A Phase 2/3 (Placebo-Controlled, Double-Blind, Comparative) Study on MT-5547 in Patients with Osteoarthritis Accompanied by Moderate to Severe Pain

Clinical Study Protocol

Sponsor

Mitsubishi Tanabe Pharma Corporation

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Note; This document was translated into English from Japanese original version.

Confidentiality

This protocol contains information that is to be provided only to persons who are directly involved in the study. The information contained in this document must not be published or disclosed to any third parties without the prior written consents of Mitsubishi Tanabe Pharma Corporation.

This study will be conducted in compliance with the Pharmaceutical Affairs Law, the Ordinance on Good Clinical Practice (GCP) and related laws and regulations, and the protocol.

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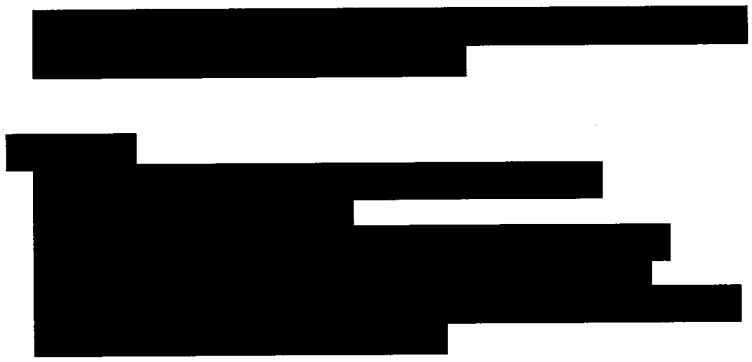


List of Abbreviations

Abbreviation	Unabbreviated Term
ACR	American College of Rheumatology
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BA	Bioavailability
BAP	Bone specific alkaline phosphatase
BMI	Body mass index
DA	Destructive arthropathy
DEXA	Dual-energy X-ray absorptiometry
DMM	Destabilization of the mouse medial meniscus
DNA	Deoxyribonucleic acid
EDC	Electronic data capture
EQ-5D-5L	EuroQol Group Questionnaire
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
γ-GTP	γ-glutamyltranspeptidase
HbA1c	Hemoglobin A1c
HBs	Hepatitis B surface
HCV	Hepatitis C-virus
HIV	Human immunodeficiency virus
IDMC	Independent Data Monitoring Committee
IgG	Immunoglobulin G
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
IRB	Institutional review board
JOA	The Japanese Orthopaedic Association
KLH	Keyhole limpet hemocyanin
LBP	Low back pain
LDH	Lactate dehydrogenase
MAR	Missing at random
MMRM	Mixed effect model for repeated measurement
MRI	Magnetic resonance Imaging
NGF	Nerve growth factor
NOAEL	No observed adverse effect level
NRS	Numerical rating scale
NSAID	Nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
[redacted]	[redacted]
OMERACT-OARSI	Outcome Measures in Rheumatology Arthritis Clinical Trials-Osteoarthritis Reseach Society International

PGA	Patient Global Assessment
[redacted]	[redacted]
PPS	Per protocol set
PTP	Press through pack
q4w	Every 4 weeks
q8w	Every 8 weeks
QOL	Quality of life
RNA	Ribonucleic acid
RPOA	Rapidly progressive osteoarthritis
RRS	Randomiazation requirements specification
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SF-36	Short Form 36-item health survey
SIF	Subchondral insufficiency fracture
SNRI	Serotonin & Norepinephrine Reuptake Inhibitors
SOP	Standard operating procedures
SSRI	Selective serotonin reuptake inhibitors
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment Emergent adverse event
[redacted]	[redacted]
TrkA	Tropomyosin related kinase A
WEB	World Wide Web
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

List of Abbreviations Associated With Pharmacokinetic Parameters

Abbreviation	Unabbreviated Term
AUC	Area under the serum concentration-time curve
ACU_{inf}	Area under the serum concentration-time curve from time 0 to infinity
C_{max}	Maximum serum concentration
$t_{1/2}$	Terminal elimination half-life

Definition of Terms

Term	Definition
Within XX before the start of screening	Periods before the start of screening are calculated starting from the day on which screening will begin. Furthermore, definitions of the following phrases/terms are provided below. Within XX days: Calculated starting from XX days before. Within XX weeks: Calculated starting from the same day of the week XX weeks before. Within XX months: Calculated starting from the same day of the month. If a month does not have the same day, then calculated starting from the day before that day. Within XX years: Calculated starting from the same day XX years before.

