MIRACLE

(Methotrexate inadequate response patient with Rheumatoid Arthritis treated by Adalimumab in combination with Low-dose Methotrexate)

Evaluation of the Optimal MTX Dose as an Add-on Therapy to Adalimumab for RA Patients in Japan, South Korea and Taiwan. (NCT03505008)

Study Protocol

Ver. 2.2 (Date prepared: November 15, 2019)

Study Protocol

MIRACLE (Methotrexate inadequate response patient with Rheumatoid Arthritis treated by Adalimumab in combination with Low-dose Methotrexate) Study

< Lead Principal Investigator >
Yuko Kaneko
Division of Rheumatology, Department of Internal Medicine
Keio University School of Medicine

<Study Investigational Operator>
Hiroya Tamai
Division of Rheumatology, Department of Internal Medicine
Keio University School of Medicine

<Study Secretariat>
Planning and Management Office
Clinical and Translational Research Center
Keio University Hospital

Contract Medical Affairs
Linical Co., Ltd.
1-9-2 Higashi-Shimbashi, Minato-ku, Tokyo 105-0021, Japan
TEL: +81-[redacted] FAX: +81-[redacted]

Ver. 2.2 (Date prepared: November 15, 2019)

List of abbreviations

Abbreviations	Definitions
ACR	American College of Rheumatology
ADA	Adalimumab
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CCP	cyclic citrullinated peptide
CDAI	clinical disease activity index
CRP	C-reactive protein
Cr	creatinine
DAS	disease activity score
DMARDs	disease-modifying antirheumatic drugs
EDC	electronic data capturing
ESR	erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FAS	full analysis set
GCP	Good Clinical Practice
γ-GTP	γ-glutamine transpeptidase
HAQ	Health Assessment Questionnaire
Hb	Hemoglobin
HBc	hepatitis B virus core
HBs	hepatitis B virus surface
HCV	hepatitis C virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IgA	immunoglobulin A
IgG	immunoglobulin G
IGRA	interferon-gamma release assay
IL	Interleukin
IWRS	Interactive Web Response System
JAK	Janus kinase
LDH	lactate dehydrogenase
LLT	lowest level terms
LOCF	Last Observation Carried Forward
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMP-3	matrix metalloproteinase-3

Abbreviations	Definitions
mTSS	modified Total Sharp Score
MTX	Methotrexate
NSAIDs	non-steroidal anti-inflammatory drugs
Plt	Platelet
PPS	per protocol set
PT	preferred term
QOL	quality of life
RA	rheumatoid arthritis
RBC	red blood cell
RF	rheumatoid factor
RNA	ribonucleic acid
SAE	serious adverse event
SDAI	simple disease activity index
SOC	system organ class
Tmax	time at which the highest drug concentration occurs
TEAE	treatment emergent adverse event
TNF	tumor necrosis factor
UA	uric acid
VAS	visual analog scale
VEGF	vascular endothelial growth factor
WBC	white blood cell

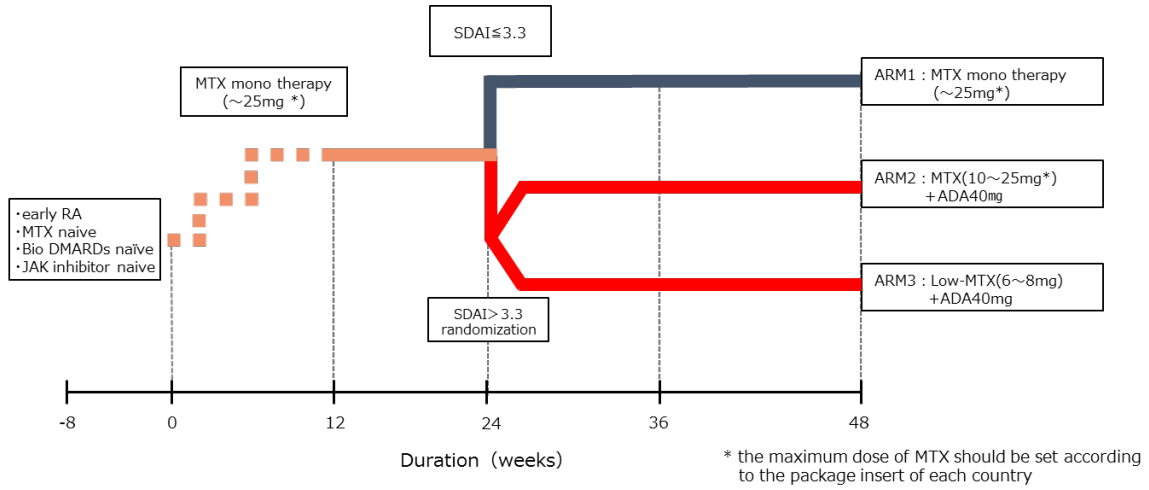
Table of contents

0. SYNOPSIS

0.1 Study title

MIRACLE (Methotrexate inadequate response patient with Rheumatoid Arthritis treated by Adalimumab in combination with Low-dose Methotrexate) Study

0.2 Schema



0.3 Objective

This study is intended to evaluate the optimal dosage of methotrexate (MTX) as an add-on therapy to adalimumab (ADA) in patients with rheumatoid arthritis (RA) who do not achieve remission by MTX monotherapy, and to measure erythrocyte MTX-polyglutamates (MTX-PG) concentration to evaluate its relation to the efficacy and safety of MTX therapy in RA patients.

0.4 Subjects

This study will be conducted in 300 patients with RA in Japan, South Korea, and Taiwan previously not treated with MTX, Janus kinase (JAK) inhibitor, or biological disease-modifying antirheumatic drugs (bDMARDs), and whose duration of disease is within 2 years from diagnosis.

RA patients (meeting the 1987 revised ACR criteria or 2010 ACR/EULAR criteria) aged ≥18 years (≥20 years in Taiwan) whose disease activity at screening is SDAI >11.

0.5 Study treatment

Study treatment will start with MTX 6 to 8 mg/week, which will be promptly escalated to the maximum tolerable dose (MTD) ≤25 mg/week (the maximum dose should be set according to the package insert of each country) in line with EULAR Recommendations 2016, and will be in principle maintained at the MTD from Week 12 onward. Also, the dosage of MTX will remain unchanged from Week 20 to 24 except for dose reduction/interruption due to an adverse drug reaction (ADR).

If the dosage of MTX is maintained ≥10 mg/week and remission (SDAI ≤3.3) is achieved at Week 24, the MTX therapy will be continued (ARM-1).
If SDAI remission is not achieved despite the dosage of MTX is maintained ≥10 mg/week at Week 24, a bDMARDs will be added to the treatment in line with EULAR Recommendations 2016. Subjects will subcutaneously receive ADA 40 mg as a bDMARD every other week up to Week 48, and be randomized to a group in which the MTD of MTX (10 to 25 mg/week) will be maintained (ARM-2) and a group in which the dosage of MTX will be reduced to 6 to 8 mg/week (ARM-3). Then, the efficacy and safety will be evaluated.
If a subject becomes intolerable to MTX ≥10 mg/week at Week 24 due to an ADR or other relevant reasons, the subject will be terminated from the study at that time. The subject will be also terminated from the study when subjects have received a non-ADA bDMARD or JAK inhibitor.
The primary endpoint will be the SDAI remission rate at Week 48 in the ADA/MTX-MTD Group (ARM-2) and ADA/MTX-Reduced Dose Group (ARM-3). Key secondary endpoints will be the SDAI remission rate at Week 24, the SDAI remission rate at Week 48 in MTX Monotherapy Group, the modified total sharp score (mTSS) at each assessment timepoint and changes from baseline to each assessment timepoint, and ACR20, ACR50, and ACR70 response rates at each assessment timepoint. Also, the correlation of the erythrocyte MTX-PG concentration to SDAI, mTSS, and ACR-N will be exploratorily evaluated.

0.6 Target number of subjects and study period

Target number of subjects	: 300 subjects
Enrollment period	: March 2018 to July 2020 (2 years and 5 months)
Intervention period	: 48 weeks
Data retrieval, analysis, and report generation periods	: 1 year
Total study period	: 4 years and 4 months

0.7 Contact

Inclusion/exclusion criteria, and others that require clinical judgment:

	Lead Principal Investigator or Study Investigational Operator
EDC entry, etc.	: Data center
AE reporting	: SAE Report Center
Others	: Operation Center

1 Overview

1.1 Study Information

1.1.1 Study title

MIRACLE (Methotrexate inadequate response patient with Rheumatoid Arthritis treated by Adalimumab in combination with Low-dose Methotrexate) Study

1.1.2 Study identifying numbers

Study protocol No. : D2E7-C000-401
ClinicalTrials.gov Identifier : NCT03505008
jRCT No. : jRCT1031180088
UMIN study ID : UMIN000030584

1.1.3 Version number and dates prepared and effective of the study protocol

Version number: 2.2
Date prepared: November 15, 2019
Effective date: The amended protocol becomes effective on the day of entry in jRCT after the approval by the Certified Review Board.

1.2 Study Organization

1.2.1 Sponsor

Keio Gijuku educational Corporation, Keio University School of Medicine
35, Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
Responsible person: Yuko Kaneko (Lead Principal Investigator)
Role: Initiates and is responsible for this study except for its funding

Eisai Co., Ltd.
4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan
Responsible person: [redacted]
Roles: Plans out this study (including the analysis plan) in conjunction with Keio University, approve the clinical study report, provide information concerning ADA, and fund the study.

1.2.2 Lead Principal Investigator

Yuko Kaneko
Associate Professor, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine
35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582
TEL: +81-3-5363-3786 FAX: +81-3-5379-5370
E-mail: ykaneko@z6.keio.jp
Roles: Represents the study group as a signatory to approve the protocol, and makes medical judgments on the whole study group as a medical expert to the study.

1.2.3 Study Investigational Operator

Hiroya Tamai

Division of Rheumatology, Department of Internal Medicine,
Keio University School of Medicine

Roles: Prepare and control protocol and other relevant documents

1.2.4 Coordinating Investigators

Tsutomu Takeuchi

Professor, Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine

Roles: Negotiate with study sites so as to efficiently carry out the study.

1.2.5 Study Efficacy and Safety Advisor

The advisor comprises 2 physicians experienced in using ADA, designated by the Lead Principal Investigator, and selected from Department of Internal Medicine (1 from Division of Gastroenterology and 1 from Division of Rheumatology), Keio University School of Medicine. Principal investigator/sub-investigator may not be assigned as a member of the Study Efficacy and Safety Advisor.

Roles: Provides suggestions concerning the acceptability to continue the study and the necessity of protocol amendment upon request of the Lead Principal Investigator.

1.2.6 Imaging Review Committee

The committee comprises physicians designated by the Lead Principal Investigator.

Roles: Reviews and evaluates the imaging data of hands and feet based on modified total sharp score (mTSS).

1.2.7 Study Sites and Principal Investigators

See the Site List

Roles: Conducts this study at each study site in accordance with the protocol upon approval of the Certified Review Board/Ethical Review Board and Site Management (principal investigator).

1.2.8 Study Biostatistician

Yasunori Sato

Head of Biostatistics Unit, Clinical and Translational Research Center,
Keio University Hospital

Roles: Prepare the statistical analysis plan, and perform statistical analysis based on the statistical analysis plan.

1.2.9 Study Secretariat

< General Secretariat>

Planning and Management Office, Clinical and Translational Research Center,

Keio University Hospital
Roles: Supports Lead Principal Investigator and Study Investigational Operator to enable efficient study conduct.

<Operation Center (Enrollment promotion, contract process, etc.)>
Contract Medical Affairs, Linical Co., Ltd.
Supervisor: [redacted], Staff: [redacted]
1-9-2 Higashi-Shimbashi, Minato-ku, Tokyo 105-0021, Japan
TEL: +81-[redacted], FAX: +81-[redacted]
Roles: To plan out measures to facilitate proactive enrollment of subjects and process contracts with sites to enable efficient study conduct.

