests			X	X		X	X		
Adverse events	◄	———	———	———	———	———	———	———	►
Serum E6011 concentration[l]		X	X	X	X	X	X		
Serum anti-E6011 antibody[l]		X	X	X	X	X	X		
Serum total FKN[l]									
Serum cytokine concentration[l], LRG1[l], Ang2[l]						X	X		
Serum TRACP-5b concentration[l]						X	X		
Immunocytes such as blood CX3CR1-positive cells[l]							X[j]		X[k]
Vectra™ DA[l]						X	X		

a.	Study drug will be administered upon completion of all the planned investigations (except for injection site findings) on the day.
b.	To measure height only at the Screening Phase and W52.
c.	To examine injection site findings after study drug administration.
d.	To perform pregnancy test in women of childbearing potential. On-site test conducted at the Observation Phase only.
e.	If any postdose abnormality is observed in neurological examination, head MRI (T1-weighted image, FLAIR image, diffusion-weighted image) will be performed within 2 weeks along with consultation to a neurologist.
f.	The interval between study treatments is at least 7 days (at least 6 days between treatments)
g.	Administration of study drug at Week 24 is done in an open-label manner.
h.	W52+2n: W54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, 102
i.	W52+4n: W56, 60, 68, 72, 80, 84, 92, 96
j.	Basically performed at study discontinuation, and a missing value is permissible only when collection of the sample is difficult due to abrupt discontinuation.
k.	Will only be conducted if blood sample is judged to be feasible at the visit.
l.	After the date Version 6 of the protocol is approved by IRB, applicable assessments will not be conducte. However, assessments of serum E6011 concentration and serum anti-E6011 antibody will be conducted at discontinuation.

9.5.2.2 Volume of Blood Samples

Table 5 shows the frequency of blood samplings and volume of blood samples obtained throughout the study period. If any deviation from reference range or any finding for which the investigator or subinvestigator considers it necessary to confirm the subject's safety, the required volume of blood samples may increase from the specified volumes tabulated below.

As it is unnecessary to conduct non-safety assessments after the date Version 6 of the protocol is approved by IRB, the volume of blood samples may be lower in applicable subjects.

Table 5 Volume of Blood Samples

Test item	Volume per sampling	Screening Phase	Observation Phase	Treatment Phase	Extension Phase	Follow-up Phase
		Days –42 to –1	Predose of Day 1	Weeks 1 to 24	Weeks 26 to 104	
Viral test, syphilis test, TB test	26 mL	once			twice	
Erythrocyte sedimentation rate	2 mL	once	once	7 times	20 times	
Hematology	2 mL	once	once	7 times	20 times	once
Blood chemistry	10 mL	once	once	7 times	20 times	once
Pregnancy test		(once)[a]		(twice)[a]	(3 times)[a]	
Serum KL-6		(once)[a]		(twice)[a]	(twice)[a]	
Anti-JCV antibody test	3 mL	once		once	3 times	
Blood CD4-positive cells	2 mL	once		twice	3 times	
RF, anti-CCP antibody, MMP-3	4 mL	once	once	7 times	20 times	once
Autoantibody	3 mL		once	twice	3 times	
Serum TRACP-5b concentration			(once)[a]	(twice)[a]	(twice)[a]	
β-D glucan	3 mL	once		twice	twice	
Vasculitis marker tests	5.8 mL		once	twice	6 times	
Serum E6011 concentration	2 or 5 mL		once[b]	8 times[b]	20 times[b]	
Serum anti-E6011 antibody			once[b]	6 times[b]	20 times[b]	
Serum total FKN			(once)[a]			
Serum cytokine concentration, serum LRG1, and Ang2	5 mL		once	3 times	twice	
Vectra™ DA			(once)[a]	(twice)[a]	(twice)[a]	
Immunocytes such as blood CX3CR1-positive cells	5 mL		once	4 times	once[c]	Once[d]
Total volume of blood samples						
Each Phase		52.0 mL	41.8 mL	225.6 mL	591.8 mL	16 mL
Screening to Week 24		319.4 mL				
Screening to Week 104		911.2 mL				
Screening to the Follow-up Phase		932.2 mL				

a: Blood collections for these items (inside the brackets) are included in those for the items just above.

b: The volume of blood sample is 5 mL at the time point for assessing both serum E6011 concentration and serum anti-E6011 antibody and 2 mL at the time point for assessing serum E6011 concentration only.

c: Twice for subjects who discontinue treatment later than Week 52

d: Will only be conducted if blood collection is judged to be feasible at the visit.

9.5.3 Appropriateness of Measurements

Efficacy endpoints of this study are set as follows:

ACR20 response rate, ACR50 response rate, ACR70 response rate, DAS 28-ESR, DAS28-CRP, HAQ, simple disease activity index (SDAI), clinical disease activity index (CDAI), Boolean remission rate, and mTSS.

According to "The Guideline for the clinical evaluation of antirheumatic drugs", it is recommended that the improvement in ACR20 be set as a primary endpoint and the improvement in ACR50 and ACR70 as secondary ones. Therefore, we consider it appropriate to set ACR20 response rate, which is a world standard, as the primary endpoint. In addition, evaluation on DAS28 and comprehensive approaches with more strict measures than ACR20, such as ACR50, ACR70, SDAI, CDAI, and remission criteria are required, given the recent progress of RA diagnosis and treatment system. For assessment of the progression of joint destruction, mTSS by the modified Sharp method using radiography has been verified globally.

The safety assessments to be performed in this study, including hematology, blood chemistry, urinalysis, and assessment of AEs, are standard evaluations to ensure subject safety. Potential risks of vasculitis and PML are set as important safety evaluation items, and the following assessments will be conducted.

1. Potential risk of vasculitis

It is expected that E6011 acts on FKN, which is strongly expressed in vascular endothelial cells in inflammatory diseases. Although there have been no findings suggestive of vasculitis in nonclinical or clinical studies reported so far, vasculitis markers will be measured in this study to investigate the potential risk of vasculitis.

2. Potential risk of PML

PML has been recognized as a potential rare complication in patients with multiple sclerosis or Crohn's disease being treated with natalizumab (humanized anti-α4-integrin monoclonal antibody) (FDA Drug Safety Communication). The pathogenesis of PML remains unclear; however, it is believed that α4-integrin might be involved. Although there have been no findings suggestive of PML in clinical studies reported so far, the mechanism of action of E6011 is to neutralize FKN, and reports that α4-integrin activity is intensified by interaction between FKN and CX3CR1 (Goda S, et al., 2000) suggest that an indirect effect of E6011 on α4-integrin cannot be entirely ruled out. Considering the potential risk of PML, subjects with blood CD4-positive cell count <200 /μL or white blood cell count <3,000 μL or subjects with neurological findings will be excluded in this study. Periodic neurological examinations will be conducted during the study, and PML evaluation expert will be appointed for enabling investigators to obtain advice on diagnosis and treatment of PML; in case neurological findings are observed after starting the study drug administration, the subject must receive a medical examination by a neurologist, have a head MRI examination within 2 weeks, and interrupt the study drug administrations until completion of evaluation by the PML expert. In addition, after the completion or discontinuation of the study, follow-up investigations on event of PML or death by phone or other means will be planned in every 6 months for 2 years from the last dose of the study drug. The pathogenesis of PML is not completely understood; however, it is believed that latent JCV being reactivated due to reduced cellular immunity results in nerve damage (Practice Guideline of Progressive Multifocal

Leukoencephalopathy); therefore, anti-JCV antibody will be assayed and the data will be collected in this study.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All serious adverse events (SAEs), regardless of their relationship to study treatment, must be reported **as soon as possible but no later than 1 business day from the date the investigator becomes aware of the event. In addition, the investigator must report to the sponsor on a completed SAE form as soon as possible.**

Serious adverse events, regardless of causality assessment, must be collected through the study and for 70 days after the subject's last dose. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

Contact information of urgent safety issues is provided in Appendix 2.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 70 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 70 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Section 9.5.4.1" Reporting of Serious Adverse Events").