Relative date	Baseline (the day of investigational drug or comparative drug administration) is defined as Day 1.
Screening period start day	The day on which patients were registered via the IWRS as having started screening.
Screening period	The maximum duration of the screening period is 30 days from the start of the screening period until the day before the start of the pre-treatment observation period.
Start of the pre-treatment observation period	7 days before (Day -7; allowable range: ±3 days) baseline (day of investigational drug or comparative drug administration). The day on which patients were registered in the IWRS as having started the pre-treatment observation period.
Pre-treatment observation period	Period from the start of the pre-treatment observation period until before the start of investigational drug or comparative drug administration at baseline
Baseline	The day on which the patient was registered via the IWRS as having started the treatment period, and the day of subject randomization (notification of randomization number and drug number).
Date of discontinuation	The date on which that assessments at discontinuation were performed (the date of the assessments). If the assessments at discontinuation could not be performed, then the data on which the decision was made to discontinue the study will be used.
Treatment period	Period from after the start of investigational drug or comparative administration at baseline until the day of assessment 48 weeks later.
Post-treatment observation period	20 weeks from the day after the day of assessment 48 weeks after treatment initiation (or from the day after discontinuation). If a joint replacement procedure is going to be performed, then the post-treatment observation period will be the period from the day after the day of discontinuation until 20 weeks after the joint replacement procedure is performed.
Study period	The period from the day of consent acquisition until the final assessments in the post-treatment observation period.
IWRS (MT-5547-J01 registration center)	A web-based system for subject enrollment, subject randomization, the issuance of drug numbers, and study drug shipment requesting and recovery.
Centralized imaging rater	An X-ray and MRI imaging rater appointed by the central testing organization ([redacted]).
Central review project office	Imaging central testing facility ([redacted]) project office
Adjudicated arthropathy	Arthropathy judged by the centralized imaging rater
K-L category	Kellgren-Lawrence category Osteoarthritis staging category based on simple X-ray; a 5-level scale from 0 to 4.
WOMAC pain score (the mean of 5 items)	The mean of the scores of the 5 items on the WOMAC pain scale (during walking, using stairs, in bed, sitting or lying, and standing). The patients who are eligible to participate in this study are patients with moderate to severe scores of 4 or higher.
WOMAC physical	The level of difficulty of activities of daily living is assessed using the 17-

function	item WOMAC physical function scale.
Evaluated joint	The joint that is evaluated in this study. The evaluated joint will be a joint for which joint replacement or some other surgical procedure is not being performed. The evaluated joint will be the joint (knee or hip) that is judged to have a K-L grade of ≥2 on X-ray test (centralized assessment) and the joint with the highest WOMAC pain score (mean of the 5 items). If the K-L score is ≥2 in more than 1 joint, the evaluated joint is the joint with the greater WOMAC pain score at screening. If 2 or more joints have a K-L score of ≥2 and the same WOMAC pain score, the evaluated joint is the joint with the greater K-L score. If multiple joints have identical K-L grades and WOMAC pain scores, then the (sub)investigator will determine which joint should be evaluated.
IVRS	An automated telephone response system used by subjects every night from the start of pre-treatment observation period until the day before Week 16 to report the NRS scores for their mean pain on walking for the evaluated joint each day.
Treatment diary	Every night, from the start of pre-treatment observation period through Week 48, patients will record in their treatment diaries the doses (number of tablets) of rescue medication (acetaminophen) they took.

Synopsis

1. Study Title

A Phase 2/3 (Placebo-Controlled, Double-Blind, Comparative) Study on MT-5547 in Patients with Osteoarthritis Accompanied by Moderate to Severe Pain

2. Study Objectives

The objective of this study is to verify the superiority of 16 weeks of MT-5547 treatment to placebo, as evidenced by the WOMAC pain score (the efficacy outcome measure), in patients with osteoarthritis of the knee or hip. Additional objectives of the study are to investigate the efficacy, safety, and pharmacokinetics of MT-5547 in long-term use.

3. Target Patient Population

3.1. Target Patient Population

Patients with moderate to severe pain associated with osteoarthritis of the knee or hip

3.2 Inclusion Criteria

Patients who satisfy all of the following inclusion criteria and have the capacity to consent to study participation will be eligible to participate in the study.

Inclusion Criteria at the Start of Screening

(1) Patients who have received a thorough explanation of participation in this study and who have freely given their written consent to participate in the study.
(2) Outpatients
(3) Japanese patients ≥40 and ≤85 years of age at the time written informed consent is obtained. Japanese patients will be considered patients whose biological parents are both Japanese.
(4) Patients who have been diagnosed with osteoarthritis of the knee or hip based on the American College of Rheumatology (ACR) criteria*. (see Attachment 1, "Osteoarthritis Diagnosis Guidelines")
    * Confirmation diagnosis based on the ACR criteria may be carried out during the screening period.
(5) Use of existing drug therapy for OA for at least the past 3 months from the start of screening period.
(6) Regular use of oral analgesic medications for OA (taken an average of 4 days or more per week for 4 or more weeks prior to screening), including NSAIDs, opioids, acetaminophen, or combinations thereof.