<SAE Report Center>
Linical Spain, S.L. Pharmacovigilance Department
Pharmacovigilance Officer: [redacted]
C/ Las Norias 92, Planta 2ª 28221 Majadahonda (Madrid), Spain
TEL: +34-[redacted] FAX: +34-[redacted]
e-mail address: [redacted]

(Japan Contact)
Contract Medical Affairs, Linical Co., Ltd.
Supervisor: [redacted], Staff: [redacted]
1-9-2 Higashi-Shimbashi, Minato-ku, Tokyo 105-0021, Japan
TEL: +81-[redacted], FAX: +81-[redacted]
Roles: Receives a report from Principal Investigator upon occurrence of a serious AE (SAE), and reports to Lead Principal Investigator.

1.2.10 Data Center

Linical Spain, S.L.
Chief Operating Officer: [redacted]
C/ Las Norias 92, Planta 2ª 28221 Majadahonda (Madrid), Spain
TEL: +34-[redacted], Fax: +34-[redacted]

(Japan Contact)
Data Management, Clinical Development, Linical Co., Ltd.
[redacted]
1-9-2 Higashi-Shimbashi, Minato-ku, Tokyo 105-0021, Japan
TEL: +81-[redacted], FAX: +81-[redacted]
Roles: Prepares and amends the sample case report forms (CRF), designs databases, checks and fixes the data, and verifies and validates the data.

1.2.11 Contract Research Organization

In addition to the operations of the Study Secretariat (Operation Center and SAE Report Center) and Data Center, monitoring and audit operations of this study will be entrusted to contract research organizations. The Lead Principal Investigator should review and approve the operational procedures prepared by the contract research organizations and have a periodic interview with the contract research organizations to supervise their operations.

<Monitoring>
Contract Medical Affairs, Linical Co., Ltd.
Supervisor: [redacted], Staff: [redacted]
1-9-2 Higashi-Shimbashi, Minato-ku, Tokyo 105-0021, Japan
TEL: +81-[redacted], FAX: +81-[redacted]
Roles: Reviews the study to ensure that it is conducted safely and in accordance with the protocol, and the data is collected accurately.

<Audit>
Audit Office, Linical Co., Ltd.
Supervisor: [redacted]
1-6-1 Miyahara, Yodogawa-ku, Osaka-shi, Osaka 532-0003, Japan
TEL: +81-[redacted], FAX: +81-[redacted]
Roles: Review the study to verify whether it is conducted in compliance with the protocol, ICH-GCP, and other relevant rules.

1.2.12 External laboratory

LSI Medience Corporation
1-13-4 Uchikanda, Chiyoda-ku, Tokyo 101-8517, Japan
TEL: +81-[redacted], FAX: +81-[redacted]
Roles: Retrieve and measure clinical specimens of investigational blood samples, and report the results

2. Background information

2.1 Indication

2.1.1 Overview of indication

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic arthritis mutilans all over the body. The prevalence rate of RA is estimated to be about 1% worldwide (Firestein GS, 2017: 1115); 600,000 to 700,000 patients in Japan alone. The peak age of disease development in women is in their most productive years of 40's to 50's, resulting in not only physical disability, but also social restrictions, economic burden, and their family's mental strain. Main clinical manifestations include pain and swelling of joints in the hands and feet, as well as joint destruction and degeneration due to prolonged disease which not only generates chronic pain but also causes remarkable restriction on activities of daily living (ADL). About 70% of patients are said to develop bone erosion within 2 years if not appropriately treated (Howard A, et al. 1989: 585-91); thus, early therapeutic intervention is very important.

2.1.2 Comorbidities related to the indication

RA causes pain, joint fracture, and joint degeneration due to destructive polyarthritis that chronically occurs all over the body. Inflammation, if persists, causes not only pain but also irreversible destructions in the joints, resulting in remarkable reduction of ADL. RA is known to be accompanied by not only joint symptoms but also a high frequency of extracapsular symptoms such as scleritis, airway lesion, interstitial pneumonia, pleurisy, vasculitis, secondary Sjogren's syndrome, and secondary amyloidosis. Pulmonary lesions particularly affect vital prognosis, and often causes acute exacerbation. Furthermore, RA patients are known to have poorer vital prognosis compared to general population due to persistent inflammation and immunological abnormality which are risk factors of arteriosclerosis and malignant disease (Wolfe F, et al. 1994: 481-94). Also, immunosuppression associated with typical treatment is a high risk factor of infection-related complications.

2.1.3 Prognostic factors of the indication

Seropositive (rheumatoid factor and anti-CCP antibody), high disease activities, and bone erosion in early stage of disease are prognostic factors of future joint destruction, (Vastesaeger N, et al. 2009: 1114-21, Visser K, et al. 2010: 1333-7), and thus, are poor prognostic factors. Moreover, as mentioned above, the presence of interstitial pneumonia, vasculitis, and other extracapsular symptoms, and persistent inflammation are risk factors of arteriosclerosis and malignant disease. In addition, immunosuppression associated with typical treatment can cause serious infection, and thus can be a determining factor of prognosis.

2.1.4 Standard of care for the indication

DMARDs are clinically used to ease inflammation and pain, and prevent joint destruction in RA patients. EULAR Recommendations 2016 recommends to start using methotrexate (MTX) promptly upon diagnosis of RA, unless contraindicated, with a therapeutic goal to

achieve clinical remission in 6 months, and if unsuccessful, consider adding bDMARDs [tumor necrosis factor (TNF)-α inhibitor, abatacept, tocilizumab, and in some cases, rituximab] (Smolen JS, et al. 2017: 960-77). Low-dose steroid is used pertinent to an early therapeutic strategy up to 6 months, but the guideline recommends to reduce dose as promptly as clinically possible. Steroid pulse and high-dose steroid are also used sometimes for acute exacerbation of interstitial pneumonia and vasculitis.
Among bDMARDs, the efficacy of some TNFα inhibitors are known to increase when used in combination with MTX (Nam JL, et al. 2014: 516-28); however, an optimal dose of MTX in such combination use is unknown.

2.2 Study drug

2.2.1 Methotrexate (MTX)

MTX was approved in 1988 by the U.S. Food and Drug Administration as a drug for treatment of RA, and since then, has been widely used all around the world. MTX not only has a high response rate for treatment of arthritis, but also prevents the progression of joint destruction, and furthermore, its efficacy in improving QOL and vital prognosis have been demonstrated; thus, it became the first choice of standard treatment (Smolen JS, et al. 2017: 960-77).
It is also much inexpensive than bDMARDs. Because of such advantages, it is remains to a first-line drug recommended by EULAR Recommendations 2016 amid the presence of various bDMARDs today. A recommended maintenance dose of MTX is maximum tolerable dose of 25 to 30 mg/week (16 mg/week in Japan) when used in combination with folic acid. Also, TNFα inhibitor and other bDMARDs are now known to be more effective when used in combination with MTX than used alone.
Meanwhile, gastrointestinal symptoms, hepatic impairment, and myelopathy are known to be dose-dependent ADRs of MTX. In ADRs of MTX, gastrointestinal symptoms and hepatic enzymes increased are known to be alleviated by concomitant use of folic acid preparation (Tishler M, et al. 1988: 906-9, Morgan SL, et al. 1990; 33: 9-18.).
Also, while erythrocyte MTX-polyglutamates (PG) concentration has been reported to reflect the efficacy and safety of MTX (de Rotte MC, et al. 2015; 74:408-14), it has been pointed out that there is a possible difference in the MTX-PG concentration by ≥1.4 fold between the Japanese and Western populations given the same dosage of MTX (Takahashi C, et al. 2017: e000363), suggesting a possibility of lower dose MTX to generate efficacy in the Japanese population when used in combination with ADA. Moreover, there has been no Asian country other than Japan in which study evaluating MTX-PG has been reported.

2.2.2 Adalimumab (ADA)

ADA was approved in the U.S. in 2002 as a drug for treatment of RA, and was launched in Japan in 2008 as the third anti-TNF-α inhibitor marketed in Japan. It has been marketed in South Korea and Taiwan since 2007. Its efficacy in preventing disease activities and progress of joint destruction has been confirmed in clinical studies (Breedveld FC, et al. 2006: 26-37).

2.3 Nonclinical and clinical studies

2.3.1 Nonclinical studies

MTX inhibited hind paw inflammation, managed body weight gain, and inhibited joint destruction in mice with collagen-induced arthritis at repeated doses of 0.05 and 0.1 mg/kg/day or 0.6 to 1.2 mg/kg/week divided into 3 doses per week. MTX also inhibited hind paw inflammation and joint destruction in the chronic phase in mice with group A streptococcal cell wall-induced arthritis, an adjuvant arthritis model, at repeated doses of 0.125 mg/kg/day. MTX inhibited inflammation of the untreated paw in mice with adjuvant arthritis at intermittent oral doses of 0.15 to 0.6 mg/kg/week or 0.375 mg/kg/3 weeks.
ADA (0.01, 0.1, 0.5, 1, and 10 mg/kg) prevented arthritis in transgenic mice bearing the human TNFα gene in a dose-dependent manner when administered intraperitoneally three times weekly from 1 to 8 weeks of age. The ED_{50}s were 0.25 mg/kg (joint score) and 0.48 mg/kg (histopathological score).

2.3.2 Clinical studies

Like other TNFα inhibitors, the efficacy of ADA used in combination with MTX has been confirmed (Breedveld FC, et al. 2006: 26-37).
Regarding dosage of MTX in combination with ADA, in a study conducted in Western MTX naïve patients which the combination of MTX with ADA was simultaneously started, the results showed no change in efficacy with dosage of MTX ≥10 mg/week (Burmester GR, et al. 2015:1037-44). Meanwhile, another study has been conducted in the U.S. to determine whether dosage of MTX may be reduced when ADA is added in MTX failure patients (Kaeley GS, et al. 2016: 1480-9), but no conclusion has been drawn.
Also, there was a study (HOPEFUL 1) conducted in Japanese subjects to evaluate the efficacy of ADA in combination with MTX (Takeuchi T, et al. 2014: 536-43); however, this study was conducted back then when the MTX dose was restricted to 8 mg/week or lower in Japan. A stratified analysis on the results of post-marketing surveillance demonstrated that the efficacy hits plateau at an MTX dose of ≥6 mg/week as a concomitant use in bDMARDs naïve patients. Meanwhile, in terms of safety, infection and other risks increase at an MTX dose of ≥10 mg/week. Accordingly, MTX 8 mg/week is proposed for concomitant therapy in bDMARDs naïve patients. Yet, the results were based on a retrospective observational study, and further researches are required.

2.4 Risks and benefits to subjects

2.4.1 Expected benefits

MTX is a drug for which the efficacy for RA as a first-line medication has been adequately proven, and is expected to effectively control RA in this study. Also, concomitant use of a bDMARD after 24 weeks of treatment with MTX is in compliance with EULAR Recommendations 2016.
Furthermore, if low-dose MTX provides adequate therapeutic effect when used in combination with ADA, it would reduce MTX-related ADRs that dose-dependently increase, which may not be of a direct benefit for subjects taking in this study, but could help

establishing more optimal drug usage, and eventually generate benefits for RA patients in the future.

2.4.2 Anticipated risks and disadvantage

Possible risks in subjects include ADRs related to MTX and ADA. MTX-related ADRs include bone marrow depression, as well as infections such as interstitial pneumonia and pneumocystis pneumonia, gastrointestinal disorder and liver disorder, and also lymphoproliferative diseases. ADRs related to ADA include lupus-like syndrome and demyelinating disease (multiple sclerosis, etc.) in addition to those mentioned above. The usages of drugs in this study are in line with EULAR Recommendations 2016, and the benefits, that is, control of disease activities, and the risk of ADRs were considered when the guideline was prepared, and this study is also in line with the guideline.
Investigational blood sampling may become disadvantage, but the amount of which is not much more than what would be required for usual clinical practice, and thus, the risk thereof should be negligible.
There is a potential risk of invasion of privacy since this study involves clinical samples and medical information, but such risk will be minimized through anonymization.