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in Section 9.5.4.1. The pregnancy report form (Appendix 13) must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported by the pregnancy outcome report form (Appendix 14) as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from the study.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

Adverse events associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose.
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event CRF and also reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event CRF.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators and the head of the medical institution and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis. For this reason, it is imperative that sites provide complete SAE information in the manner described above (see Section 9.5.4.1"Reporting of Serious Adverse Events").

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above (see Section 9.5.4.1"Reporting of Serious Adverse Events"). Any broken code will be clearly justified and documented. The sponsor must be notified immediately of the blind break.

Procedures for emergency blind break are as follows.

Procedures for emergency blind break

1. The investigator or the sponsor will request the emergency code center to break the subject's emergency unblinding code.
2. The emergency code center will obtain the necessary information (investigational site /department, name of person requesting blind break, drug number, study title, and the person to contact when returning the information) from the person requesting code breaking (the investigator or the sponsor).
3. If unblinding is judged appropriate, the emergency code center will unblinding the emergency code for the subject and promptly inform the result to the person to contact (the investigator or the sponsor).
4. When the unblinding request is made by an investigator, the emergency code center will promptly notify the sponsor of the necessary information obtained by the investigator and the result of unblinding.
5. When the unblinding request is made by the sponsor, the sponsor will notify the investigator of the reason, course, and result of the unblinding.

Contact information of the emergency code center is provided in Appendix 2.

9.5.4.6 Regulatory Reporting of Adverse Events

Adverse events will be reported to regulatory authorities in compliance with local law and established guidance. The format of these reports will be dictated by the local requirements.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to discontinue the study at any time for any reason. All subjects who discontinue the study are to complete the study's early discontinuation procedures indicated in the Schedule of Procedures/Assessments (Section 9.5.2.1, Table 4).

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the

status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

Subjects who discontinue early from the study will be discontinued for 1 of these primary reasons: AE(s), lost to follow-up, subject choice, inadequate therapeutic effect, progression of disease, withdrawal of consent, pregnancy, study terminated by sponsor, or other. In addition to the primary reason, the subject may indicate 1 or more secondary reason(s) for discontinuation. Study disposition information will be collected on the CRF.

9.5.6 Abuse or Diversion of Study Drug

Not applicable.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator, subinvestigator, or clinical research coordinator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator or subinvestigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by GCP, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 Statistical Methods

Statistical analyses will be performed by using SAS or other validated statistical software as needed after unblinding. In this study, the statistical analysis in the Treatment Phase will be performed after the database in the Treatment Phase is locked and the data is unblinded, and then final analysis will be performed by using all data after the database throughout the study period is locked. The details will be described separately in the Statistical Analysis Plan (SAP). SAP for the Treatment Phase and the entire study (the Treatment and Extension Phases) will be finalized before each database lock.

9.7.1 Statistical and Analytical Plans

The statistical analyses of study data are described in this section. Analyses in the Treatment Phase are mainly described in the following sections to Section 9.7.1.8, while analyses in the Extension Phase are described in Section 9.7.1.9.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

- ACR20 response rate at Week 12

ACR20 response rate: A subject is defined as ACR20 responder if all of the following 3 criteria are met, and ACR 20 response rate refers to the percentage of subjects with ACR20 response:

1. Greater than or equal to 20% reduction from baseline in the tender joint counts (out of 68 joints)
2. Greater than or equal to 20% reduction from baseline in the swollen joint counts (out of 66 joints)
3. Greater than or equal to 20% reduction from baseline in at least 3 of the following 5 assessments:
   - Physician’s disease activity assessment
   - Patient’s disease activity assessment
   - Patient’s pain assessment
   - HAQ
   - CRP

9.7.1.1.2 SECONDARY ENDPOINTS

- ACR20, ACR50, and ACR70 response rates at each evaluation time point (excluding ACR20 response rate at Week 12)
- Values and change from baseline in ACR components (number of tender joints, number of swollen joints, VAS [Patient's pain assessments/disease activity global assessments and physician's disease activity global assessment], patient's physical function assessment [HAQ], and CRP/ESR), DAS28-ESR, DAS28-CRP, SDAI, and CDAI at each evaluation time point
- EULAR response criteria and disease activity classification based on DAS28-ESR or DAS28-CRP at each evaluation time point
- Remission rate calculated based on each remission criterion (DAS28-ESR, DAS28-CRP, SDAI, CDAI, and Boolean) at each evaluation time point
- Values and change from baseline in mTSS at each evaluation time point

The ACR50 response rate is defined similarly to the ACR20 response rate, except for a 50% reduction as threshold.

The ACR70 response rate is defined similarly to the ACR20 response rate, except for a 70% reduction as threshold.

DAS28-CRP: This will be calculated on the following formula, and disease activity is categorized as High at >4.1, Moderate at >2.7 and ≤4.1, Low at ≤2.7, and Remission at <2.3.

$0.56\times\sqrt{}$[Number of tender joints (28 joints)]+$0.28\times\sqrt{}$[Number of swollen joints (28 joints)]+0.36×ln (CRP×10+1)+0.014×Patient's disease activity assessments + 0.96

DAS28-ESR: This will be calculated on the following formula, and disease activity is categorized as High at >5.1, Moderate at >3.2 and ≤5.1, Low at ≤3.2, and Remission at <2.6.

$0.56\times\sqrt{}$[Number of tender joints (28 joints)]+ $0.28\times\sqrt{}$[Number of swollen joints (28 joints)]+0.70×ln (ESR)+0.014×Patient's disease activity assessments

EULAR Response Criteria:

Present DAS28	DAS28 reduction from baseline		
	<–1.2	≥–1.2 and <–0.6	≥–0.6 (missing included)
Low	Good response	Moderate response	No response
Moderate	Moderate response	Moderate response	No response
High	Moderate response	No response	No response

The CDAI will be calculated on the following formula, and disease activity is categorized as High at >22, Moderate at >10 and ≤22, Low at ≤10, and Remission at ≤2.8.

Number of swollen joints (28 joints) +Number of tender joints (28 joints)
+ Patient's disease activity assessments/10
+ Physician's disease activity assessment/10

SDAI: This will be calculated on the following formula, and disease activity is categorized as High at >26, Moderate at >11 and ≤26, Low at ≤11, and Remission at ≤3.3.

Number of swollen joints (28 joints) +Number of tender joints (28 joints)
+ Patient's disease activity assessments/10
+ Physician's disease activity assessment/10+CRP

Boolean remission: A subject is judged to have Boolean remission if all of the following conditions are satisfied:

1. Tender joint counts (out of 68 joints) ≤1
2. Swollen joint counts (out of 66 joints) ≤1
3. CRP ≤1
4. Patient's disease activity assessment ≤10

9.7.1.2 Definitions of Analysis Sets

The Full Analysis Set (FAS) is the group of randomized subjects who received the study drug and had at least 1 evaluable postdose primary efficacy measurement.

The Per Protocol Analysis Set (PPS) is the group of subjects who sufficiently complied with the protocol. Details of the PPS criteria will be determined before database lock and unblinding and will be specified in the Statistical Analysis Plan.

The Safety Analysis Set is the group of subjects who received the study drug and had at least 1 evaluable postdose safety assessment.

9.7.1.3 Subject Disposition

The number of subjects who provided signed informed consent, and who failed screening along with the reason for such screen failure will be summarized.