Inclusion Criteria at the Start of the Pre-treatment Observation Period

Patients who were confirmed to be suitable for study participation during the screening period and who satisfy all of the following inclusion criteria at the start of the pre-treatment observation period.

(7) Patients with an evaluated joint* (knee or hip) with a K-L (Kellgren-Lawrence) score of ≥2 based on the X-ray test performed at screening (centralized assessment).

*Evaluated joint

The evaluated joint will be a joint for which joint replacement or some other surgical procedure is not being performed (one of the right knee, left knee, right hip, or left hip). If the K-L score is ≥2 in more than 1 joint, the evaluated joint is the joint with the greater WOMAC pain score (average of the 5 items) at screening. If 2 or more joints have a K-L score of ≥2 and the same WOMAC pain score, the evaluated joint is the joint with the greater K-L score. If multiple joints have identical K-L grades and WOMAC pain scores, then the (sub)investigator will determine which joint should be evaluated.

(8) Moderate to severe pain in the evaluated joint, defined as a WOMAC pain score of ≥4 (mean of the 5 items), on the WOMAC assessments performed at screening
(9) Patients who satisfy both 1) and 2) below.
  1) Inadequate osteoarthritis pain relief from at least 1 oral NSAID.
  2) Intolerance to or inadequate osteoarthritis pain relief from at least 1 opioid (including combination drugs), or unwillingness to take opioid therapy
(10) Patients who agree to not change their current lifestyle (daily living activities and exercise) throughout the study.
(11) Patients who are able to complete post-operative follow-up for any joint replacement surgery that is performed during the study
(12) Body mass index at screening ≤39
(13) Patient who are able to understand and answer endpoint questions used in the study.

Inclusion Criteria at Baseline

(14) Moderate to severe pain in the evaluated joint, defined as a WOMAC pain score of ≥4 (mean of the 5 items), on the WOMAC assessments performed at baseline.

3.3 Exclusion Criteria

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

Exclusion Criteria at Screening

(1) Presence of symptoms of carpal tunnel syndrome within 6 months before screening.
(2) Any of the following intra-articular injections of hyaluronic acid.
  1) An intra-articular injection of sodium hyaluronate (average molecular weight 500,000 to 1,200,000; trade names: ARTZ, ARTZ Dispo; including generics) in any joint within 2 weeks prior to screening.
  2) An intra-articular injection of sodium hyaluronate (average molecular weight: 1,500,000 to 3,900,000; trade names: Suvenyl Dispo 25 mg, Suvenyl Vial 25 mg; including generics) in any joint within 4 weeks prior to screening.
  3) An intra-articular injection of sodium hyaluronate crosslinked polymer/sodium hyaluronate crosslinked polymer crosslinked with vinyl sulfone (trade name: Synvisc 2 mL) within 13 weeks prior to screening.
(3) Systemic (excluding topical, intranasal, ophthalmic, and inhaled formulations) corticosteroids within 4 weeks prior to screening.
(4) Use of a monoamine reuptake inhibitor (e.g., tricyclic antidepressant, SSRI, SNRI) for the treatment of pain within 4 weeks prior to screening.
(5) History of transient cerebral ischemic attack or cerebrovascular disorder within 12 months prior to screening, or history of myocardial infarction or acute coronary syndrome within 6 months prior to screening.
(6) New major illness diagnosed within 2 months prior to screening (Grade 3 in "Criteria for Seriousness of Adverse Reactions to Drugs, etc.").
(7) History of malignancy within 5 years prior to screening, except patients who have been treated successfully with no recurrence for ≥1 year of basal or squamous cell carcinoma of the skin or in situ cervical cancer.
(8) History of alcohol dependency, alcohol abuse, or drug or analgesic abuse within 5 years prior to screening.

(9) Participation in other studies and treatment with an investigational drug within 4 weeks or 5 half-lives of the investigational drug prior to the start of screening.
(10) MRI cannot be performed.
(11) Intolerance to naproxen.
(12) Presence of peptic ulcer or gastrointestinal bleeding. History of peptic ulcer or gastrointestinal bleeding and may recur during the study.
(13) Presence or history of aspirin asthma.
(14) History of hypersensitivity to oral NSAIDs.

Exclusion Criteria at the Start of the Pre-treatment Observation Period

The subjects' eligibility for participation in the study will be checked during the screening period, and any patients meeting any of the following exclusion criteria at the start of the pre-treatment observation period will be excluded from the study. The check of eligibility will include a check of the results of the central assessments of the imaging tests (X-ray and MRI tests). However, if the MRI test results cannot be obtained by the start of the pre-treatment observation period, then the eligibility of the patient for the study will be confirmed by baseline (for details, see "9.1.1 Test/Observation Schedule" and "9.1.2 Re-screening").