2.5 Route of administration, dosage and administration, and duration of treatment

<MTX>
MTX should be started at a dosage of 6 to 8 mg/week, and promptly escalated to the maximum tolerable dose (MTD) ≤25 mg/week (the maximum dose should be set according to the package insert of each country), and in principle maintained at the MTD from Week 12 onward. Also, the dosage of MTX should remain unchanged from Week 20 to 24 except for dose reduction/interruption due to an ADR. The drug will be taken orally. In principle, a weekly dosage should be taken once or twice in a day. The package insert of each country should be referred to for the details of dosage regimen. The duration of treatment will be 48 weeks.
The route of administration, and dosage and administration were selected within the range specified in the package insert of each country by referring to the EULAR Recommendations 2016. The duration of treatment was defined as the duration required for the efficacy assessments in reference to the EULAR Recommendations 2016.

<ADA>
If a subject maintains MTX ≥10 mg/week and SDAI remission is not achieved at Week 24, the subject should start receiving ADA 40 mg subcutaneously every other week up to Week 48 (thus, the duration of treatment will be 24 weeks). The package insert of each country should be referred to for the details of dosage regimen.
The route of administration, and dosage and administration were selected according to the package insert. The duration of treatment was defined as the duration required for the efficacy assessments in reference to the EULAR Recommendations 2016.

2.6 Applicable rules, etc.

All investigators involved in this study must comply with "World Medical Association, Declaration of Helsinki (Revised version dated October 2013)," "ICH-GCP," and this protocol when conducting this study. In Japan, "Clinical Trials Act" must also be complied.

2.7 Study population

The study population will be patients with RA in Japan, South Korea, and Taiwan previously not treated with MTX, JAK inhibitor, or bDMARDs, and whose duration of disease is within 2 years from diagnosis. Subjects will be stratified by countries (Japan, South Korea, and Taiwan) as a stratification factor.

2.8 Reference and data

See Chapter 16.2.

3 Objective

3.1 Background

The efficacy of ADA for treatment of RA patients is known to increase when used in combination with MTX. However, an optimal dose of MTX in such combination use is not fully studied, and thus, the dosage of MTX monotherapy is often continued to use clinically.

3.2 Objective

This study is intended to evaluate the optimal dosage of MTX as an add-on therapy to ADA in patients with rheumatoid arthritis (RA) who did not achieve remission by MTX monotherapy, and to measure erythrocyte MTX-polyglutamates (PG) concentration to evaluate its relation to the efficacy and safety of MTX therapy in RA patients.

3.3 Purpose

A lower dosage of MTX, which is effective in combination with ADA in MTX-refractory RA patients is expected to reduce MTX-related ADRs that dose-dependently increase.

4 Study design

4.1 Endpoints

4.1.1 Primary endpoint

- SDAI remission rate at Week 48 in Concomitant ADA MTX Maximum Tolerable Dose Extended Treatment Group and Concomitant ADA MTX Dose Reduction Group

4.1.2 Secondary endpoints

- SDAI remission rate at Week 24
- SDAI remission rate at Week 48 in MTX Monotherapy Group

- ACR20, ACR50, and ACR70 response rate at each assessment timepoint
- HAQ remission rate at each assessment timepoint
- SDAI, CDAI, DAS28-ESR, and DAS28-CRP at each assessment timepoint, and change from baseline to each assessment timepoint
- Tender joint count, swollen joint count, VAS (physician- and patient-reported), HAQ, CRP, ESR, MMP-3, RF, and anti-CCP antibody at each assessment timepoint, and change from baseline to each assessment timepoint
- Modified total sharp score (mTSS) at each assessment timepoint, and change from baseline to each assessment timepoint
- Structural remission (mTSS ≤0.5) rate at each assessment timepoint
- Vital signs and laboratory findings at each assessment timepoint, and change from baseline to each assessment timepoint
- Status of AE (Up to Week 24, and up to Week 48 for each ARM)

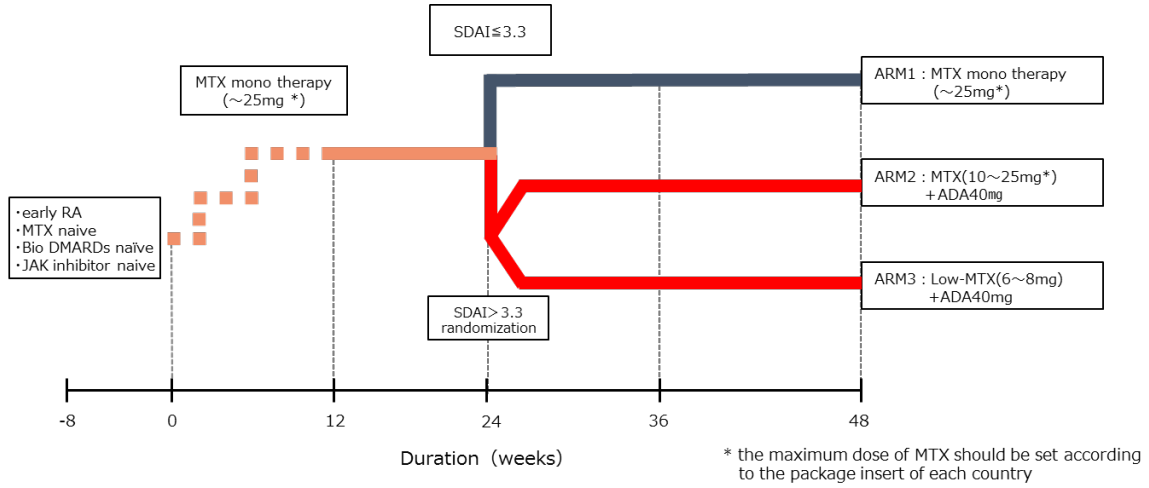
4.1.3 Exploratory endpoints

- Erythrocyte MTX-PG concentration at Weeks 0, 4, 8, 12, 24, 36, and 48
- Blood cytokine (IL-6, VEGF) at Weeks 0, 24, and 48
- Plasma micro RNA at Week 24
- Serum anti-adalimumab antibody at Weeks 24 and 48

[Rationale]
RA may be clinically evaluated from 3 aspects; the activity, function, and structure of arthritis. The standard indices of RA assessments internationally recognized are SDAI and ACR20/50/70 for disease activity assessment, HAQ for functional assessment, and TSS for structural assessment.

4.2 Study method

This is a multicenter, open-label, randomized, interventional study conducted in patients with RA in Japan, South Korea, and Taiwan.
Principal investigator/sub-investigator shall confirm the inclusion/exclusion criteria of each patient, and upon his/her consent, enter necessary information in IWRS. If there is no issue with the information entered in IWRS, the subject will be given a subject ID. The enrollment completes when the subject ID for a patient is entered into the EDC system.
After obtaining the consent, a subject will start receiving MTX, and if the subject achieves the SDAI remission at Week 24, will continue to receive MTX until Week 48. If the subject does not achieve the SDAI remission, ADA 40 mg should be started as an add-on therapy up to Week 48, and the subject will be randomized to either a group in which the dosage of MTX is maintained or a group in which the dosage of MTX is reduced.



4.3 Bias

4.3.1 Randomization

If a subject does not achieve to clinical remission (SDAI ≤3.3) at Week 24 despite the maintenance of MTX dose at ≥10 mg/week, the subject will start receiving ADA as an add-on therapy. Subjects then will be stratified by countries (Japan, South Korea, and Taiwan) as a stratification factor, and for each stratum, subjects will be randomized at a 1:1 ratio to either a group in which the MTD of MTX (10 to 25 mg/week) will be maintained (ARM-2), and a group in which the dosage of MTX will be reduced to 6 to 8 mg/week (ARM-3).
Upon completion of Week 24 assessments, principal investigator/sub-investigator shall enter the Week 24 dosage of MTX, tender joint count (28 joints), swollen joint count (28 joints), VAS (physician- and patient-reported; 10 cm scale), and CRP in IWRS. If all necessary information is entered, a relevant treatment group in line with the status of randomization (ARM-1, ARM-2 or ARM-3) will be issued by IWRS.
The MTX dosage shall be either 6 mg/week or 7.5 mg/week in subjects in ARM-3 whose maintenance dose of MTX at Week 24 is 10 mg/week.

4.3.2 Blinding

No blinding will be performed in this study.

4.4 Information on study drug

4.4.1 Methotrexate (MTX)

Nonproprietary name: Methotrexate
Brand name: Rheumatrex®, etc.
Dosage form/Dosage: Capsules/Tablets, 2 mg/2.5 mg

Pharmacokinetics:

The maximum blood MTX concentration was in 1 to 2 hours postdose among 17 RA patients orally receiving MTX 6 mg/week for 12 weeks. MTX binds with albumin by 53% to 60% in the serum. Meanwhile, the MTX concentration in the erythrocyte remains the same throughout treatment with MTX even if the serum concentration is low. There are 3

known metabolic pathways in human, including that by which it is metabolized to 7-OH-MTX by aldehyde oxidase in the liver, that by which it is metabolized to MTX-PG via polyglutamate in the liver or erythrocyte, and that by which it is metabolized to APA by carboxy peptidase in enteric bacteria.

Characteristics and action mechanism of the drug:

MTX is an antifolic drug synthesized for the first time in 1947, and acts on DHFR which produces active folic acid necessary for nucleic acid synthesis, and inhibits thymidylate synthesis and purine synthesis to obstruct cellular proliferation. It has an immunosuppressive and anti-inflammatory effects against T cell, B cell, macrophage, neutrophil, vascular endothelial cell, and fibroblast cell, and by which, is thought to provide its antirheumatic action. Basically, it should be administered via weekly intermittent dose.

Application to autoimmune disease:

Upon synthesis in 1947, it was widely used for treatment of various types of malignant tumor, and then, later confirmed to have an efficacy for rheumatoid arthritis, and then, approved in 1988 in the U.S. as an antirheumatic drug. Thereafter, MTX was confirmed to have an effect to prevent progression of osteoclasis and to improve vital prognosis, and became a first-line drug for treatment of RA. In Japan, it was approved in 1999 after completion of phase III study. The maximum dose in Japan is about half of the standard dose used overseas, and was approved in February 2011 through an application for partial change in the authorization status, and a dosage up to 16 mg/week was allowed for use. Also, its efficacy in combination use with bDMARDs has been demonstrated; to date, it is still an anchor drug of RA treatment.

Main ADRs (serious ADRs and other relevant reactions: Rheumatrex® Package Insert, version 20):

Shock/anaphylaxis, bone marrow depression, infection, tuberculosis, fulminant hepatitis/hepatic failure, acute renal failure/tubular necrosis/severe nephropathy, interstitial pneumonia/pulmonary fibrosis/pleural effusion, toxic epidermal necrolysis (TEN)/oculomucocutaneous syndrome (Stevens-Johnson syndrome), hemorrhagic enterocolitis/necrotising enterocolitis, pancreatitis, osteoporosis, cerebropathy (including leukoencephalopathy), and lymphoproliferative disorder

4.4.2 Adalimumab (ADA)

Nonproprietary name: Adalimumab (recombinant)
Brand name: Humira®
Dosage form/Dosage: Syringe/Pen, 40 mg

Pharmacokinetics:

The serum drug concentration increased dose-proportionally in subjects receiving a single dose of 20, 40, 80 mg; T_{max} was 204 hours in the 40 mg group, and its half-life was 298.0 hours. The steady-state trough concentration of ADA was about 3 μg/mL in Japanese RA patients subcutaneously receiving ADA 40 mg every other week. It is a human IgG, and like the intrinsic immunoglobulin metabolic process, is taken into the reticular system, and assumed to be broken down to its components, amino-acid and glucose in the endosome.