The number of randomized subjects, subjects who are treated/not treated (after randomization), completed/discontinued the study, and the reason for the discontinuation will be summarized for each treatment group and the overall subjects.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group and the overall subjects. Continuous variables include age, RA duration; categorical variables include sex, race, etc.

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the FAS by treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. All medications will be presented in subject data listings.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for the efficacy analyses, while the PPS will be used as a supportive population for the efficacy analyses.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

ACR20 response rate at Week 12 will be analyzed using a logistic regression model with CRP level at the Screening Phase, disease duration and history of biologics treatment as covariates, for the comparison between placebo and either E6011 200 mg or 400 mg. Overall significance level is α=0.025 (one-sided). The Hochberg method will be used to adjust the multiplicity. Subjects with missing primary efficacy endpoint due to early discontinuation or other reasons will be considered nonresponders. In case that the number of subjects in each category of covariates is very small, integration of the categories will be planned. ACR20 response rate and its 2-sided 95% confidence interval for each treatment group will be calculated. The difference in ACR20 response rate between each of E6011 doses and placebo and its 2-sided 95% confidence interval will also be calculated. Subgroup analyses or sensitivity analyses will be conducted as needed.

In addition, the following analyses will be conducted for ACR20 response rate at Week 12.

- To compare ACR20 response between E6011 100 mg and placebo using a logistic regression model with CRP level at the Screening Phase, disease duration and history of biologics treatment as covariates. The difference in ACR20 response rate between E6011 100 mg and placebo and its 2-sided 95% confidence interval will also be calculated.
- To estimate the dose-response relationship using a statistical model, such as E_{max} model, if appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The multiplicity adjustment will not be considered for secondary efficacy analyses.

For ACR20 (excluding Week 12), ACR50, and ACR70 response rates at each time evaluation time point, similar analyses to primary analyses will be conducted.

For each component of ACR (number of tender joints, number of swollen joints, VAS [patient's pain assessment and patient's disease activity global assessment, and physician's disease activity global assessment], patient's physical function assessment [HAQ] and CRP/ESR), DAS28-ESR, DAS28-CRP, SDAI, and CDAI in each evaluation time point, summary statistics (mean, standard deviation, median, and range) for the values and the changes from baseline will be calculated by treatment group and evaluation time point. The changes from baseline will also be analyzed using ANCOVA with baseline value, CRP level at the Screening Phase, disease duration and history of biologics treatment as covariates. The significance level for comparisons between placebo and each treatment group with E6011 (100 mg, 200 mg, and 400 mg) is α=0.05 (2-sided).

For mTSS, summary statistics for values and change from baseline will be calculated by treatment group and evaluation time point. The changes from baseline will be analyzed using ANCOVA in the same manner as above.

For EULAR response classification and disease activity classification based on DAS28-ESR and DAS28-CRP, shift tables will be created by treatment group and evaluation time point.

For remission rates calculated based on remission criteria (DAS28-ESR, DAS28-CRP, SDAI, CDAI, and Boolean), similar analyses to primary analyses will be conducted.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

For the Treatment Phase, summary statistics for serum E6011 concentrations will be calculated by treatment group and evaluation time point. Serum E6011 concentration-time profiles will be plotted.

Population pharmacokinetic analyses will be conducted. Data from other studies will be integrated as necessary. Serum E6011 concentration data will be used to build PK models. The models may be used to explore the relationship between PK and covariates. The relationship between serum E6011 concentrations and biomarkers and/or efficacy will also be investigated through population PK/PD modeling. For population PK analyses, the details will be described in the separately prepared analysis plan and its report, and the results will not be included in the clinical study report.

9.7.1.7.2 PHARMACOGENOMIC, BIOMARKER, AND IMMUNOGENICITY ANALYSES

Pharmacogenomic Analyses

Not applicable.

Biomarker Analyses

For the Treatment Phase, summary statistics for serum RF concentration, serum anti-CCP antibody concentration, and serum MMP-3 concentration, serum TRACP-5b concentration,

serum cytokine concentration, serum LRG1 concentration, serum Ang2 concentration, Vectra™ DA and its component (VCAM-1, EGF, VEGF-A, IL-6, TNF-RI, MMP-1, MMP-3, YKL-40, leptin, resistin, SA and CRP) value, change from baseline and percent change from baseline, by treatment group and evaluation time point, will be calculated. Exploratory investigations of the relationship between efficacy and biomarkers will be conducted. Details and results of analyses of immunocytes such as blood CX3CR1-positive cells will be provided in a separate report, and will not be included in the clinical study report.

Immunogenicity Analyses

All immunogenicity analyses will be performed using the Safety Analysis Set.

The percentage and frequency of occurrences will be calculated for serum anti-E6011 antibodies by treatment group and evaluation time point. If anti-E6011 antibody develops, the frequency and percentage of any anti-E6011 antibody neutralization activity and isotypes will be calculated.

9.7.1.8 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. For the Treatment Phase, summary statistics for safety data, presented by treatment group, will be calculated on an "as treated" basis (e.g., n, mean, standard deviation, median, minimum, maximum for continuous variables; n and percentage for categorical variables). Safety variables include AEs, clinical laboratory parameters, vital signs, 12-lead ECG results, chest x-ray, neurological findings, and blood CD4-positive cell count. In safety analysis, the date of starting study treatment is treated as Day 1.

9.7.1.8.1 Extent of Exposure

The duration of exposure to study drug will be characterized by treatment group using summary statistics.

9.7.1.8.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 19.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by highest CTCAE grade.

The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study treatment. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by highest CTCAE grade.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units. For continuous variables, summary statistics for the actual value and the change from baseline will be summarized by visit.

For ordinal classification parameters, laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. The number (percentage) of subjects by LNH will be summarized on shift tables (the baseline vs. each postbaseline visit) by treatment group. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value after starting the study drug administration.

9.7.1.8.4 VITAL SIGNS

Summary statistics for values and changes from baseline of vital sign parameters (i.e., systolic and diastolic BP, pulse, temperature, and weight) will be calculated by evaluation time point and treatment group.

9.7.1.8.5 ELECTROCARDIOGRAMS

The number and percentages of subjects with normal/abnormal findings in 12-lead ECG will be summarized on shift tables by treatment group.

9.7.1.8.6 OTHER SAFETY ANALYSES

Chest x-ray

The number and percentages of subjects with normal/abnormal findings in chest x-ray will be summarized on shift tables by treatment group.

Neurological findings

The number and percentages of subjects with normal/abnormal findings in neurological examination will be summarized on shift tables by treatment group.

Blood CD4-positive cell counts

For Blood CD4-positive cell counts, summary statistics for the actual value and the change from baseline will be calculated by evaluation time point and treatment group. Blood CD4-positive cell counts will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the reference range, and summarized on shift tables by treatment group.

9.7.1.9 Extension Phase Analyses

Similar analyses to those described in the above sections for the Treatment Phase will be conducted for efficacy, pharmacokinetics (except for population PK and PK/PD analyses), biomarker, immunogenicity, and safety endpoints by treatment group of the Treatment Phase.

9.7.2 Determination of Sample Size

The sample size is based on an expected ACR20 response rate of 30% at Week 12 in the placebo group and at least 60% in both of the E6011 200 mg and 400 mg groups, as per results of Study 103 and studies of similar drugs. Although multiplicity adjustment using the Hochberg method will be carried out in the primary analysis, sample size was conservatively calculated at a 1-sided significance level of $\alpha=0.0125$ ($\alpha=0.025/2$). The sample sizes of 50 for E6011 200 mg, 400 mg, and placebo will have 91% power to detect a difference in response rate of 35% between placebo and each E6011 group and will have 79% power to detect a difference in response rate of 30% based on a chi-square test.