(15) Trauma to the evaluated joint within 3 months prior to screening (except for cases where no abnormal findings could be confirmed in images obtained at the time of the trauma).
(16) Presence or history of inflammatory joint diseases other than osteoarthritis (eg, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudogout, gout, spondyloarthropathy, joint infections within 5 years prior to screening), vertebral, pelvic, or femoral Paget's disease, multiple sclerosis, fibromyalgia, vertebral tumors or infections, or renal osteodystrophy.
(17) Presence or history, confirmed by imaging, of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive osteoarthritis type 1 or 2), neuropathic joint arthropathy, hip dislocation (except for artificial hip dislocation or developmental hip dislocation), knee dislocation (except for patella dislocation), extensive subchondral cyst, marked bone destruction or bone loss, or pathologic fractures.
(18) Need or desire for joint replacement surgery during the study.
(19) History of sickle cell disease, including S-C disease and S-β thalassemia.
(20) Regional pain caused by lumbar or cervical compression with radiculopathy or other moderate to severe pain that may confound assessments of the pain associated with OA.
(21) Presence or history of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy such as reflex sympathetic dystrophy at screening.
(22) Presence or history of chronic familial dysautonomia (pure autonomic failure, multiple system atrophy [Shy-Drager syndrome]).
(23) Autonomic neuropathy diagnosed in the assessment of autonomic nerve symptoms performed at screening (for details, see "9.2.4.1.7 Autonomic Nerve Assessments").
(24) Presence or history of orthostatic hypotension at the orthostatic hypotension assessments performed at screening (for details, see "9.2.4.1.8 Standing Blood Pressure Assessment").
(25) Surgical procedure (including joint replacement) scheduled during the term of the study.
(26) History of acetaminophen intolerance or hypersensitivity.
(27) Allergy or hypersensitivity to doxycycline or related compounds, or monoclonal antibodies.
(28) Inability to undergo the scheduled tests.
(29) Intra-articular corticosteroids in the evaluated joint within 12 weeks prior to screening, or in any other joint within 4 weeks prior to screening.
(30) Patients for whom the use of the prohibited concomitant medications cannot be prohibited (see Attachment 4, "List of Prohibited Concomitant Medications").

(31) Resting heart rate of <50 bpm or >100 bpm at screening.
(32) Presence or history of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS, or bifascicular block by ECG assessment at screening.
(33) Presence of poorly controlled hypertension:
  1) Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg at screening
  2) Systolic blood pressure of 160 mmHg to 179 mmHg or diastolic blood pressure of 100 mmHg to 109 mmHg on the screening tests, AND a history of organ damage (i.e., left ventricular hypertrophy, heart failure, angina, myocardial infarction, stroke, transient ischemic attack, peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema]).
(34) Congestive heart failure with New York Heart Association (NYHA, 1994) Classification of stage III or IV.
(35) Poorly controlled diabetes (HbA1c >9.0%).
(36) ALT or AST ≥2.5 times ULN at screening.
(37) Concomitant psychiatric, cardiac, renal, hepatic, neurological, endocrinological, metabolic, or lymphatic disease (Grade 2 in "Criteria for Seriousness of Adverse Reactions to Drugs, etc.") that, in the opinion of the (sub)investigator, would adversely affect the patient's participation in the study, or some other significant concomitant illness (Grade 3 in "Criteria for Seriousness of Adverse Reactions to Drugs, etc.") (including serious blood disorders).
(38) Presence or history of ophthalmic herpes simplex, herpes simplex virus (HSV) pneumonia, or HSV encephalitis.
(39) Presence or history of human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection, except that patients with a history of hepatitis B are eligible if negative for HBs antigen and positive for HBs antibodies, and patients with a history of hepatitis C are eligible if the hepatitis C virus RNA test results are negative.
(40) Use of an anti-NGF antibody in the past, or apparent hypersensitivity or intolerance to anti-NGF antibodies.
(41) Women who are pregnant, breastfeeding, or may be pregnant (positive serum pregnancy test) women of childbearing potential for whom pregnancy test results are not available, or women of childbearing potential, or men with female partners of childbearing potential, who are unwilling to use contraception during the study and for 20 weeks after the last dose of investigational drug or comparative drug.
(42) Patients otherwise judged by the (sub)investigator to be unsuitable for the study.