Characteristics and action mechanism of the drug:

It is the world's first human anti-human TNFα monoclonal antibody that neutralizes TNFα, which is a cytokine that involves in inflammatory response and immune reaction, and by which, reduces the concentration of TNFα.

Application to autoimmune disease:

It was approved in December 2002 in the U.S., and in September 2003 in EU. In Japan, the dosage of MTX in combination use was different from that in the development programs in the U.S. and Europe, and therefore, an ADA monotherapy study was conducted in Japan, and the efficacy and safety similar to Western RA patients were confirmed in Japanese RA patients, and upon which, it was approved in April 2008. Also, a clinical study was conducted in RA patients previously untreated with MTX or leflunomide and whose duration of disease was within 2 years, and in which, its efficacy in preventing progress of joint destruction was confirmed; upon which, the indication, "Rheumatoid arthritis (including prevention of structural joint injury)" was approved in August 2012.

Key ADRs (serious ADRs: Humira® Package Insert, version 30):

Serious infections such as sepsis/pneumonia, tuberculosis, Lupus-like syndrome, demyelinating disease, serious allergy, serious hematologic disorders (pancytopenia/thrombocytopenia/leukopenia/granulocytopenia), interstitial pneumonia, and hepatitis fulminant/hepatic impairment/jaundice/hepatic failure

4.5 Study period

This study will be started upon the approval in each study site. The total study duration is assumed to be 4 years and 4 months, and the study is scheduled to be completed in June 2022.

Enrollment period:	March 2018 to July 2020 (2 years and 5 months)
Intervention period:	48 weeks
Data collection, analysis, and report generation periods:	1 year
Total study period:	4 years and 4 months

4.6 Study interruption/discontinuation

The withdrawal criteria for individual subject are as shown in 5.3.

The entire study will be discontinued if either of the below criteria is met. The Lead Principal Investigator shall notify the principal investigator of each study site promptly upon her decision to discontinue the study. Then, each principal investigator shall promptly notify his/her subjects, and provide appropriate medical intervention and take other necessary actions.

1) Certified Review Board which the Lead Principal Investigator request to review recommends not to continue the study.
2) There is a safety concern that prevents this study from continuing further.
3) The Lead Principal Investigator judges that the entire study should be discontinued.

4.7 Management of study drug

Study drug will be obtained and controlled in accordance with each country's relevant regulations.
In Japan, the study drug will be used within the scope of the healthcare insurance; accordingly, subjects will obtain and use study drugs available in the market through pharmacies.

4.8 Storage of randomization code, and unblinding process

Randomization code for this study will be retained in the IWRS system. This is not a blinded study, and therefore, no unblinding process will be specified.

4.9 Specification of source data

All of the data recorded in EDC must be consistent with the source materials. Source materials are defined as documents, data, and records that were documented for the first time, such as subjects' informed consent form, medical record (clinical chart), clinical laboratory data, ECG data, and X-ray data.
If the following information is not provided in medical or other record, EDC will be considered as the source data.

- Status of study drug administration (e.g., reason for treatment discontinuation, reason for dose modification, etc.)
- Reason for using concomitant therapy (including drugs and non-drug therapies)
- Information concerning study discontinuation (e.g., lost to follow)
- Information concerning AEs (e.g., severity, causality, outcomes, etc.)

5 Inclusion/exclusion/withdrawal criteria

RA patients meeting all of the following inclusion criteria and not applicable to any of the following exclusion criteria will be eligible for this study.

5.1 Inclusion criteria

1) Patients aged ≥18 years (≥20 years in Taiwan) at the time of informed consent
2) Patients who meet the 1987 revised ACR criteria or 2010 ACR/EULAR criteria

3) Patients who have RA within 2 years from initial diagnosis to informed consent
4) Patients who were previously untreated with MTX, JAK inhibitor, or bDMARDs
5) Patients who have disease activity of SDAI >11 at screening
6) Patients who are no need for concomitant use of DMARDs other than study drugs and hydroxychloroquine (only in South Korea and Taiwan) during the study as judged by principal investigator/sub-investigator at screening
7) Patients who are no need for concomitant use of corticoid steroid equivalent to >10 mg/day prednisolone during the study as judged by principal investigator/sub-investigator at screening.
8) Female of child-bearing potential who can use appropriate contraceptive during the study, female in whom time from menopause to informed consent is ≥1 year, or female of no child-bearing potential through sterilization (bilateral tubal ligation, bilateral ovariectomy or hysterectomy, etc.)
9) Virile male who can use appropriate contraceptive during the study
10) Patients who can adequately understand this study procedures, and voluntarily consent in writing to take part in this study
(consent of a legally-acceptable representative is also required for patients aged <20 years in Japan and aged <19 years in South Korea)

5.2 Exclusion criteria

1) Patients who currently have a malignant tumor, except for non-melanoma forms of skin cancer limited within epidermis, and uterine cervix cancer limited within epidermis
2) Patients who have serious infections such as sepsis
3) Patients who have active tuberculosis
4) Patients who have a history or current complication of demyelinating disease such as multiple sclerosis
5) Patients who have congestive heart failure
6) Pregnant female, or female who intend to conceive during the study period
7) Patients who have bone marrow depression and whom investigator considered ineligible
8) Patients who have chronic liver disease and whom investigator considered ineligible, or who is positive for HBs antigen
9) Patients who have nephropathy and whom investigator considered ineligible
10) Lactating female
11) Patients who have pleural effusion or ascites
12) Patients with a known hypersensitivity to MTX or ADA
13) Patients otherwise whom principal investigator/sub-investigator considered medically ineligible to participate in the study

5.3 Withdrawal criteria

Subjects should be withdrawn from this study if applicable to any of the discontinuation criteria presented below. Upon withdrawal, subjects should undergo assessments and tests for early termination. Also, the reason for withdrawal should be as necessary explained to the subject, and treatment after withdrawal should be given in a faithful manner to ensure there will be no disadvantage to the subject.

Principal investigator/sub-investigator shall record the date of and reason for withdrawal in EDC. Also, for the traceable subjects, their clinical courses are followed up and reported to the Study Secretariat. Subjects withdrawn from this study do not need to be replaced regardless of the reason for withdrawal.

1) Subject wishes to discontinue his/her study treatment
2) Subject wishes to withdraw his/her consent
3) Serious (or significant) AE occurs, and the study treatment is determined to be difficult to continue
4) A comorbidity (complication, etc.) exacerbates, and the study treatment is determined to be difficult to continue
5) Definitive exacerbation of RA is confirmed
6) Use of bDMARDs other than ADA or use of JAK inhibitor
7) MTX at a dosage ≥10 mg/week cannot be maintained at Week 24 due to ADR, etc.
8) MTX at a specified dosage (ARM-2: 10 to 25 mg/week [the maximum dose should be set according to the package insert of each country], ARM-3: 6 to 8 mg/week) cannot be maintained after Week 24 due to ADR, etc.
9) An increased dosage of MTX is required after Week 24 due to loss of efficacy, etc.
10) Confirmed pregnancy
11) Confirmed critical protocol deviation
12) Found to be applicable to an exclusion criterion after enrollment in the study
13) Other reasons by which the study is not appropriate for continuation as judged by principal investigator/sub-investigator

6 Study treatment

6.1 Treatment procedure

Subjects who fulfill the above inclusion criteria, do not meet any of the exclusion criteria, will start receiving MTX 6 to 8 mg/week after completing assessments at Week 0. Also, 10 mg of folic acid will be orally administered once a week 48 hours after the first MTX dosing day of the week to prevent ADRs related to MTX (A daily dosage of 1 mg folic acid is acceptable in South Korea on a condition that the dosage cannot be changed during the study period).

To achieve remission, the dosage of MTX will be promptly escalated to the maximum tolerable dose (MTD) ≤25 mg/week (the maximum dose should be set according to the package insert of each country) in line with EULAR Recommendations 2016, and will be in principle maintained at the MTD from Week 12 onward. Also, the dosage of MTX will

remain unchanged from Week 20 to 24 except for dose reduction/interruption due to an ADR. Weekly dose of MTX will be administered orally at once or twice a day in principle.
If the dosage of MTX is maintained ≥10 mg/week and SDAI remission is achieved at Week 24, the MTX therapy will be continued until Week 48 (ARM-1).
If SDAI remission is not achieved despite the maintenance of ≥10 mg/week MTX dose at Week 24, ADA 40 mg will be administered subcutaneously every other week until Week 48.
Subjects then will be stratified by countries (Japan, South Korea, and Taiwan) as a stratification factor, and for each stratum, subjects will be randomized at a 1:1 ratio to either a group in which the MTD of MTX (10 to 25 mg/week) will be maintained (ARM-2), and a group in which the dosage of MTX will be reduced to 6 to 8 mg/week (ARM-3).
The MTX dosage shall be either 6 mg/week or 7.5 mg/week in subjects in ARM-3 whose maintenance dose of MTX at Week 24 is 10 mg/week.
Subjects in whom MTX at a dosage ≥10 mg/week cannot be maintained at Week 24 due to ADR, etc. will be withdrawn from the study.
Subjects in whom MTX at a dosage of ≥10 mg/week in ARM-2 or ≥6 mg/week in ARM-3 cannot be maintained after Week 24 due to ADR, etc. will also be withdrawn from the study. Also, subjects will be withdrawn from the study when an increased dosage of MTX is required after Week 24 due to loss of efficacy, etc.
The dose status of MTX, folic acid, and ADA, as well as the treatment groups in Week 24 onward (ARM-1 to -3) should be recorded in EDC.

6.1.1 Dose selection of MTX for study treatment

This study is intended to evaluate the optimal dosage of MTX in combination with ADA by comparing between a group (ARM-2) maintaining the dosage of MTX at the maximum tolerable dose (MTD； ≥10 mg/week) and a group (ARM-3) reducing the dosage of MTX to 6 to 8 mg/week.
In ARM-2, MTX is maintained at the MTD. Not overlapping the dosage of MTX in ARM-3, the lower limit of MTD was determined to be 10 mg/week based on the results of the HAWK post-marketing surveillance study of ADA in which the mean dosage of the combined use of MTX was 12.7 mg/week, and it also showed the dosage of MTX of ≥10 mg/week could be maintained in combination with ADA (Tanaka Y, et al. 2018: 1-9) and the results of the CONCERTO study conducted in the US and Europe, which confirmed no differences in efficacy among MTX doses of ≥10 mg/week in combination with ADA (Burmester GR, et al. 2015:1037-44).
The dosage of MTX in ARM-3 was determined based on the results of the HOPEFUL 1 study, which confirmed that MTX is effective at doses of 6 to 8 mg/week in combination with ADA (Takeuchi T, et al. 2014: 536-43).

6.2 Concomitant therapies

Allowed concomitant therapy and prohibited concomitant therapy are as follows. The dosage and administration route of drugs used for treatment of RA during the study should be recorded in EDC.

6.2.1 Allowed concomitant therapy

Oral and suppository formulations (both ≤10 mg/day prednisolone equivalents) and external application (dermatologics, eye-drops, nasal drops, and inhalants) of corticosteroids and NSAIDs are allowed for concomitant use; provided that the dosages of corticosteroid oral drug and suppository should in principle remain unchanged from Week 24 to 48. Moreover, subjects are allowed to use corticosteroids via an intracapsular administration (except for 28 days before efficacy assessment), intravenous corticosteroids (10 mg/day prednisolone equivalents) temporarily prescribed because of difficulties in oral administration and other reasons, and corticosteroids temporarily prescribed for indications other than rheumatoid arthritis.

6.2.2 Prohibited concomitant therapy

DMARDs other than MTX and ADA are prohibited during the study. Concomitant use of Hydroxychloroquine in South Korea and Taiwan is acceptable, on condition that in principle the dosage should not change between Week 24 and 48. Subjects receiving a non-ADA bDMARD or JAK inhibitor will be withdrawn from the study immediately upon the start of such treatment.