The sample size of 25 for E6011 100 mg was set for the purpose of estimating the dose-response curve.

9.7.3 Interim Analysis

No interim analysis is planned for this study.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

FDA Drug Safety Communication: New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab). Safety Announcement. 01-20-2012 http://www.fda.gov/Drugs/DrugSafety/ucm288186.htm

Goda S, Imai T, Yoshie O, Yoneda O, Inoue H, Nagano, et al. CX3C-chemokine, fractalkine-enhanced adhesion of THP-1 cells to endothelial cells through integrin-dependent and -independent mechanisms. J Immunol. 2000; 164(6);4313-20.

Imai T, Nishimura M, Nanki T, Umehara H. Fractalkine and inflammatory disease [in Japanese]. Jpn. J. Clin. Immunol. 2005;28(3):131-9.

Josef SS, Robert L, Ferdinand CB, Maya B, Gerd B, Maxime D, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update

Joseph R. Berger, Sidney A. Houff & Eugene O. Major. Monoclonal antibodies and progressive multifocal leukoencephalopathy. mAbs. 2009 Nov;1 (6): 583–9

Koizumi K, Saitoh Y, Minami T, Takeno N, Tsuneyama K, Miyahara T, et al. Role of CX3CR1/fractalkine in osteoclast differentiation and bone resorption. J Immunol. 2009; 183(12): 7825-31.

Kremer JM. Rational use of new and existing disease-modifying agents in rheumatoid arthritis. Ann Intern Med. 2001;134:695–706.

Maini R, St Clair EW, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet. 1999;354(9194):1932–9

Miyasaka N. Paradigm shift and future perspectives in rheumatoid arthritis [in Japanese]. Nihon Rinsho. 2013:71;1141–6.

Nanki T, Imai T, Nagasaka K, Urasaki Y, Nonomura Y, Taniguchi K, et al. Migration of CX3CR1-Positive T Cells Producing Type 1 Cytokines and Cytotoxic Molecules into the Synovium of Patients With Rheumatoid Arthritis. Arthritis Rheum. 2002; 46(11):2878-83.

Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66(9):1162–7

Ochi T, Yamamoto K, Ryu J. Diagnosis and Treatment Guidelines for Rheumatoid Arthritis based on EBM (revised) 2004 [in Japanese]. Japan Rheumatism Foundation.

Research group of Prion disease and slow virus infection, Ministry of Health, Labour and Welfare Sciences Research Grant, Research Committee on Epidemiology of Intractable Diseases. “Clinical Guideline 2013: Progressive Multifocal Leukoencephalopathy (PML)” [in Japanese].

Singh JA, Saag KG, Bridges SL Jr, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26.

Takeuchi T. Rheumatoid arthritis: progress in diagnosis and treatment, Differential diagnosis of arthritis [in Japanese]. Nihon Naika Gakkai Zasshi. 2010:99;2392–400.

Takeuchi T, Yamanaka H, Ishiguro N, Miyasaka N, Mukai M, Matsubara T, et al. Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. Ann Rheum Dis. 2014;73(3):536-43.

Tanaka Y. Paradigm shift of diagnosis and treatment of rheumatoid arthritis [in Japanese]. Nihon Naika Gakkai Zasshi. 2011:100;1978–86.

Tani K, Takayanagi R, Yokoyama H, Yamada Y. Theoretical analysis of efficacy of biological agent for rheumatoid arthritis based on target molecular binding occupancy: Rheumatol Int. 2013:33(7);1791-5

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation.

Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require additional approval by the applicable IRBs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor and the IRB for the site must be notified immediately. The sponsor must notify the regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB. In these cases, the sponsor may be required to send a letter to the IRB and the Competent Authorities detailing such changes.

11.2 Adherence to the Protocol

The investigators and subinvestigators will conduct the study in strict accordance with the protocol.

11.3 Monitoring Procedures

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB review.

In accordance with the GCP, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IVRS/IWRS, x-rays, and other imaging reports (eg, sonograms, CT scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, EEGs, polysomnographs, pulmonary function tests)

regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded in the CRF must reflect the corresponding source documents. For the following items, the data recorded directly in the CRF are to be considered source data:

- Status of study treatment (eg, reasons for discontinuation of study treatment, reasons of the dose change)
- Reason for providing prior/concomitant therapy (including nonpharmacotherapies)
- Information on study discontinuation (eg, no visit to an investigational site)
- Information on AE (eg, severity, causal relationship to the study drug, outcome)

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the head of the medical institution is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, ICFs, and IRB correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database

for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product. As this investigational product is expected to be designated as a biological product, the site must preserve name and address of a subject, date of drug administration, and lot number for at least 10 years after the last drug administration to identify individuals.

It is requested that at the completion of the required retention period, the site contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of GCP and all applicable local regulations.

11.8 Handling of Study Drug

All study drug will be supplied to the investigator (or a designated pharmacist/or designee) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist/or designee) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist/or designee) will return all unused drug and a copy of the completed drug disposition form (if requested) to the sponsor.

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between the head of the medical institution and the sponsor.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the subinvestigator, the clinical research coordinator, and the IRB and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the head of the medical institution and the sponsor.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the head of the medical institution and the sponsor.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators, heads of the medical institutions, and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the head of the medical institution where applicable, and the investigator/ the head of the medical institution should promptly inform the sponsor and the IRB and provide the sponsor and the IRB with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

If no subjects are enrolled in an investigational site for 3 months or more from the initiation of the recruits at the site, discontinuation of contract with the site will be considered.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Investigational sites and investigators

Appendix 2 Study administrative structure

Appendix 3 ACR 1987 revised criteria for the classification of rheumatoid arthritis, and the 2010 ACR/EULAR classification criteria for rheumatoid arthritis

Appendix 4 Classification of functional capacity in rheumatoid arthritis (ACR 1991 revised criteria)

Appendix 5 Identification, package, and labeling of investigational products

Appendix 6 List of prohibited/restricted concomitant drugs

Appendix 7 Assessment sheet for tender and swollen joint counts (sample)

Appendix 8 Physician’s disease activity assessment form (sample)

Appendix 9 Patient’s pain/disease activity assessment form (Sample)

Appendix 10 Health assessment questionnaire (Sample)

Appendix 11 Neurological finding checklist

Appendix 12 Neurological finding report form

Appendix 13 The pregnancy report form

Appendix 14 The pregnancy outcome report form

Appendix 15 Information on unauthorized medical devices (blood collection tube, etc.) in Japan

Overview of Protocol Amendment between Ver. 1 and Ver. 2

A Dose Response Study of E6011 in Subjects with Rheumatoid Arthritis Inadequately Responding to Methotrexate

(The parts of change: underline)

Protocol body

Pertinent page	Before Amendment (Ver.1, August 31, 2016)	After Amendment (Ver. 2, October 13, 2016)	Reason for Amendment
P38, 9.5.1.5.7 OTHER SAFETY ASSESSMENTS Pregnancy test	For female subjects of childbearing potential, blood test (quantitative, the central laboratory) will be performed at the Screening Phase, Weeks 12, 24, 52, 76, 104, and at discontinuation, and urinalysis test (qualitative, on-site) will be performed during the Observation Phase.	For female subjects of childbearing potential, blood test (quantitative, the central laboratory) will be performed at the Screening Phase, Weeks 12, 24, 52, 76, 104, and at discontinuation, and on-site test will be performed during the Observation Phase. All the test results will be recorded in the medical charts at the site.	For on-site pregnancy test during the Observation Phase, either urine tests (qualitative) or blood tests (quantitative) can be performed.
P44, 9.5.2.2 Table 5 Volume of Blood Samples	See below.		The volume of blood samples for anti-JCV antibody was changed (decreased). correction