Exclusion Criteria at Baseline

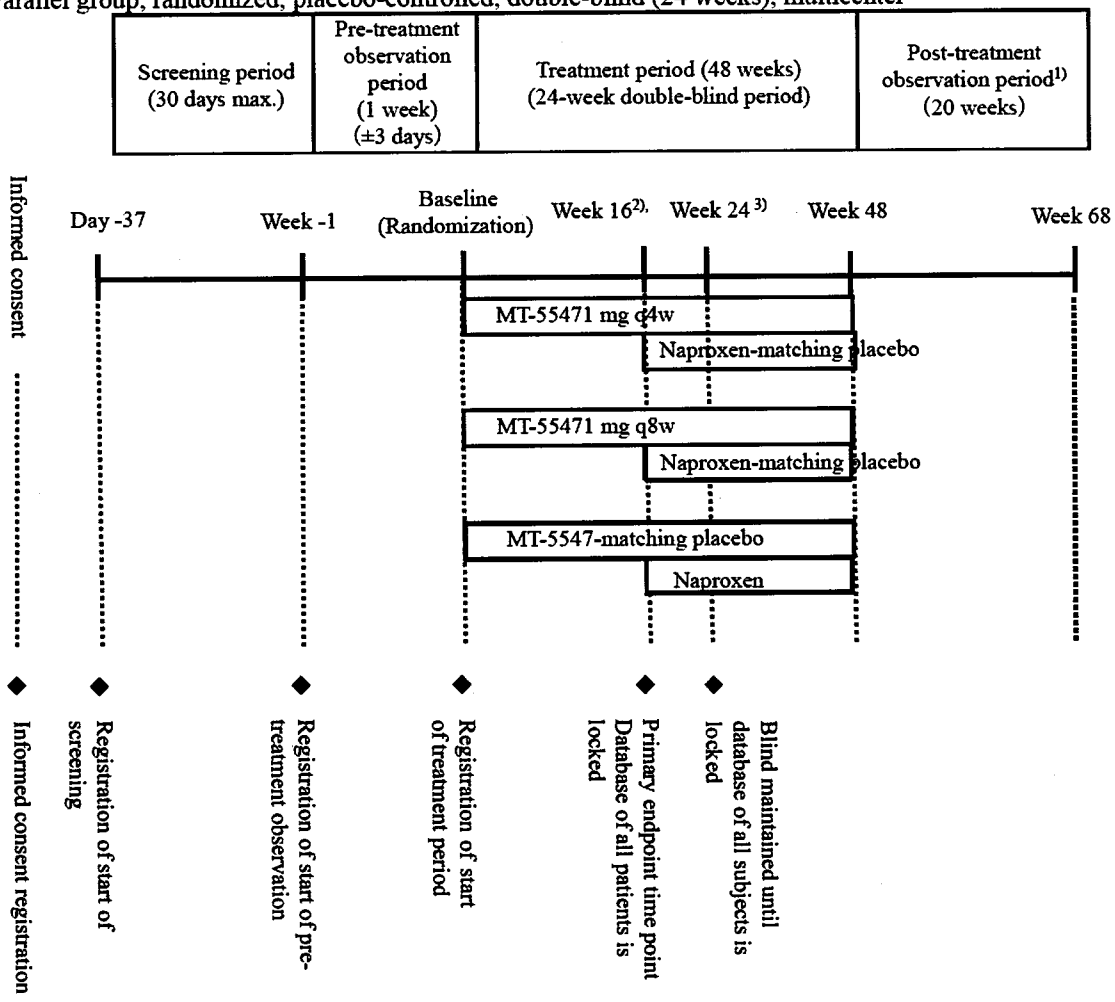
(43) Autonomic neuropathy diagnosed in the assessment of autonomic nerve symptoms performed at baseline (for details, see "9.2.4.1.7 Autonomic Nerve Assessments").
(44) Orthostatic hypotension found at the orthostatic hypotension assessments performed at baseline (for details, see "9.2.4.1.8 Standing Blood Pressure Assessment").
(45) Resting heart rate of <50 bpm or >100 bpm at baseline.
(46) Use of a prohibited concomitant medication during the pre-treatment observation period (see Attachment 4, "List of Prohibited Concomitant Medications").
(47) Women who may be pregnant based on a positive urine pregnancy test result, and women of childbearing potential for whom no pregnancy test results are available.
(48) Presence of adjudicated arthropathy by the central rater based on the MRI tests performed at screening.
(49) Patients who forget to input their NRS data (average pain on walking in the evaluated joint over 1 day) 4 or more times during the IVRS training in the pre-treatment observation period.

(50) Patients otherwise judged by the (sub)investigator to be unsuitable for the study (a check will be performed of the exclusion criteria that were checked in the screening period and pre-treatment observation period as well to ensure that there has been no change to these findings).