Concomitant use of opioid analgesics except for Tramadol is prohibited in this study. Although the use of Tramadol is possible, when used it should be administered except for 3 days prior to the efficacy assessment.

6.3 Compliance

Principal investigator/sub-investigator shall verify with each subject at each visit the status of dose (self-administration) concerning MTX, folic acid, and ADA to ensure their dose compliance. The patient compliance instruction should be provided at any time upon finding non-compliance to the instruction on dose (self-administration) given by the doctor. The data on dose compliance concerning study drugs to be recorded in EDC must be based on the record of actual dose (self-administration).

7 Assessments

7.1 Demography

The following information should be collected and recorded in EDC at Screening (within 8 weeks before the start of study treatment). In addition to the information, subject ID, the status of informed consent, and the results of eligibility assessment should also be recorded in EDC.

1) Gender

2) Age (at consent)
3) Race
4) Height and body weight
5) Time of RA diagnosis
6) Compliance to 1987 ACR revised criteria or 2010 ACR/EULAR criteria
7) RA treatment history (steroid, DMARDs, NSAIDs, etc.)
8) History of RA surgery
9) Medical history/Complication
10) Smoking history
11) 12-lead ECG (Not required if performed within 12 weeks before consent)
12) Infection disease test (Not required if performed within 2 years before consent):
    - Either skin tuberculin test or interferon gamma release assay (IGRA)
    - HBs antigen, HBs antibody, HBc antibody, and anti-HCV antibody

When a HBs Antigen (Ag)-negative subject is HBs Antibody (Ab) positive and/or HBc Ab positive, the subject must be tested for HBV-DNA quantification for at least once every 6 months.

7.2 Efficacy assessments

7.2.1 X rays of hands and feet

In accordance with the assessment schedule presented in the following table, X rays of subjects' hands and feet will be performed at screening, and Weeks 24 and 48 (or at early termination). The X-rays of the hands and feet are unnecessary to be performed for early termination if early termination occurs within 28 days after the last X-rays. The X-ray image of the hands and feet should be sent to the study secretariat along with the subject ID.
The X-ray image of the hands and feet will be independently reviewed by the X-ray Imaging Review Committee to evaluate bone erosions in the regions specified on the left side of the figure shown below, and also to evaluate joint space narrowing in the regions specified on the right side of the figure shown below, both in terms of mTSS, and the results will be sent to the data center.
Bone erosions will be evaluated for each region in accordance with the following score:

Score 1: Small bone erosion
Score 2: Large bone erosion (Not extend over the imaginary middle of the bone)
Score 3: Large bone erosion (Extends over the imaginary middle of the bone)
Score 5: Complete collapse of the joint

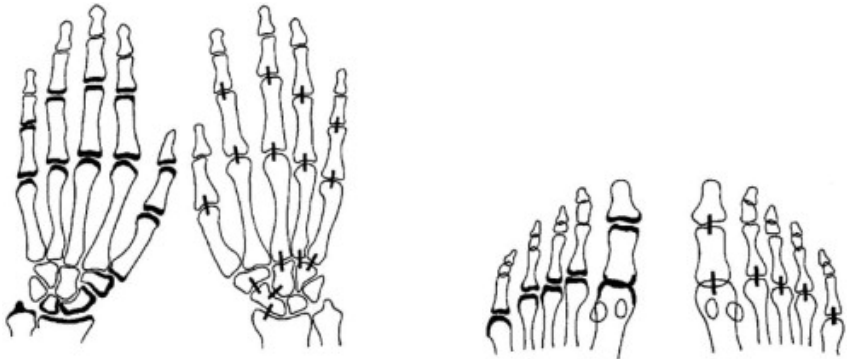
The score will be 0 to 5 for each hand region, and 0 to 10 for each foot region. The maximum total erosion score of both hands will be 160 points, and that of both feet will be 120 points.

Joint space narrowing will be evaluated for each region in accordance with the following score:

Score 1: Localized or merely suspected
Score 2: Generalized narrowing (≥50% joint space remaining)
Score 3: Generalized narrowing (≤50% joint space remaining) or subluxation

Score 4: Disappearance of joint space, or anchylosis or luxation

The maximum total joint space narrowing score of both hands will be 120 points, and that of both feet will be 48 points.



Source: Swinkels HL, et al. 2001: 176-90

7.2.2 Tender joint count, swollen joint count, VAS (physician- and patient-reported), and HAQ

In accordance with the assessment schedule presented in the following table, tender joint count, swollen joint count, VAS (physician- and patient-reported disease activities, and patient-reported pain score), and HAQ will be evaluated, and the results will be recorded in EDC.

HAQ score ≤0.5 is defined as functional remission.

7.2.3 CRP, ESR, MMP-3, RF, and anti-CCP antibody

In accordance with the assessment schedule presented in the following table, blood samples for CRP, ESR, MMP-3, RF, and anti-CCP antibody will be collected and evaluated. In South Korea and Taiwan, MMP-3 will be measured at the external laboratory only at the essential time points (blood collection at screening will be performed at Week 0 together with other assessments measured at the external laboratory). The results of measurement will be recorded in EDC.

7.2.4 SDAI

SDAI will be calculated with the following formula and based on the evaluation results of tender joint count, swollen joint count, VAS (physician- and patient-reported; 10 cm scale), and CRP.

- Tender joint count (28 joints) + Swollen joint count (28 joints) + Patient-reported disease activity / 10 + Physician-reported disease activity / 10 + CRP

Disease activities will be categorized to High disease activity: >26, Moderate disease activity: >11 to ≤26, Low disease activity: ≤11, and Remission: ≤3.3.

7.2.5 CDAI

CDAI will be calculated with the following formula and based on the evaluation results of tender joint count, swollen joint count, and VAS (physician- and patient-reported; 10 cm scale).

- Tender joint count (28 joints) + Swollen joint count (28 joints) + Patient-reported disease activity / 10 + Physician-reported disease activity / 10

Disease activities will be categorized to High disease activity: >22, Moderate disease activity: >10 to ≤22, Low disease activity: ≤10, and Remission: ≤2.8.

7.2.6 ACR 20, 50, 70 response rates, and ACR-N

ACR 20 response is defined as a subject meeting all of the following 3 criteria based on the evaluation results of tender joint count, swollen joint count, VAS (physician- and patient-reported), HAQ, and CRP. Also, the proportion of ACR 20 response will be referred to as ACR 20 response rate.

- ≥20% improvement in the tender joint count (of the total 68 joints) compared to Week 0 of treatment
- ≥20% improvement in the swollen joint count (of the total 66 joints) compared to Week 0 of treatment
- ≥20% improvement in ≥3 of 5 parameters (physician- and patient-reported disease activities, patient-reported pain score, HAQ, and CRP) compared to Week 0 of treatment

ACR 50 response, ACR 50 response rate, ACR 70 response, and ACR 70 response rate are defined by the standards that 20% improvement of ACR 20 response and ACR 20 response rate is replaced to 50% and 70% improvement, respectively.

Also, ACR-N will be the lowest improvement rate among the following 3 parameters:

- Improvement rate of the tender joint count (of the total 68 joints) compared to Week 0 of treatment
- Improvement rate of the swollen joint count (of the total 66 joints) compared to Week 0 of treatment
- The 3rd highest improvement rate among the 5 parameters (physician- and patient-reported disease activities, patient-reported pain score, HAQ, and CRP) compared to Week 0 of treatment

7.2.7 DAS28-ESR

DAS28-ESR will be calculated with the following formula and based on the evaluation results of tender joint count, swollen joint count, VAS (patient-reported; 100 mm scale), and ESR.

- DAS28-ESR = $0.56 \times \sqrt{}$ [Tender joint count (28 joints)] + $0.28 \times \sqrt{}$ [Swollen joint count (28 joints)] + $0.70 \times \ln$ (ESR) + $0.014 \times$ Patient-reported disease activity

Disease activities will be categorized to High disease activity: >5.1, Moderate disease activity: >3.2 to ≤5.1, Low disease activity: ≤3.2, and Remission: <2.6.

7.2.8 DAS28-CRP

DAS28-CRP will be calculated with the following formula and based on the evaluation results of tender joint count , swollen joint count, VAS (patient-reported; 100 mm scale), and CRP.

- DAS28-CRP = 0.56 × √ [Tender joint count (28 joints)] + 0.28 × √ [Swollen joint count (28 joints)] + 0.36 × ln (CRP × 10 + 1) + 0.014 × Patient-reported disease activity + 0.96

Disease activities will be categorized to High disease activity: >4.1, Moderate disease activity: >2.7 to ≤4.1, Low disease activity: ≤2.7, and Remission: <2.3.

7.3 Biomarkers assessment (investigational blood sampling)

7.3.1 Erythrocyte MTX-polyglutamates concentration

In accordance with the assessment schedule presented in the following table, an anticoagulant-containing blood collection tube (EDTA-2K) will be used to draw blood (≤3 mL) for the measurement of erythrocyte MTX-polyglutamates (PG) concentration. The erythrocyte layer will be separated in accordance with the following sample processing procedure, and submitted to the external laboratory along with the subject ID. The measurement will be performed by the external laboratory, and the results will be sent to the data center directly from the laboratory.

<Sample processing procedure>

[1] Draw and collect the blood in EDTA-2K, and immediately centrifuge the sample in the collection tube (1,400×g, 5 minutes, 4°C).
[2] Remove the plasma and leucocyte layers.
[3] Add normal saline by the same amount as the erythrocyte layer, and invert and mix the sample.
[4] Centrifuge the sample (1,400×g, 5 minutes, 4°C) to remove the layer of the normal saline.
[5] Transfer the erythrocyte layer (about ≥300 μL) to a polypropylene microfuge tube, and store it in a freezer at a temperature -20°C to -80°C.

The specimen should be handled at 4°C or in icy environment as much as possible.
If the sample cannot be centrifuged immediately following blood collection in EDTA-2K, the sample tube should be stored in a refrigerator, and processed in principle within the same day (within 24 hours at the latest).

7.3.2 Blood cytokine level

In accordance with the assessment schedule presented in the following table, a blood sample (≤20 mL) will be collected for measurement of blood cytokine (IL-6: serum, VEGF: plasma). The sample (serum and plasma) should be processed in accordance with the procedures separately specified, and submitted to the external laboratory along with the subject ID. The measurement will be performed by the external laboratory, and the results will be sent to the data center directly from the laboratory.

7.3.3 Plasma micro RNA

A blood sample (3 mL) for measurement of plasma micro RNA will be collected at Week 24 visit. The plasma sample should be processed in accordance with the procedures separately specified, and submitted to the external laboratory along with the subject ID. The measurement of plasma micro RNA will be performed only for subjects receiving ADA (ARM-2 and ARM-3); the samples will be measured by the external laboratory, and the results will be sent to the data center directly from the laboratory.

7.3.4 Serum anti-adalimumab antibody

In accordance with the assessment schedule presented in the following table, a blood sample (3 mL in Japan, 5 mL in South Korea and Taiwan) will be collected for measurement of serum anti-adalimumab antibody. The sample should be processed in accordance with the procedures separately specified, and submitted to the external laboratory along with the subject ID. The measurement of serum anti-adalimumab antibody will be performed only for subjects receiving ADA (ARM-2 and ARM-3); the samples will be measured by the external laboratory, and the results will be sent to the data center directly from the laboratory.

7.4 Safety assessment

In accordance with the assessment schedule presented in the following table, the following assessments and tests will be performed, and the results will be recorded in EDC. Clinical laboratory should be performed in the study site.