(Before) Table 1 Volume of Blood Samples

Test item	Volume per sampling	Screening Phase	Observation Phase	Treatment Phase	Extension Phase	Follow-up Phase
		Days –42 to –1	Predose of Day 1	Weeks 1 to 24	Weeks 26 to 104	
Viral test, syphilis test, TB test	26 mL	once			twice	
Erythrocyte sedimentation rate	2 mL	once	once	7 times	20 times	
Hematology	2 mL	once	once	7 times	20 times	once
Blood chemistry	10 mL	once	once	7 times	20 times	once
Pregnancy test		(once)[a]	(once)[a]	(twice)[a]	(3 times)[a]	
Serum KL-6		(once)[a]		(twice)[a]	(twice)[a]	
Anti-JCV antibody test	3.5 mL	once		once	3 times	
Blood CD4-positive cells	2 mL	once		twice	3 times	
RF, anti-CCP antibody, MMP-3	4 mL	once	once	7 times	20 times	once
Autoantibody	3 mL		once	twice	3 times	
Serum TRACP-5b concentration			(once)[a]	(twice)[a]	(twice)[a]	
β-D glucan	3 mL	once		twice	twice	
Vasculitis marker tests	5.8 mL		once	twice	6 times	
Serum E6011 concentration	2 or 5 mL		once[b]	8 times[b]	20 times[b]	
Serum anti-E6011 antibody			once[b]	6 times[b]	20 times[b]	
Serum total FKN			(once)[a]			
Serum cytokine concentration, serum LRG1, and Ang2	5 mL		once	3 times	twice	
Vectra™ DA			(once)[a]	(twice)[a]	(twice)[a]	
Immunocytes such as blood CX3CR1-positive cells	5 mL		once	4 times	once	
Total volume of blood samples						
Each Phase		52.5 mL	41.8 mL	226.1 mL	593.3 mL	16 mL
Screening to Week 24		320.4 mL				
Screening to Week 104		913.7 mL				
Screening to the Follow-up Phase		929.7 mL				

(After) Table 2 Volume of Blood Samples

Test item	Volume per sampling	Screening Phase	Observation Phase	Treatment Phase	Extension Phase	Follow-up Phase
		Days –42 to –1	Predose of Day 1	Weeks 1 to 24	Weeks 26 to 104	
Viral test, syphilis test, TB test	26 mL	once			twice	
Erythrocyte sedimentation rate	2 mL	once	once	7 times	20 times	
Hematology	2 mL	once	once	7 times	20 times	once
Blood chemistry	10 mL	once	once	7 times	20 times	once
Pregnancy test		(once)[a]		(twice)[a]	(3 times)[a]	
Serum KL-6		(once)[a]		(twice)[a]	(twice)[a]	
Anti-JCV antibody test	3 mL	once		once	3 times	
Blood CD4-positive cells	2 mL	once		twice	3 times	
RF, anti-CCP antibody, MMP-3	4 mL	once	once	7 times	20 times	once
Autoantibody	3 mL		once	twice	3 times	
Serum TRACP-5b concentration			(once)[a]	(twice)[a]	(twice)[a]	
β-D glucan	3 mL	once		twice	twice	
Vasculitis marker tests	5.8 mL		once	twice	6 times	
Serum E6011 concentration	2 or 5 mL		once[b]	8 times[b]	20 times[b]	
Serum anti-E6011 antibody			once[b]	6 times[b]	20 times[b]	
Serum total FKN			(once)[a]			
Serum cytokine concentration, serum LRG1, and Ang2	5 mL		once	3 times	twice	
Vectra™ DA			(once)[a]	(twice)[a]	(twice)[a]	
Immunocytes such as blood CX3CR1-positive cells	5 mL		once	4 times	once	
Total volume of blood samples						
Each Phase		52.0 mL	41.8 mL	225.6 mL	591.8 mL	16 mL
Screening to Week 24		319.4 mL				
Screening to Week 104		911.2 mL				
Screening to the Follow-up Phase		927.2 mL				

Overview of Protocol Amendment between Ver. 2 and Ver. 3

A Dose Response Study of E6011 in Subjects with Rheumatoid Arthritis Inadequately Responding to Methotrexate

(The parts of change: underline)

Protocol body

Pertinent page	Before Amendment (Ver.2, October 13, 2016)	After Amendment (Ver. 3, February 23, 2017)	Reason for Amendment
P5, 2 CLINICAL PROTOCOL SYNOPSIS Exclusion criteria P23, 9.3.2 Exclusion criteria	(23) Tested positive for any of the following in the Screening Phase: HIV, hepatitis B virus surface antigen (HBs antigen), hepatitis B virus surface antibody (HBs antibody), hepatitis B virus core antibody (HBc antibody), hepatitis B virus DNA (HBV DNA), hepatitis C virus antibody (HCV antibody), human T-lymphotrophic virus type I antibody (HTLV-1 antibody), or syphilis (except if positive for the HBs antibody only, and it is clear that this is due to hepatitis B vaccination)	(23) Tested positive for any of the following in the Screening Phase: HIV, hepatitis B virus surface antigen (HBs antigen), hepatitis B virus surface antibody (HBs antibody), hepatitis B virus core antibody (HBc antibody), hepatitis B virus DNA (HBV DNA), hepatitis C virus antibody (HCV antibody), human T-lymphotrophic virus type I antibody (HTLV-1 antibody), or syphilis (except if positive for the HBs antibody only, and it is clear that this is due to hepatitis B vaccination. <u>In case of positive RPR and negative TP antibody results, the positive result is not considered valid if a false positivity is confirmed by repeated TP antibody negative results of other syphilis tests performed 21 days or more later.)</u>	To allow enrollment of patients with a false positive syphilis test result.
P7, 2 CLINICAL PROTOCOL SYNOPSIS Concomitant Drug/Therapy P30,	<Prohibited concomitant therapies and drugs> ·Over-the-counter medications containing folic acid as main component	<Prohibited concomitant therapies and drugs> ·<u>Folic acid preparation</u> or over-the-counter medications containing folic acid as main component	To clarify the description.

Pertinent page	Before Amendment (Ver.2, October 13, 2016)	After Amendment (Ver. 3, February 23, 2017)	Reason for Amendment
9.4.7.1.1 PROHIBITED CONCOMITANT THERAPIES AND DRUGS			
P7, 2 CLINICAL PROTOCOL SYNOPSIS Concomitant Drug/Therapy P30, 9.4.7.1.2RESTRICTED CONCOMITANT DRUGS	<Restricted medicine> -MTX and folic acid are to be continued at a stable dose regimen until completion of the Extension Phase (or until study discontinuation). If an adverse event associated with MTX is noted, dose reduction is permitted. If the event disappears after dose reduction, the dose can be increased to the previous level.	<Restricted medicine> -MTX and folic acid are to be continued at a stable dose regimen until completion of the Extension Phase (or until study discontinuation). If an adverse event associated with MTX is noted during the Extension Phase, dose reduction or interruption is permitted. If the event disappears after dose reduction or interruption, the dose can be increased to the previous level.	To clarify the description.
P20, 9.1.1 Screening Phase	For subjects who require prophylactic treatments with isoniazid based on the results of the tuberculosis test at the Screening Phase, the prophylactic treatments are needed for at least 21 days before starting the study treatment, so the duration of the Screening Phase is allowed to be extended until 21 days from the start of isoniazid administrations.	For subjects who require prophylactic treatments with isoniazid based on the results of the tuberculosis test at the Screening Phase, the prophylactic treatments are needed for at least 21 days before starting the study treatment, so the duration of the Screening Phase is allowed to be extended until 21 days from the start of isoniazid administrations. If a patient requires another syphilis test based on the result in the Screening Phase, reexamination has to be performed after an interval of 21 days or longer during the Screening Phase. The	Following reconsideration of Exclusion Criterion (23).