4 Study Design

Based on recommendations from the IDMC, the 3 mg q4w and 6 mg q8w groups were removed and the 1 mg q8w group was newly added. The revised study is the following 3-arm design (Protocol Ver 04.00.00000).

Study Phase : Phase 2/3
Type of Study : Confirmatory Study
Parallel group, randomized, placebo-controlled, double-blind (24 weeks), multicenter



All patients who were randomized to 3 mg q4w or 6 mg q8w group and were discontinued from study drug based on IDMC recommendation will move onto the post-treatment observation period and will continue all tests/observations in the period (ref. 9.1.1 Test/Observation Schedule (2)).

1) The post-treatment observation period will be the 20 weeks from the day after the day of the 48-week treatment period. Furthermore, for subjects discontinued from the study, the post-treatment observation period will be the 24 weeks from the administration of MT-5547 or MT-5547 placebo. If a joint replacement procedure is going to

be performed, the postoperative test observation period will be the period from the day after the day of discontinuation until 20 weeks after the joint replacement procedure is performed.

2) From Week 16 to Week 48, the placebo group will receive an additional dose of naproxen tablets to reduce the dropout rate in the placebo group. The MT-5547 group will receive an additional dose of naproxen placebo tablets.
   For each subject, the data for up through Week 16 will be fixed prior to the Week 20 visit, and the fixed data will be prepared.
3) The blind will be maintained, including for the study sponsor, until the key code is opened after the data have been fixed for all subjects in Week 24. In addition, in order to eliminate any bias that could affect the study assessments, to the extent possible, the blind will be maintained with respect to the study site and the subject even after the opening of the study sponsor key code.

5 Study Drugs, and Dosage and Administration

5.1 Names of study drugs

(1) Investigational drug

Name: MT-5547

Generic name: Fasinumab

Dosage form and strength:

MT-5547 1 mg: Contains 0.5 mL of 1 mg fasinumab per prefilled syringe (2 mg/mL).

(2) Comparative drug

Name: MT-5547 placebos

Dosage form and strength: MT-5547 placebo: A prefilled syringe that does not contain any fasinumab, and that contains 0.5 mL of a placebo that is externally indistinguishable from MT-5547.

(3) Control drugs

Names: Naproxen tablets and naproxen placebo tablets

Dosage forms and contents:

Naproxen 100 mg tablets: Each tablet contains 100 mg of naproxen.

Naproxen placebo tablets: Placebo tablets that are externally indistinguishable from naproxen 100 mg tablets

5.2 Dosage and Administration

(1) MT-5547 and MT-5547 placebos

Assigned investigational drug and comparative drug will be administered subcutaneously every 4 weeks between Week 0 and Week 44.

MT-5547 1 mg q4w group: MT-5547 1 mg q4w from Week 0 to Week 44

MT-5547 1 mg q8w group: MT-5547 1 mg q8w on Weeks 0, 8, 16, 24, 32, and 40, and MT-5547 placebo q8w on Weeks 4, 12, 20, 28, 36, and 44

MT-5547 placebo group: MT-5547 placebo q4w from Week 0 to Week 44

Furthermore, subjects who have consented to perform self-injections will perform self-injections subcutaneously at the study site from Week 24 on.

(2) Naproxen tablets and naproxen placebo tablets:

Naproxen tablets or naproxen placebo tablets 3 to 6 tablets (300 to 600 mg/day) will be administered 2 to 3 times a day by mouth with water from the morning of the day after the Week 16 assessment day until the end of the Week 48 assessments. Administration will be by mouth,

with administration in a fasted condition avoided whenever possible. At each visit, the dosage and administration may be changed at the discretion of the (sub)investigator. The (sub)investigator instructs the examinee to keep the naproxen tablets or naproxen placebo tablet in a shading bag.

5.3 Treatment Period
48 weeks

6 Concomitant Drugs/Therapies
6.1 Prohibited Concomitant Drugs/Therapies
The coadministration of the drug products/therapies (including over-the-counter medications) shown below will be prohibited throughout the following period.

(1) For 60 weeks from the start of the pre-treatment observation period or until 16 weeks after the final dose of investigational drug or comparative drug
NSAIDs (including oral, injectable, topical, or ophthalmic dosage forms), except in the following cases
1) Up to 100 mg/day of aspirin taken for thrombus/embolism prophylaxis in patients with cardiovascular and cerebrovascular disease
2) Temporary use of combination cold medicines that contain NSAIDs
3) From the morning of the day after the Week 16 assessment day until the end of the Week 48 assessments. Control drug (naproxen)