1) General symptoms
2) Vital signs (blood pressure, pulse rate, and body temperature)
3) Height and body weight
4) Chest X ray
5) Physical examinations
6) Clinical laboratory
   [1] Hematology: WBC, differential count, RBC, Hb, MCV, and Plt
   [2] Chemistry: BUN, Cr, UA, total bilirubin, AST, ALT, LDH, γGTP, ALP, total protein, and albumin
   [3] Immunology: IgG

7.4.1 Evaluation of AEs

Principal investigator/sub-investigator shall monitor for possible occurrence of AEs throughout the course of this study, and record in EDC all AEs that occur in the study.
The following ADRs are known for the study drug; for which, treatment should be given according to respective symptoms. Also, any event suspected to be related to the study drug or for which treatment discontinuation is expected to improve conditions or prevent progression should be managed with dose reduction or treatment discontinuation.
<MTX>

1) Shock, anaphylaxis
2) Bone marrow depression

3) Infection
4) Tuberculosis
5) Hepatitis fulminant/hepatic failure
6) Acute renal failure, tubular necrosis, severe nephropathy
7) Interstitial pneumonia/pulmonary fibrosis/pleural effusion
8) Toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome)
9) Enterocolitis haemorrhagic, necrotising enterocolitis
10) Pancreatitis
11) Osteoporosis
12) Encephalopathy (including leukoencephalopathy)
13) Lymphoproliferative disorder

<ADA>

1) Serious infections such as sepsis/pneumonia
2) Tuberculosis
3) Lupus-like syndrome
4) Demyelinating disease
5) Serious allergy
6) Serious hematologic disorders (pancytopenia, thrombocytopenia, leucopenia, granulocytopenia)
7) Interstitial pneumonia
8) Fulminant hepatitis, hepatic impairment, jaundice, hepatic failure

7.5 Assessment schedule

Assessments should be performed in accordance with the following schedule.
Screening period will be within 8 weeks before the start of study treatment. Assessment time points are counted from Week 0, and assessments should be performed within ±1 week from each timepoint (Week 4 to 12), and ±2 weeks from each timepoint (Week 24 onward).

Assessments	Screening period	Wk 0	Wk 4	Wk 8	Wk 12	Wk 24	Wk 36	Wk 48 or ET
Informed consent	○*1							
Demographics	○							
Eligibility	○							
History of disease/surgery	○							
Concomitant therapy	◄———	———	———	———	———	———	———	———►
General symptoms	○	○	○	○	○	○	○	○
Vital signs	(○)	○				○		○
Height, body weight	○					○		○
Physical examinations	○	○	○	○	○	○	○	○
Tender joint count, swollen joint count	○	○	○	○	○	○	○	○
Evaluation using VAS (physician- and patient-reported)	○	○	○	○	○	○	○	○
Assessment using HAQ	(○)	○	○	○	○	○	○	○
12-lead ECG	○*2							
Chest X ray	○*2					○		○
X ray of hands and feet	○*2					○		○*4
Infection disease test	○*3							
Clinical laboratory (hematology, chemistry)	(○)	○	○	○	○	○	○	○
IgG	○*2					○		○
CRP, ESR	○	○	○	○	○	○	○	○
MMP-3, RF	○*2	(○)	(○)	(○)	○	○	○	○
Anti-CCP antibody	○*3							(○)
MTX-PG		○	○	○	○	○	○	○
Cytokine		○				○		○
Micro RNA						○		
Anti-adalimumab antibody						○		○
AEs	◄———	———	———	———	———	———	———	———►

*1 : The informed consent of the study should be obtained prior to the screening test. However, the data before obtaining the consent may be included in the study if they have been assessed within the designated period.

*2 : The test results may be used if they were obtained within 12 weeks before consent. Also, the test may be performed at Week 0

*3 : The test results may be used if they were obtained within 2 years before consent. Also, the test may be performed at Week 0

*4 : The X rays of the hands and feet is unnecessary to be performed for early termination if early termination occurs within 28 days after the last X-rays.

○: Essential items, (○): Optional items

8 Adverse events

8.1 Definition

8.1.1 Definition of adverse event (AE)

AE is any untoward medical occurrence in a subject administered the study drug, whether or not it is related to the study treatment. That is, an adverse event is any exacerbation of conditions pre-existed prior to the start of study treatment, any untoward or unintended clinical signs, and abnormal change in vital signs.

Exacerbation of the underlying disease (RA) should also be handled as an AE if such exacerbation is beyond the scope of initial expectation. An abnormal change in clinical laboratory value or vital sign should be handled as an AE if it results in discontinuation of study treatment, requires intervention, or is otherwise determined to be an AE by principal investigator or sub-investigator.

AEs that occur or exacerbate after the initial dose and no later than Week 48 of study treatment shall be handled as an AE.

8.1.2 Definition of serious adverse events (SAE)

SAE is any untoward medical event occurring regardless of the dosage of study drug that;

- Results in death;
- Is life-threatening (the term "life-threatening" in this definition refers to an event in which the subject is at immediate risk of death given the nature of event that is present; it does not refer to an event that hypothetically might cause death if it were more severe, or the study treatment had continued);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in perpetual or significant disability/incapacity; or
- Is a congenital anomaly/birth defect (that is observed in a child of a patient who has been 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.

The principal investigator judges whether an AE is a “SAE” or not.

An SAE shall be followed up until it is resolved, or its symptoms stabilize if not expected to be resolved.

Meanwhile, hospitalization not accompanied by an AE shall not be handled as an SAE, such as;

- Hospitalization for temporary recuperation due to a reason other than AEs;
- Hospitalization that has been scheduled prior to informed consent (for conditions that required hospitalization before the start of study treatment, and remain unchanged after the start of study treatment);
- Hospitalization required for the administration of study drug; or
- Hospitalization intended for periodic maintenance of medical device (e.g., battery replacement) that has been used since before the start of study treatment.

8.1.3 Evaluation of severity

Principal investigator or sub-investigator shall evaluate the severity of AEs for 3 levels (mild, moderate, and severe), and record the results in EDC.

- Mild: Discomforting but not to an extent that obstructs activities of daily living
- Moderate: Discomfort that obstructs activities of daily living
- Severe: Unable to work or carry out normal activities of daily living

The severity assessment of AEs is different from the assessment of seriousness (See section 8.1.2).

8.1.4 Evaluation of causal relation with the study drug

Causal relation of AEs with each study drug shall be evaluated for the following 2 levels, and accordingly recorded in EDC.

- Related: There is a possible reasonable causality between the study treatment and AE.
- Unrelated: There is no reasonable causality between the study treatment and AE.

Causality between the study treatment and AE should be evaluated in consideration of;

- Temporal relationship between the timing of AE and the start of study treatment;
- Clinical course of AE, especially the effect of discontinuation and/or resumption of study treatment if applicable;
- Whether the AE is known for the study drug or drugs of the same class;
- The presence/absence of risk factor that may increase the incidence of AE in subjects with the underlying disease; and
- The presence/absence of confounding factors related to AE but unrelated to the study drug.

8.2 Procedures for collection, documentation, and reporting of SAEs

Upon detection of an SAE, the principal investigator shall report all SAEs regardless of the causality with the study drug to the study secretariat (SAE Report Center) as promptly as possible (within 1 business day in principle) using the SAE report form (Attachment 1). The principal investigator shall also report the information to Hospital Director (also to the Ethical Review Board in South Korea and Taiwan) if he/she judges that the SAE is causally "related" to the study drug. When sub-investigators, etc. other than the principal investigator detect a suspected SAE, they shall report it to the principal investigator promptly.
The study secretariat (SAE Report Center) reports to the Lead Principal Investigator and Eisai Co., Ltd. within 2 business days after receiving the information. The Lead Principal Investigator reports a drug-related SAE to the Certified Review Board within the period specified by the Clinical Trials Act and also should report it to the principal investigators of the other study sites. In Japan, the principal investigators who receive the report shall report the event to Hospital Director of the study site to which they belong.
All SAEs that occur on or before the final study-related visit should be collected regardless of the causality with the study treatment. All SAEs must be followed up until they are resolved,

or their symptoms stabilize if not expected to be resolved. Any SAE after study completion, for which a causality with the study drug (or protocol-specified procedures) cannot be ruled out as judged by the principal investigator or sub-investigator, must be reported to the study secretariat regardless of the time from study completion.
It is important to complete the initial SAE report Form as detailed as possible including the evaluation of causality with the study treatment as determined by the principal investigator or sub-investigator.
Any follow-up information received on SAEs should be forwarded by the principal investigator to the study secretariat 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 report 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 study secretariat.

8.2.1 Reportable events

All SAEs that occur between the commencement of study treatment and the final study visit are reportable regardless of causality with the study treatment or protocol-defined procedures. For subjects receiving ADA, all cases of premalignancies and malignancies, pregnancy, and breastfeeding from subjects who received ADA should also be reported to the study secretariat (SAE Report Center) using the same SAE report form. Furthermore, the overdose, misuse, abuse, medication error, off-label use, occupational exposure, accidental exposure, and unexpected therapeutic effect of ADA and AEs attributable to suspected transmission of any infectious agent should also be reported using the SAE report form (see section 8.2). Among these events, regarding AEs attributable to suspected transmission of any infectious agent from subjects receiving ADA, the Lead Principal Investigator should report a drug-related AE to the Certified Review Board within the period specified by the Clinical Trials Act and also should report it to the principal investigators of the other study sites. In Japan, the principal investigators receiving the report shall report the event to Hospital Director of the study site to which they belong to. All other events will be handled as an SAE only if applicable to the definition of SAE in section 8.1.2; those not applicable as an SAE do not need to be reported to Certified Review Board (Japan)/Ethical Review Board (South Korea and Taiwan) nor Hospital Director. Meanwhile, all of these AEs should be recorded in EDC whether applicable to the above SAE definition or not.

8.3 Follow-up of subjects after AEs

8.3.1 Follow-up

All AEs must be followed up for 70 days from the final dose of study drug or until recovery, whichever comes first; provided that an SAE must be followed up until it is resolved, or its symptoms stabilize if not expected to be resolved.

8.3.2 Insurance for health damage

A health damage related to the study treatment should be handled pertinent to the subject's healthcare insurance coverage. Patients will incur the cost for treatment of health damage based on the health system of each country.
A clinical study insurance will be purchased by sponsor as a measures for a compensation for death and severe impairment (grade 1 or 2) that may occur in subjects taking part in this study.

9 Statistical analysis

9.1 Statistical analysis set

(1) Full analysis set (FAS)
FAS is defined as a group of subjects who receive study drug (MTX) and have evaluable efficacy data at 1 or more time points following the administration of study drug.
Modified FAS (mFAS) is defined as a group of subjects who are randomized after Week 24, receive study drug (ADA), and have evaluable efficacy endpoint at 1 or more time points following the administration of study drug.

(2) Per Protocol Set (PPS)
PPS is defined as a group of subjects among mFAS who adequately complied with the protocol. The detailed criteria to determine the suitability of subjects to the analysis sets will be finalized before database lock, and specified in the statistical analysis plan.

(3) Safety analysis set:
Safety analysis set is defined as a group of subjects who receive study drug (MTX) and have evaluable safety data at 1 or more time points following the administration of study drug.

9.2 Analytical method

9.2.1 Method of efficacy analysis

The analysis of primary efficacy endpoint will be performed on mFAS as the main analysis set, and on PPS as a supplementary analysis set. All other analyses will be performed exclusively on FAS.

9.2.1.1 Method of analysis for primary efficacy endpoint

The primary analysis for this study is intended to demonstrate the non-inferiority of ADA/MTX-Reduced Dose Group (ARM-3) to ADA/MTX-MTD Group (ARM-2) in terms of the primary endpoint, that is, SDAI remission rate at Week 48. The intergroup difference in the SDAI remission rate and its two-tailed 90% confidence interval will be calculated based on a stratified analysis with country as a factor in mFAS as the main statistical analysis set. The non-inferiority margin shall be -15%.

Moreover, a multivariate statistical analysis on the SDAI remission rate at Week 48 will be performed for the following variables; age, gender, autoantibody profile, SDAI at screening, and change in mTSS from screening to Week 24.