Pertinent page	Before Amendment (Ver.2, October 13, 2016)	After Amendment (Ver. 3, February 23, 2017)	Reason for Amendment
		Screening Phase can be extended until the reexamination result is obtained.	
P25, 9.3.3 Removal of Subjects From Therapy or Assessment	(8) Tested positive for any of the following: HIV, HBs antigen), HBV DNA, HCV antibody, HTLV-1 antibody, or syphilis.	(8) Tested positive for any of the following: HIV, HBs antigen, HBV DNA, HCV antibody, HTLV-1 antibody, or syphilis (Confirmed false positive syphilis test result is excluded).	Following reconsideration of Exclusion Criterion (23).
P43, Table 4 Schedule of Procedures/Assessments in Study E6011-J081-201 At discontinuation: Immunocytes such as blood CX3CR1-positive cells note	(Not mentioned)	j: Basically performed at study discontinuation, and a missing value is permissible only when collection of the sample is difficult due to abrupt discontinuation.	Anticipating some cases of abrupt discontinuation, when collection of the specimen is difficult.

Overview of Protocol Amendment between Ver. 3 and Ver. 4

A Dose Response Study of E6011 in Subjects with Rheumatoid Arthritis Inadequately Responding to Methotrexate

(The parts of change: underline)

Protocol body

Pertinent page	Before Amendment (Ver.3, February 23, 2017)	After Amendment (Ver. 4, April 24, 2017)	Reason for Amendment
P30, 9.4.9 Drug Supplies and Accountability	The drug accountability logs must be made available, upon request, for inspection by a CRA or a representative of a health authority. The study drug manager (or designee) must check the number of all unused study drugs, exchange the documentation of drug return and collection with the sponsor, and return unused study drugs <u>(including empty boxes)</u> to the sponsor. The CRA collects study drugs returned from the site and stores in the depot designated by the sponsor.	The drug accountability logs must be made available, upon request, for inspection by a CRA or a representative of a health authority. The study drug manager (or designee) must check the number of all unused study drugs, exchange the documentation of drug return and collection with the sponsor, and return unused study drugs to the sponsor. The CRA collects study drugs returned from the site and stores in the depot designated by the sponsor.	Instruction for handling of empty box was described in the instructions for handling of investigational products
P39, 9.5.2.1 Schedule of Procedures/Assessments	Each assessment will be performed within 3 days before or after the scheduled date during Weeks 1 to 12 or within 7 days before or after the scheduled date after Week 14 using Week 0 as a reference point. In the Follow-up Phase, each assessment will be performed within 7 days before or after the scheduled date (“within after 7 days” for the interview at “70 days after	Each assessment will be performed within 3 days before or after the scheduled date during Weeks 1 to 12 or within 7 days before or after the scheduled date after Week 14 using Week 0 as a reference point. In the Follow-up Phase, each assessment will be performed within 7 days before or after the scheduled date (“within after 7 days” for the interview at “70 days after the last dosing”). However, the interval	To clarify the description (omitted unnecessary words)

Pertinent page	Before Amendment (Ver.3, February 23, 2017)	After Amendment (Ver. 4, April 24, 2017)	Reason for Amendment
	the last dosing"). However, the interval between study treatments should be at least 3 days until 2 weeks after the start of study treatment, and at least 6 days after 4 weeks have elapsed since the start of study treatment. If any scheduled assessment or administration of the study drug cannot perform within the above period, such event will be considered as a protocol deviation. In such a case, each assessment will still be performed, but administration of the study drug will be skipped.	between study treatments should be at least 3 days treatment until 2 weeks after the start of study treatment, and at least 6 days after 4 weeks have elapsed since the start of study treatment. If any scheduled assessment or administration of the study drug cannot perform within the above period, each assessment will still be performed, but administration of the study drug will be skipped.	
P59, 11.8 Handling of Study Drug	All drug supplies are to be used only for this study and not for any other purpose. The investigator (or study drug manager/designee) must not peel off any drug labels or discard any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or study drug manager/designee) will return all used drugs and unused drug containers, and submit a copy of the completed drug accountability ledger (if requested) to the sponsor.	All drug supplies are to be used only for this study and not for any other purpose. The investigator (or study drug manager/designee) must not peel off any drug labels or discard any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or study drug manager/designee) will return all unused drugs and submit a copy of the completed drug accountability ledger (if requested) to the sponsor.	Instruction for handling of used drugs and the box was described in the instructions for handling of investigational products

Overview of Protocol Amendment between Ver. 4 and Ver. 5

A Dose Response Study of E6011 in Subjects with Rheumatoid Arthritis Inadequately Responding to Methotrexate

(The parts of change: underline)

Protocol body

Pertinent page	Before Amendment (Ver. 4, April 24, 2017)	After Amendment (Ver. 5, August 31, 2018)	Reason for Amendment
P2, 2. CLINICAL PROTOCOL SYNOPSIS Study Design	(text omitted) When subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase (show no improvement from the Observation Phase in both of tender joint counts and swollen joint counts at 2 consecutive assessments with an interval of ≥1 week), dose escalation will be allowed only once (6 administrations of E6011 400 mg every 2 weeks). (text omitted) *: When subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase (show no improvement from the Observation Phase in both of tender joint counts and swollen joint counts at 2 consecutive assessments with an interval of ≥1 week), dose escalation will be allowed only once (6 administrations of E6011 400 mg every 2 weeks).	(text omitted) If the investigator or subinvestigator judges that the response to treatment is insufficient in the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed (reduction of the dose back to 200 mg after an increase to 400 mg will also be allowed). (text omitted) *: If the investigator or subinvestigator judges that response to treatment is insufficient during the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed.	To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations

Pertinent page	Before Amendment (Ver. 4, April 24, 2017)	After Amendment (Ver. 5, August 31, 2018)	Reason for Amendment
P6, 2. CLINICAL PROTOCOL SYNOPSIS Study Treatments	(text omitted) Extension Phase: E6011 200 mg will be subcutaneously administered every 2 weeks until Week 102. When subjects insufficiently respond to the treatment or when their disease relapses, dose escalation will be allowed only once (6 repeated subcutaneous administrations of 400 mg E6011 every 2 weeks). (text omitted) However, 4 mL of the study drug may be given subcutaneously in 2 separate sites, 2 mL each, only if the investigator or subinvestigator judges that the study drug can be administered properly.	(text omitted) Extension Phase: E6011 200 mg will be subcutaneously administered every 2 weeks until Week 102. When subjects insufficiently respond to the treatment, repeated subcutaneous administration (400 mg of E6011 every 2 weeks) will be allowed. (text omitted) However, 2 mL of the study drug may be given subcutaneously in 1 site only if the investigator or subinvestigator judges that the study drug can be administered properly.	To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations Because the safety of administering 2 mL at 1 site was confirmed
P19, 9.1 Overall Study Design and Plan	(text omitted) When subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase (show no improvement from the Observation Phase in both of tender joint counts and swollen joint counts at 2 consecutive assessments with an interval of ≥1 week), dose escalation will be allowed only once (6 administrations of E6011 400 mg every 2 weeks). (text omitted) *: When subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase	(text omitted) If the investigator or subinvestigator judges that the response to treatment is insufficient in the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed (reduction of the dose back to 200 mg after an increase to 400 mg will also be allowed). (text omitted) *: If the investigator or subinvestigator judges that response to treatment is insufficient during the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed.	To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations

Pertinent page	Before Amendment (Ver. 4, April 24, 2017)	After Amendment (Ver. 5, August 31, 2018)	Reason for Amendment
	(show no improvement from the Observation Phase in both of tender joint counts and swollen joint counts at 2 consecutive assessments with an interval of ≥1 week), dose escalation will be allowed only once (6 administrations of E6011 400 mg every 2 weeks).		
P20, 9.1.4 Extension Phase	(text omitted) When subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase (show no improvement from the Observation Phase in both of tender joint counts and swollen joint counts at 2 consecutive assessments with an interval of ≥1 week), dose escalation will be allowed only once (6 administrations of 400 mg every 2 weeks).	(text omitted) If the investigator or subinvestigator judges that the response to treatment is insufficient in the Extension Phase, administration of E6011 400 mg every 2 weeks will also be allowed (reduction of the dose back to 200 mg after an increase to 400 mg will also be allowed).	To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations
P21, 9.2 Discussion of Study Design, Including Choice of Control Groups	(text omitted) Furthermore, when subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase (show no improvement from the Observation Phase in both of tender joint counts and swollen joint counts at 2 consecutive assessments with an interval of ≥1 week), dose escalation will be allowed only once (6 administrations of E6011 400 mg every 2 weeks).	(text omitted) Furthermore, if the subjects insufficiently respond to the treatment in the Extension Phase, the design also allows for administration of E6011 400 mg every 2 weeks	To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations

<table>
<tr><th>Pertinent page</th><th>Before Amendment (Ver. 4, April 24, 2017)</th><th>After Amendment (Ver. 5, August 31, 2018)</th><th>Reason for Amendment</th></tr>
<tr><td>P25,
9.4.1 Treatments Administered</td><td>(text omitted)
Extension Phase: Subjects will receive E6011 200 mg every 2 weeks from Week 24 to Week 102 by repeated subcutaneous administration. When subjects insufficiently respond to the treatment or when their disease relapses, dose escalation will be allowed only once (6 repeated subcutaneous administrations of E6011 400 mg every 2 weeks).
(text omitted)
However, 4 mL of the study drug may be given subcutaneously in 2 separate sites, 2 mL each, only if the investigator or subinvestigator judges that the study drug can be administered properly.</td><td>(text omitted)
Extension Phase: Subjects will receive E6011 200 mg every 2 weeks from Week 24 to Week 102 by repeated subcutaneous administration. When subjects insufficiently respond to the treatment, repeated subcutaneous administration (400 mg of E6011 every 2 weeks) will be allowed.
(text omitted)
However, 2 mL of the study drug may be given subcutaneously in 1 site only if the investigator or subinvestigator judges that the study drug can be administered properly.</td><td>To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations

Because the safety of administering 2 mL at 1 site was confirmed</td></tr>
<tr><td>P26,
9.4.1 Treatments Administered</td><td>Table 1 Dose and Administration of the Study Drug
<table><tr><td rowspan="2">Extension Phase: Weeks 24 to 102 (Open label)</td><td>200 mg</td><td>2 mL (2 vials[d])</td><td>Study drug will be given subcutaneously in 2 separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh.</td></tr><tr><td>400 mg[a]</td><td>4 mL (4 vials[e])</td><td>Study drug will be given subcutaneously in 4</td></tr></table></td><td>Table 1 Dose and Administration of the Study Drug
<table><tr><td rowspan="2">Extension Phase: Weeks 24 to 102 (Open label)</td><td>200 mg</td><td>2 mL (2 vials[d])</td><td>Study drug will be given subcutaneously in 2 separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh.
(2 mL of the study drug may be given</td></tr></table></td><td>To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations

Because the safety of administering 2 mL at 1 site was</td></tr>
</table>

Pertinent page	Before Amendment (Ver. 4, April 24, 2017)	After Amendment (Ver. 5, August 31, 2018)	Reason for Amendment
	separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh. (The study drug may be given subcutaneously in 2 separate sites, 2 mL each, only if the investigator or subinvestigator judges that the study drug can be administered properly.) a: When subjects insufficiently respond to the treatment or when their disease relapses, dose escalation from 200 mg to 400 mg will be allowed only once (6 repeated subcutaneous administrations of E6011 400 mg every 2 weeks).	subcutaneously in 1 site only if the investigator or subinvestigator judges that the study drug can be administered properly.) 400 mg[a] / 4 mL (4 vials[e]): Study drug will be given subcutaneously in 4 separate sites, 1.0 mL each, among the following sites: right or left upper arm, right or left abdomen, or right or left thigh. (The study drug may be given subcutaneously in 2 separate sites, 2 mL each, only if the investigator or subinvestigator judges that the study drug can be administered properly.) a: When subjects insufficiently respond to the treatment, repeated subcutaneous administration (400 mg of E6011 every 2 weeks) will be allowed.	confirmed

Pertinent page	Before Amendment (Ver. 4, April 24, 2017)	After Amendment (Ver. 5, August 31, 2018)	Reason for Amendment
P28, 9.4.4 Selection of Doses in the Study	(text omitted) In the Extension Phase, subjects will receive 200 mg administrations of E6011 (central dose) every 2 weeks. When subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase (show no improvement from the Observation Phase in both of tender joint counts and swollen joint counts at 2 consecutive assessments), dose escalation will be allowed only once (6 administrations of E6011 400 mg every 2 weeks). As the guidelines indicate that drug therapies for RA should be reviewed every 3 or 6 months, it is appropriate to set the period for administration of E6011 400 mg every 2 weeks to be 3 months (6 administrations).	(text omitted) In the Extension Phase, subjects will receive 200 mg administrations of E6011 (central dose) every 2 weeks. However, when subjects insufficiently respond to the treatment (E6011 200 mg every 2 weeks), dose escalation will be allowed (E6011 400 mg every 2 weeks).	To revise the dose escalation criteria and abolish the restrictions on the number of dose escalations
P43, Table 4 Schedule of Procedures/Assessments in Study E6011-J081-201 70 days after the last dosing: Immunocytes such as blood CX3CR1-positive cells	(no text)	X^k (Blood collection for immunocytes such as blood CX3CR1-positive cells 70 days after administration was added) k. Will only be conducted if blood sample is judged to be feasible at the visit.	To evaluate changes in parameters such as CX3CR1-positive cells after administration as an exploratory investigation

Pertinent page	Before Amendment (Ver. 4, April 24, 2017)	After Amendment (Ver. 5, August 31, 2018)	Reason for Amendment
P44, 9.5.2.2 Volume of Blood Samples Table 5	See following pages		To evaluate changes in parameters such as CX3CR1-positive cells after administration as an exploratory investigation To revise the text

(Before Amendment) Table 5 Volume of Blood Samples

Test item	Volume per sampling	Screening Phase Days –42 to –1	Observation Phase Predose of Day 1	Treatment Phase Weeks 1 to 24	Extension Phase Weeks 26 to 104	Follow-up Phase
Viral test, syphilis test, TB test	26 mL	once			twice	
Erythrocyte sedimentation rate	2 mL	once	once	7 times	20 times	
Hematology	2 mL	once	once	7 times	20 times	once
Blood chemistry	10 mL	once	once	7 times	20 times	once
Pregnancy test		(once)[a]		(twice)[a]	(3 times)[a]	
Serum KL-6		(once)[a]		(twice)[a]	(twice)[a]	
Anti-JCV antibody test	3 mL	once		once	3 times	
Blood CD4-positive cells	2 mL	once		twice	3 times	
RF, anti-CCP antibody, MMP-3	4 mL	once	once	7 times	20 times	once
Autoantibody	3 mL		once	twice	3 times	
Serum TRACP-5b concentration			(once)[a]	(twice)[a]	(twice)[a]	
β-D glucan	3 mL	once		twice	twice	
Vasculitis marker tests	5.8 mL		once	twice	6 times	
Serum E6011 concentration	2 mL or 5 mL		once[b]	8 times[b]	20 times[b]	
Serum anti-E6011 antibody			once[b]	6 times[b]	20 times[b]	
Serum total FKN			(once)[a]			
Serum cytokine concentration, serum LRG1, and Ang2	5 mL		once	3 times	twice	
Vectra™ DA			(once)[a]	(twice)[a]	(twice)[a]	
Immunocytes such as blood CX3CR1-positive cells	5 mL		once	4 times	once	
Each Phase		52.0 mL	41.8 mL	225.6 mL	591.8 mL	16 mL
Screening to Week 24		319.4 mL				
Screening to Week 104		911.2 mL				
Screening to the Follow-up Phase		927.2 mL				

a: Blood collections for these items (inside the brackets) are included in those for the items just above.

b: The volume of blood sample is 5 mL at the time point for assessing both serum E6011 concentration and serum anti-E6011 antibody and 2 mL at the time point for assessing serum E6011 concentration only.