About following NSAIDs which has a long half-life, prohibit comcomitant period will be set, respectively.
1) For 60 weeks starting from 12 days before baseline, or until 16 weeks after the final dose of investigational drug or comparative drug
Oxaprozin, Piroxicam (including oral and topical dosage forms)
2) For 60 weeks starting from 10 days before baseline, or until 16 weeks after the final dose of investigational drug or comparative drug
Ampiroxicam
3) For 60 weeks starting from 7 days before baseline, or until 16 weeks after the final dose of investigational drug or comparative drug
Meloxicam

(2) For 48 weeks from 2 weeks before the start of screening, or until discontinuation
Sodium hyaluronate (average molecular weight 500,000 to 1,200,000; brand name: Artz® Joint Injection, Artz Disposable® Joint Injection, including generics)

(3) For 48 weeks from 4 weeks before the start of screening, or until discontinuation
1) Sodium hyaluronate (average molecular weight 1,500,000 to 3,900,000; brand name: Suvenyl® Disposable Joint Injection 25 mg and Suvenyl® Vial Joint Injection 25 mg, including generics)
2) Corticosteroid (excluding topical, intranasal, ophthalmic, and inhaled dosage forms, and intraarticular injections into the evaluated joint)
3) Monoamine reuptake inhibitor used for analgesic effect (tricyclic antidepressant, SSRI, SNRI, etc.)

(4) For 48 weeks from 12 weeks before the start of screening, or until discontinuation

Intraarticular injections of corticosteroids into the evaluated joint

(5) For 48 weeks from 13 weeks before the start of screening, or until discontinuation

Sodium hyaluronate crosslinked polymer/sodium hyaluronate crosslinked polymer crosslinked with vinyl sulfone (brand name: Synvisc Disposable® Joint Injection 2 mL)

(6) For 16 weeks from the starting day of the pre-treatment observation period, or until discontinuation

1) Glucosamine
2) Chondroitin

(7) For 48 weeks from the starting day of the pre-treatment observation period, or until discontinuation

1) Opioids (including combination drugs)
2) Tizanidine
3) Drugs intended for analgesic effects (pregabalin, etc.)
4) Nerve block therapy and trigger point injections
5) Physical therapy (such as non-pharmacological transcutaneous electrical nerve stimulation, acupuncture, and exercise therapy)

However, concomitant therapy will be permitted if the patient has been receiving stable physical therapy on an ongoing basis since before screening and the extent and frequency is changed as little as possible during the study period.

6) Chinese herbal medicines that are indicated for osteoarthritis

(8) From the start of the pre-treatment observation period until the end of the post-treatment observation period

1) Immunosuppressants (e.g., cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, tofacitinib)
2) Biological drug products (e.g., anti-TNF antibodies, IL-1 inhibitors, IL-6 inhibitors, abatacept, rituximab, denosumab)

(9) From the earliest day of 4 weeks before the start of screening, or 5 half-lives of the investigational drug until the end of the post-treatment observation period

All investigational drugs other than this investigational drug

6.2 Restricted concomitant medications

The coadministration of the following drugs (including over-the-counter medications) will be restricted (or caution must be exercised when using the following drugs) throughout the following periods.

(1) For 48 weeks from the starting day of the pre-treatment observation period, or until discontinuation

1) Acetaminophen (the rescue medication)

The concomitant use of acetaminophen will be permitted as the rescue medication in this study.

Until the Week 48 visit, if relief from pain associated with osteoarthritis is inadequate, acetaminophen 300-1000 mg will be taken orally as needed every 4 to 6 hours, or more, as the rescue medication. This dose may be adjusted depending on the age and symptoms of the subject. The combined OA-pain and non-OA pain should not exceed 4000 mg in a single day. In addition, administration in a fasted state should be avoided. For 48 weeks starting from

screening, or until treatment period discontinuation, acetaminophen may not be used from 48 hours before each scheduled visit until after the efficacy assessments have been completed in order to minimize the effects of the rescue drug on the efficacy outcome measure.

2) Acetaminophen (the use for the acute-phase therapy of conditions other than osteoarthritis)
Acetaminophen can also be used for acute treatment of non-OA pain, and will be reported as concomitant medication. The combined OA-pain and non-OA pain should not exceed 4000 mg in a single day. For 48 weeks starting from screening, or until treatment period discontinuation, acetaminophen may not be used from 48 hours before each scheduled visit until after the efficacy assessments have been completed in order to minimize the effects of the rescue drug on the efficacy outcome measure.

(2) For 60 weeks from the start of the pre-treatment observation period, or until 16 weeks after the final dose of investigational drug or comparative drug
The following NSAIDs

1) Low-dose aspirin
The concomitant use of aspirin will be permitted at doses of up to 100 mg when it is being used to prevent thrombosis/embolism in cardiovascular or cerebrovascular diseases.