9.2.1.2 Method of analysis for secondary efficacy endpoints

SDAI remission rate at Week 24, SDAI remission rate at Week 48 in MTX Monotherapy Group (ARM-1), ACR20, ACR50, and ACR70 response rates, HAQ remission rate, and structural remission rate at each assessment timepoint, and their two-tailed 95% confidence intervals will be calculated for each ARM. Furthermore, ARM-2 and ARM-3 at Week 48 will be compared using a stratified analysis with country as a factor.
Summary statistics (mean, standard deviation, median, and range) in each ARM at each assessment timepoint will be calculated for SDAI, CDAI, DAS28-ESR, DAS28-CRP, tender joint count, swollen joint count, VAS (physician- and patient-reported), HAQ, CRP, ESR, MMP-3, RF, anti-CCP antibody, and mTSS, and their changes from baseline to each assessment timepoint. For mTSS at Week 48, changes from Week 24 will also be analyzed for the summary statistics. In addition, ARM-2 and ARM-3 will be compared in terms of changes from Week24 to Week 48 using a stratified analysis with country as a factor.

9.2.2 Method of biomarker analysis

The biomarker analysis will be performed on FAS.
Summary statistics in each ARM will be calculated for erythrocyte MTX-PG concentrations and blood cytokine levels, as well as change from baseline and % change from baseline.
Also, the correlation of SDAI, mTSS, and ACR-N to erythrocyte MTX-PG concentration will be evaluated. Furthermore, the correlation of SDAI and ACR-N to plasma microRNA will be evaluated.
For serum anti-adalimumab antibody, the frequency of and the proportion of subjects with the antibody expression will be calculated.

9.2.3 Method of safety

The safety analysis will be performed on the safety analysis set. Summary statistics concerning safety data (Continuous variables: the number of subjects, mean, standard deviation, median, minimum, and maximum, and Categorical variables: the number and proportion of subjects) will be computed for each ARM. Variables of safety analysis include AEs, clinical laboratory, and vital signs.

9.2.3.1 Adverse events (AEs)

AEs recorded in EDC will be reinterpreted with ICH Medical Dictionary for Regulatory Activities (MedDRA). AEs recorded in EDC will be reinterpreted to the closest MedDRA lowest level terms (LLT) (Ver. 19.0 or later version). Preferred term (PT) and system organ class (SOC) will also be entered in the database.

Treatment-emergent adverse events (TEAE) means AEs not confirmed before the study treatment (MTX) and emerges for the first time after the start of study treatment. TEAE also includes:

- Events confirmed before the study treatment which disappears immediately before the start of study treatment, but reemerges during the study treatment; and
- Events confirmed before the study treatment, which becomes severer during the study treatment compared to the level of severity before the start of study treatment.

TEAE will be used for the analysis of AEs. The number (proportion) of subjects with TEAE in each ARM will be tabulated in SOC and PT. Two or more AEs with the same MedDRA term may be reported in a single subject; in such case, the AEs will be interpreted and counted as 1 subject pertinent to the analysis, and also the AE with the highest severity will be counted in for the analysis on the number (proportion) of subjects with the TEAE. Furthermore, the number (proportion) of subjects with TEAE will be tabulated by the presence/absence of causality.
In addition, TEAE for which causality with the study treatment cannot be ruled out (ADR) will be tabulated in terms of SOC and PT, and the AEs with the highest severity will be counted in for the analysis on the number (proportion) of subjects.
The incidence of TEAE that occur from Week 24 to 48 will be compared between ARM-2 and ARM-3 using a Fisher's exact test or other relevant method.

9.2.3.2 Clinical laboratory

For continuous variables, summary statistics of measurements at each timepoint and their changes from baseline will be calculated.
As an order categorical variable, clinical laboratory values will be categorized to Lower than the reference (L), Within the reference (N), and Higher than the reference (H), and then the number and proportion of subjects by L, N, and H will be presented in a shift table (baseline vs. each visit during treatment) for each ARM. In addition, the maximum and minimum values after the start of treatment will be presented in a shift table for comparison with baseline.

9.2.3.3 Vital signs and body weight

Summary statistics of vital signs (diastolic blood pressure, systolic blood pressure, pulse rate, body temperature) and body weight at each assessment timepoint and their changes from baseline will be computed for each ARM.

9.3 Significance level

The analysis on non-inferiority will be performed with a two-tailed confidence interval of 90%. A two-tailed significance level of 5% will be used for all other analyses unless specified otherwise.

9.4 Number of subjects

- Target number of subjects to be enrolled

300 subjects (target number of subjects to be enrolled in each study site is shown in the list of study sites.)

- Randomization ratio
  Subjects will be stratified by countries (Japan, South Korea, and Taiwan) as a stratification factor, and for each stratum, randomized to ARM-2 and ARM-3 at the ratio of 1:1.

9.4.1 Sample size selection

Assuming that the SDAI remission rate is 30% for both ARM-2 and ARM-3, and the non-inferiority margin is -15%, the number of subjects required for the lower bound of a two-tailed 90% confidence interval for the intergroup difference in SDAI remission rate to exceed the non-inferiority margin at 80% power of detection would be 220 subjects in total (110 in each group).
Past reports suggest that the remission rate of MTX monotherapy is about 15%. Also, it has been reported that about 10% of patients cannot continuously receive MTX ≥10 mg/week (Atsumi T, et al. 2016: 75-83). Thus, in order to randomize 220 subjects between ARM-2 and ARM-3, 288 subjects need to be enrolled, and considering some dropouts, a sample size of 300 subjects was selected as the target number of subjects to be enrolled.

<Justification for the estimated SDAI remission rate in ADA/MTX-Reduced Dose Group (ARM-3)>

The estimated SDAI remission rate in ARM-3 was calculated in reference to the results of the MTX Monotherapy → ADA+MTX Group in HOPEFUL 1 Study in which Japanese MTX naïve patients receiving ADA+MTX or MTX alone for 26 weeks, and then, all subjects receiving ADA+MTX for another 26 weeks (Takeuchi T, et al. 2014: 536-43). Since the maximum dosage of MTX in HOPEFUL 1 Study was 8 mg/week (6.6±0.8 mg/week: Mean±SD), the results cannot be directly extrapolated to this study in which the maximum dosage of MTX up to Week 24 will be 16 mg/week; yet, the results would be appropriate to use as a reference for the SDAI remission rate in ARM-3 in which the dosage of MTX will be reduced to 6 to 8 mg/week from Week 24 onward.
ARM-3 is designed for patients who have not achieved to SDAI remission at Week 24; thus, assuming that the subjects with SDAI remission at Week 26 in HOPEFUL 1 Study (20 subjects = 163 subjects × 12%) remain to be remission at Week 52, the Week-52 SDAI remission rate among the subjects with SDAI non-remission at Week 26 was calculated to be 31.5% [45/143 subjects, that is (65 subjects - 20 subjects)/(163 subjects - 20 subjects)]. Therefore, the SDAI remission rate in ARM-3 was assumed to be 30%.

<Justification for the estimated SDAI remission rate of ≤3.3 in ARM-2 (ADA/MTX-MTD Group)>

There is no data on SDAI remission rate on ADA as add-on therapy given in Japanese patients previously receiving adequate amount of MTX for ≥6 months. However, it has been reported that there was no difference in efficacy of MTX at dosage ≥10 mg/week in a clinical study in which Western MTX naïve patients started concomitantly receiving ADA

and MTX at the same time (Burmester GR, et al. 2015:1037-44), and that there was no difference in DAS28-ESR remission rate between a low-dose concomitant MTX group (8 to ≤12 mg/week) and high-dose concomitant MTX group (>12 to 16 mg/week) according to a stratified analysis on a study in which Japanese MTX naïve patients started concomitantly receiving certolizumab pegol (CZP) and MTX at the same time (Atsumi T, et al. 2016: 75-83). Thus, the SDAI remission rate in ARM-2 was assumed to be 30% just like in ARM-3.

<Justification for the non-inferiority margin>

Both ARM-2 and ARM-3 are designed for patients who have not achieved to SDAI remission at Week 24; thus, assuming the SDAI remission rate is 0% in patients continuously receiving MTX alone without adding bDMARDs, a half of the SDAI remission rate of 30% in ARM-2, which is 15%, was selected as a non-inferiority margin.

<Justification for the estimated SDAI remission rate in MTX Monotherapy Group>

In studies conducted in Japanese MTX naïve patients, the SDAI remission rate in 6 months of treatment with MTX alone was 12.3% (21/171 subjects) and 29.3% (46/157 subjects) (Atsumi T, et al. 2016: 75-83, Takeuchi T, et al. 2014: 536-43). Also, in studies conducted in Western MTX naïve patients, the SDAI remission rate in 6 months of treatment with MTX alone was 11.2% (13/116 subjects) and 16.4% (47/287 subjects) (Emery P, et al. 2015: 19-26, Smolen JS, et al. 2016: 1081-91.). Accordingly, the remission rate of MTX monotherapy was estimated to be 15%.

9.5 Study discontinuation criteria

The entire study will be discontinued if either of the below criteria is applicable. The Lead Principal Investigator shall notify the principal investigator of each study site promptly upon his/her decision to discontinue the study. Then, each principal investigator shall promptly notify his/her subjects, and provide appropriate medical intervention and take other necessary actions.

- The number of subjects enrolled is much below the target number or many subjects achieve SDAI remission at Week 24 so that only a small group of the subjects are assigned to ARM-2 or ARM-3; from either of which the Lead Principal Investigator or Study Biostatistician judges it difficult to achieve the goal even if the study continues.

9.6 Handling of study data

Subjects with missing data at an assessment timepoint of SDAI remission, ACR20, ACR50, and ACR70 response, HAQ remission, and structural remission due to study discontinuation or other relevant reasons will be considered as a “non-responder” at the specific timepoint. Any missing data on SDAI, CDAI, DAS28-ESR, and DAS28-CRP will be considered as missing at the specific timepoint. A missing data on the assessment of SDAI, CDAI, DAS28-

ESR, DAS28-CRP, and mTSS will be complemented with the last observation carried forward (LOCF).

9.7 Data evaluation

Prior to the final analysis, the data obtained before randomization will be summarized in the course of the study for the purpose of presentations at academic conferences. The summary of the data are allowed to be presented at academic conferences after the completion of subject enrollment in principle. This study will not be biased as the data obtained before randomization are collected.

9.8 Deviation from statistical analysis plan

If there is a revision required in the statistical analysis plan after the start of this study, the Lead Principal Investigator shall determine the effect of such revision on this study, and how to apply such revision. The details of the revision shall be specified in the clinical study report of this study.

10 Direct access to source data and document

Principal investigators and study sites must allow direct access to the study-related source data and documents during study monitoring, audit, Certified Review Board’s/Ethical Review Board's review, and authorities' inspection.

11 Monitoring and audit

11.1 Monitoring

Monitoring will be performed on this study to ensure the compliance with ICH-GCP, the Clinical Trials Act, study protocol, and all other applicable regulations and procedures, accurate data collection, appropriate informed consent process, and adequate safety assurance of subjects.

Monitoring will include central monitoring of EDC data and on-site monitoring, both of which will be conducted in accordance with the monitoring plan to be separately set out.

11.2 Audit

To enhance the assurance activities of this intervention study, audit staff will examine this study to ensure its compliance to ICH-GCP, the Clinical Trials Act, the study protocol, and all other regulations and procedures.

12 Ethics

12.1 Benefits and disadvantages to subjects

It is unlikely that this study offers direct benefits to the subjects since the study treatment is a standard treatment within usual clinical practice. However, the results of the study to

establish the optimal usage of ADA and MTX is expected to eventually generate benefits for RA patients in the future.
Meanwhile, potential disadvantages associated with this study may be ADRs of MTX and ADA, as with other standard treatments. Also, investigational blood sampling may become a disadvantage. However, this is only additional collection of very small volume blood to routine blood collection in clinical practice; thus, the risk thereof will be negligible.