(After Amendment) Table 5 Volume of Blood Samples

Test item	Volume per sampling	Screening Phase Days –42 to –1	Observation Phase Predose of Day 1	Treatment Phase Weeks 1 to 24	Extension Phase Weeks 26 to 104	Follow-up Phase
Viral test, syphilis test, TB test	26 mL	once			twice	
Erythrocyte sedimentation rate	2 mL	once	once	7 times	20 times	
Hematology	2 mL	once	once	7 times	20 times	once
Blood chemistry	10 mL	once	once	7 times	20 times	once
Pregnancy test		(once)[a]		(twice)[a]	(3 times)[a]	
Serum KL-6		(once)[a]		(twice)[a]	(twice)[a]	
Anti-JCV antibody test	3 mL	once		once	3 times	
Blood CD4-positive cells	2 mL	once		twice	3 times	
RF, anti-CCP antibody, MMP-3	4 mL	once	once	7 times	20 times	once
Autoantibody	3 mL		once	twice	3 times	
Serum TRACP-5b concentration			(once)[a]	(twice)[a]	(twice)[a]	
β-D glucan	3 mL	once		twice	twice	
Vasculitis marker tests	5.8 mL		once	twice	6 times	
Serum E6011 concentration	2 mL or 5 mL		once[b]	8 times[b]	20 times[b]	
Serum anti-E6011 antibody			once[b]	6 times[b]	20 times[b]	
Serum total FKN			(once)[a]			
Serum cytokine concentration, serum LRG1, and Ang2	5 mL		once	3 times	twice	
Vectra™ DA			(once)[a]	(twice)[a]	(twice)[a]	
Immunocytes such as blood CX3CR1-positive cells	5 mL		once	4 times	once[c]	once[d]
Each Phase		52.0 mL	41.8 mL	225.6 mL	591.8 mL	21 mL
Screening to Week 24		319.4 mL				
Screening to Week 104		911.2 mL				
Screening to the Follow-up Phase		932.2 mL				

a: Blood collections for these items (inside the brackets) are included in those for the items just above.

b: The volume of blood sample is 5 mL at the time point for assessing both serum E6011 concentration and serum anti-E6011 antibody and 2 mL at the time point for assessing serum E6011 concentration only.

c: Twice for subjects who discontinue treatment later than Week 52

d: Will only be conducted if blood collection is judged to be feasible at the visit.

Overview of Protocol Amendment between Ver. 5 and Ver. 6

A Dose Response Study of E6011 in Subjects with Rheumatoid Arthritis Inadequately Responding to Methotrexate

(The parts of change: underline)

Protocol body

Pertinent page	Before Amendment (Ver. 5, August 31,2018)	After Amendment (Ver. 6, March 25, 2019)	Reason for Amendment
P7, 2. CLINICAL PROTOCOL SYNOPSIS Concomitant Drug/Therapy P31, 9.4.7.1.2 Restricted Concomitant Drugs	(no text)	<Restricted Concomitant Drugs> ·After the date Version 6 of the protocol is approved by IRB, dose reduction, dose interruption, dose increase following the dose reduction (up to the initial dose level), and restarting administration after interruption will be allowed for MTX, folic acid, corticosteroids, or herbal medicine indicated for RA). There will be no restrictions in using NSAIDs (oral, suppository, or topical).	Because it was considered unnecessary to conduct any non-safety assessments
P8, 2. CLINICAL PROTOCOL SYNOPSIS Assessments	(no text)	After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct assessments other than <safety>.	Because it was considered unnecessary to conduct any non-safety assessments
P19, 7. INTRODUCTION	(no text)	The last subject entered the Extension Phase (open-label) in March 2018, and all subjects had completed 52 weeks of treatment with E6011 by March 2019. Consequently, it was considered unnecessary to conduct any non-safety assessments after March 2019, and the protocol will be revised to Version 6.	Because it was considered unnecessary to conduct any non-safety assessments

Pertinent page	Before Amendment (Ver. 5, August 31,2018)	After Amendment (Ver. 6, March 25, 2019)	Reason for Amendment
P26, 9.3.3 Removal of Subjects From Therapy or Assessment	(no text)	(9) When the investigator or subinvestigator judges that efficacy of E6011 is insufficient, after the date Version 6 of the protocol was approved by IRB (10) When the investigator or subinvestigator judges that there are other effective treatment options available besides continuing this study, after the date Version 6 of the protocol was approved by IRB	To add provisions
P30, 9.4.7 Prior and Concomitant Therapy	(no text)	After the date Version 6 of the protocol is approved by IRB, it is unnecessary to record concomitant medications/therapies in the CRF.	Because it was considered unnecessary to conduct any non-safety assessments
P33, 9.5.1.3 Efficacy Assesments	(no text)	After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct assessments for efficacy.	Because it was considered unnecessary to conduct any non-safety assessments
P34, 9.5.1.4 Pharmacokinetic, Pharmacogenomic, Biomarker, and Immunogenicity Assessments	(no text)	After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct assessments for pharmacokinetic, pharmacogenomic, biomarker, and immunogenicity. However, pharmacokinetic and immunogenicity assessments will be conducted at discontinuation.	Because it was considered unnecessary to conduct any non-safety assessments

Pertinent page	Before Amendment (Ver. 5, August 31,2018)	After Amendment (Ver. 6, March 25, 2019)	Reason for Amendment
P40, 9.5.2.1 Study Schedule	(no text)	After the date Version 6 of the protocol is approved by IRB, it is unnecessary to conduct "tender and swollen joint counts/ESR", "VAS/HAQ", "joint X-rays", "RF/anti-CCP antibody/MMP-3", "serum E6011 concentration", "serum anti-E6011 antibody", "serum total FKN concentration", "cytokines/LRG1/Ang2", "TRACP-5b", "CX3CR1-positive cell count", or "Vectra™ DA". However, assessments of "serum E6011 concentration" and "serum anti-E6011 antibody" will be conducted at discontinuation.	Because it was considered unnecessary to conduct any non-safety assessments
P44, 9.5.2.1 Study Schedule Table 4 Remarks	(no text)	l After the date Version 6 of the protocol is approved by IRB, applicable assessments will not be conducte. However, assessments of serum E6011 concentration and serum anti-E6011 antibody will be conducted at discontinuation.	Because it was considered unnecessary to conduct any non-safety assessments
P45, 9.5.2.2 Volume of Blood Samples	(no text)	As it is unnecessary to conduct non-safety assessments after the date Version 6 of the protocol is approved by IRB, the volume of blood samples may be lower in applicable subjects.	Because it was considered unnecessary to conduct any non-safety assessments

Page(s) removed - non-English text removed