12.2 Informed consent

12.2.1 Inform patient

Before enrollment of each patient, the principal investigator/sub-investigator shall hand out to the patient the informed consent document approved by the Certified Review Board (Japan)/Ethical Review Board (South Korea and Taiwan), and orally describe in words easy to understand;

1) The study title, the research aspect of the study, and the fact that the study is approved by the head of the study site;
2) The name of the study site, and the name of the principal investigator;
3) Study objective and purpose:
4) Study methodology (including the treatment given in the study, the probability to be randomized to each group, study procedures including all invasive procedures, and the purpose for use of samples and information obtained from subjects), as well as the anticipated duration of subjects' enrollment in this study, and the number of subjects taking part in the study;
5) Reason for the patient to be selected as a study subject;
6) Subjects' responsibilities, the experimental aspect of this study, the burden on subjects, and anticipated risks and benefits;
7) Subjects' rights to withdraw their consent at any time even after having consented to start or continue the study;
8) Assurance that in no event will subjects or any other related-party be penalized in any way for not consenting to start or continue the study, or withdrawing their consent;
9) Method used to publicly release study-related information;
10) Subjects' rights to obtain or review the protocol and other materials on study procedures within the scope that would not interfere with the protection of other subjects’ personal information or the originality of this study, and the method to obtain or review such materials;
11) Handling of personal information, etc. (Protection of confidential information that could track down subjects' identifies unless otherwise required by laws, and protection of subjects' identity even if the study results are publicly released);
12) Method for storage and disposal of samples and information;
13) Source of funding for the study, conflict of interest and individuals' profits concerning the study at the site, and conflict of interest among study staff;

14) Handling of consultation requested by subjects and other related personnel (liaison for subjects' further inquiry on information concerning this study and the subjects' rights thereto related, or subjects' reporting of health damage that occur in the study);
15) Economic burden or benefit for subjects, and the contents thereof;
16) Other therapeutic options if the study involves a medical intervention beyond the scope of ordinary clinical practice;
17) Medical intervention to be provided to subjects after the study if the study involves a medical intervention beyond the scope of ordinary clinical practice;
18) Handling of study results concerning individual subjects (including incidental findings) if there is a possibility to obtain important information concerning subjects' health, genetic characteristics transmitted to the descendants, or other finding pertinent to this study;
19) Health damage that could occur in the study and the presence/absence and contents of any compensation program if the study involves invasive procedures;
20) Possible uses of subjects samples and information for future researches that are not identified at the time of subjects' informed consent, possible transfer of subjects' samples and information to other research facilities, and the contents thereof anticipated at the time of informed consent;
21) Disclosure of subjects' samples and information to persons conducting monitoring/audit, Certified Review Board/Ethical Review Board, and regulatory agency to an extent necessary and under an assumption that subjects' confidentiality will be protected, if the study involves invasive procedures(except for minor invasive procedure), and that the signature on the consent form is construed as the subject's and his/her legally-acceptable representative's acceptance to allow for direct access to such source documents;
22) Procedures by which any information that could affect the subjects' willingness to continue taking part in the study will be communicated to subjects and their legally-acceptable representatives at an appropriate timing; and
23) Conditions by which subjects' withdrawal from the study can be anticipated, and the reason therefor.

12.2.2 Consent

Request the patient to take part in this study only after completing the patient briefing and confirming that the patient has fully understood the study contents.
Upon the subject's consent to take part in the study, the consent form approved by the Certified Review Board (Japan)/Ethical Review Board (South Korea and Taiwan) should be used to record the name of the briefing physician, the name of the consenting patient, the date of consent, and to have signature of the physician and patient. Three copies of the identical consent form should be in principle prepared; 1 copy should be handed to the patient, 1 should be retained by the principal investigator, and 1 should be submitted to the on-site study secretariat while the actual procedures should be in compliance with each site's operating procedures.

12.2.3 Representative

A legally-acceptable representative needs to be assigned and consent in writing on behalf of a subject aged <20 years in Japan and <19 years in South Korea at the time of informed consent.
Even if the consent is to be obtained from such a legally-acceptable representative, the patient should still be requested to take part in this study after completing the patient briefing and confirming that the patient has fully understood the study contents; in which case, a written consent should be separately obtained from the patient.

12.3 Protection of subjects' privacy and patient identification

The data concerning a subject enrolled in this study will be entered in EDC after anonymized and encoded to a subject ID issued at the registration; subject's name, address, telephone number, and other information that could directly identify an individual subject will not be recorded in the database.
Also, in no event shall any information concerning subjects' privacy be divulged to a third party by a study staff exposed to such information during this study.

12.4 Certified Review Board/Ethical Review Board

12.4.1 Approval

Before conducting this study, the Lead Principal Investigator shall submit the protocol, written information for patient, written informed consent form, and other necessary documents to the Certified Review Board and obtain its approval to conduct this study.
Also in South Korea and Taiwan, the principal investigator shall submit the necessary documents to the Ethical Review Board, and obtain its approval to conduct this study. Upon obtaining approval of the site, the approval format shall be retained at the site, and its copy shall be sent to the study secretariat (Operation Center).

12.4.2 Annual review

The Lead Principal Investigator must report study progress (e.g., the number of subjects enrolled, status of AEs, protocol deviation, etc.) to the Certified Review Board at least once a year , and have the Certified Review Board review and approve the continuation of this study.
In South Korea and Taiwan, the principal investigator must report to the Ethical Review Board at least once a year of the study progress, and have the Ethical Review Board review and approve the continuation of this study.

12.5 Disclosure of study-related information

This study will be registered in ClinicalTrials.gov, Japan Registry of Clinical Trials (jRCT), and UMIN Clinical Trial Registration (UMIN-CTR) to disclose its information.

12.6 Handling of inquiry from subjects and related parties

If a staffer other than principal investigator/sub-investigator receives an inquiry from subjects or related party, such staffer will promptly contact the principal investigator or sub-investigator, and the inquiry will be handled by the principal investigator or sub-investigator, or as necessary by the Lead Principal Investigator.

12.7 Conflicts of interest

This study is a collaborative research conducted by Keio University School of Medicine and Eisai Co., Ltd., the distributor of Humira® and funded by Eisai Co., Ltd. under a collaborative research contract between the parties that define the responsibilities of each party. While this study is conducted based on the specified responsibilities and roles, Eisai Co., Ltd. shall not be involved in data management including database access during the study as well as statistical operation so as to prevent possible bias of the study results; provided that Eisai will be involved in the preparation of and changes to the protocol (including statistical analysis plan), approval of the clinical study report, and delivery of relevant information. Pfizer Japan Inc., the marketing authorization holder of Rheumatrex® and AbbVie GK, the marketing authorization holder of Humira® shall not be involved in this study.
Also, necessary information concerning conflicts of interest associated with principal investigators/sub-investigators and Study Biostatistician of this study and Eisai Co., Ltd., AbbVie GK, and Pfizer Japan Inc. will be disclosed to a department in charge of the management of conflicts of interest at each study site and then will be appropriately managed. Furthermore, in Japan, the conflicts-of-interest management plan will be reviewed by the Certified Review Board in accordance with the Clinical Trials Act.

12.8 Handling of subjects after end of study

Treatment after completion and discontinuation of this 48-week study will not be specified.

12.9 Handling of important findings concerning genetic characteristics, etc.

Genetic characteristics will not be analyzed in this study, and thus, important findings thereto related are not anticipated.

12.10 Retention and future research use of clinical samples, and transfer thereof to other research facilities

Investigational blood samples collected in this study will be retained at an external laboratory until study completion, and in principle all be disposed of immediately upon study completion;
However, upon a separate consent of subjects and approval of Certified Review Board, the clinical samples will be retained in Keio University for future research use for 5 years from the date of study completion report or 3 years from the publication of study results, whichever comes later, and may be transferred to other research facilities as necessary.

13 Handling of data, and retention of record

13.1 Handling of data

In this study, subject ID will be issued through IWRS, and all data except for SAE report will be collected through EDC. The principal investigator or sub-investigator will enter data in EDC promptly upon completion of the evaluation/assessment in each subject.
Based on a separate data management plan, the data center shall send reminders for overdue data, investigate the data and generate data clarification, correct the data according to the data clarification, manage the database, and also, prepares a dataset for statistical analysis based on the data entered in the database.

13.2 Retention of records

Principal investigator shall appropriately retain the data and records concerning this study for at least 5 years from the date of study completion report or 3 years from the last publication date of study results, whichever comes later.

14 Economic burden on subjects, and insurance and other measures

14.1 Economic burden on subjects

The medical cost associated with this study including that for drugs and tests (except for off-label use of special tests) during the study will be paid in accordance with each country's healthcare scheme. In Japan, the study treatment to be provided is within the scope of general clinical practice using the approved drugs, and the cost will be paid by the health insurance and subjects.
Reward for subjects to take part in this study shall be paid in accordance with each country's rule.

14.2 Insurance

Adequate caution shall be in place for treatment of known SAEs. Upon occurrence of an AE during this study, the principal investigator/sub-investigator shall promptly take necessary actions (tests, treatment, study discontinuation, etc.) to ensure the safety of the subject, and with technologies covered by the insurance, take initiative in to provide the best available treatment and other procedures for the subject.
The sponsor shall carry a clinical study insurance as a measures to secure the compensation for death and severe impairment (grade 1 or 2) that may occur in this study.

15 Publication of study results

Key study results will be published in a journal in English language upon completion of the final analysis. Presentation at academic conferences will be arranged and performed by Lead Principal Investigator, Study Investigational Operator, and Coordinating Investigators. The presenter will be selected by Lead Principal Investigator upon approval of Eisai Co., Ltd.

Prior to the publication of key study results, the data collected before randomization may be analyzed in the course of the study for the purpose of presentations at academic conferences. Also in this case, presentation at academic conferences will be arranged and performed by the Lead Principal Investigator, Study Investigational Operator, and Coordinating Investigators, and the presenter will be selected by the Lead Principal Investigator upon approval of Eisai Co., Ltd.

16 Appendix

16.1 Criteria for RA

In the past, a set of criteria released in 1987 has been used widely, but in order to facilitate early diagnosis and early treatment, a new set of criteria was released in 2010. In this study, those meeting 1987 revised ACR criteria or 2010 ACR/EULAR criteria are considered as RA.

16.1.1 ACR revised criteria (1987)

[1] Morning stiffness of ≥1 hour for ≥6 weeks
[2] ≥3 swollen joints for ≥6 weeks
[3] Swollen wrist joint, metacarpophalangeal (MCP) joint, or proximal interphalangeal (PIP) joint for ≥6 weeks
[4] Symmetrical swollen joint for ≥6 weeks
[5] Radiological findings of bone erosion typical with RA, or clear bone decalcification in the hands
[6] Rheumatoid nodule (subcutaneous nodule)
[7] Rheumatoid factor positive

A condition meeting 4 of the above 7 is categorized as RA.

16.1.2 ACR/EULAR criteria (2010)

Patients meeting both of the following criteria will be applicable, and scored accordingly.

1) At least one joint with definite clinical synovitis (swelling)
2) Synovitis is not better explained by another disease

Scoring: ≥6 points = Definitive RA

A. Joint involvement
- 1 large joint 0 points
- 2 - 10 large joints 1 point
- 1 - 3 small joints (with or without involvement of large joints) 2 points
- 4 - 10 small joints (with or without involvement of large joints) 3 points
- ≥ 11 joints (at least 1 small joint) 5 points

B. Serology (at least 1 tests result is needed for classification)
- Negative RF *and* negative anti-CCP antibody 0 points
- Low-positive RF *or* low-positive anti-CCP antibody 2 points
- High- positive RF *or* high-positive anti-CCP antibody 3 points

C. Acute-phase reactant (at least 1 tests result is needed for the classification)
- Normal CRP *and* normal ESR 0 points
- Abnormal CRP *or* abnormal ESR 1 point

D. Duration of symptoms
- <6 weeks 0 points
- ≥6 weeks 1 point

16.2 Reference

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