2) Combination cold medicines that contain NSAIDs
The temporary use of combination cold medicines that contain NSAIDs will be permitted if the subjects have colds. The use of such medicines will be restricted to 3 days in a row, and as a rule at least 1 month must be allowed to pass before such medicines are used again. The use of such medicines will not be permitted from 48 hours before each scheduled visit until after the efficacy assessments have been completed.

(3) For 48 weeks from the start of the pre-treatment observation period, or until discontinuation
Monoamine reuptake inhibitors used other than for analgesic effect (such as tricyclic antidepressants, SSRIs, and SNRIss).
The concomitant use of these drugs will be permitted provided that as a rule, the subject has been continuing to take them since at least 8 weeks before the start of screening, and that they are taken using a fixed dosage starting from at least 4 weeks before the start of screening and continuing during the planned period of participation in this study.

(4) From Week 16 until Week 48 or discontinuation
The following drugs, which need to be used carefully when being coadministered with naproxen

1) Hydantoin anticonvulsants (phenytoin)
2) Sulfonyl urea hypoglycemic agents (e.g., chlorpropamide, tolbutamide, glivenclamide)
3) Anticoagulants (e.g., warfarin, dabigatran etexilate)
4) Anti-platelet agents (e.g., clopidogrel)
5) Probenecid
6) Methotrexate
7) Antihypertensive agents (e.g., beta blockers, diuretics, ACE inhibitors, A-II receptor blockers): Especially, when patients take combination of diuretics with ACE inhibitors or A-II receptor blockers, the (sub)investigator should be careful to monitor renal function.
8) Lithium preparations (lithium carbonate)

9) Zidovudine
10) New quinolone antibacterial agents
11) Iguratimod
12) Low-dose aspirin

There are no particular restrictions on drugs or therapies other than the ones listed above.
Furthermore, because naproxen will be administered concomitantly from Week 16 on, the (sub)investigator will investigate the need for the concomitant use of H2 blocker, misoprostol or a proton pump inhibitor etc. to protect the gastrointestinal tract.

7 Endpoints
7.1 Efficacy Endpoints
(1) Primary efficacy endpoint
WOMAC pain score (change from baseline at Week 16)
(2) Key secondary efficacy endpoint
WOMAC physical function score (change from baseline at Week 16)
(3) Secondary efficacy endpoint
1) Patient Global Assessment (PGA) (change from baseline at each assessment time point)
2) WOMAC pain score (change from baseline at each assessment time point)
3) WOMAC physical function score (change from baseline at each assessment time point)
4) WOMAC stiffness score (change from baseline at each assessment time point)
5) WOMAC global score (change from baseline at each assessment time point)
6) Proportions of subjects exhibiting improvements of 30% and 50% in the WOMAC pain score compared to baseline (Weeks 16 and 24)
7) Proportions of subjects exhibiting improvements of 30% and 50% in the WOMAC physical function score compared to baseline (Weeks 16 and 24)
8) Numerical rating scale (NRS) score for the mean pain on walking in the evaluated joint (change from baseline at each assessment time point)
9) SF-36 (change from baseline at each assessment time point)
10) EQ-5D-5L (change from baseline at each assessment time point)
11) Proportion of responders based on the Outcome Measures in Rheumatology Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria (Weeks 16 and 24)
12) Rescue medication dose (number of days taken, and amount (number of tablets) taken)

7.2 Safety Endpoints
(1) Adverse events and adverse reactions (for more detailed information, see "9.2.4.2. Adverse Events")
(Adjudicated arthropathy, sympathetic nerve disorders and altered peripheral sensation are defined as adverse events of special interest (AESI))
(2) General clinical laboratory tests
(3) Weight
(4) Vital Signs
(5) ECG
(6) Physical examination
(7) Joint pain questionnaire
(8) Survey of autonomic symptoms
(9) Standing blood pressure
(10) Neurological assessments

(11) Bone Density
(12) Imaging Tests
(13) Injection site assessments
(14) Assessments if a Joint Replacement Procedure Is Scheduled

7.3 Pharmacokinetic Endpoints
(1) Serum MT-5547 concentration
(2) Anti- MT-5547 antibodies

7.4 Other
(1) [redacted]
(2) [redacted]

8 Target Sample Size
The original target sample size is 568 treated subjects (142 subjects per group)
(MT-5547 1 mg q4w group: 142 subjects; MT-5547 3 mg q4w group: 142 subjects; MT-5547 6 mg q8w group: 142 subjects; placebo group: 142 subjects)

After initiation of this study, based on the recommendations from the IDMC, the 3 mg q4w and 6 mg q8w groups were removed and 1 mg q8w group was newly added to the treatment groups.
The amended target sample size is 506 treated subjects, in total of the subjects who were randomized to 1 mg q4w/placebo groups before the amendment (approximately 40 subjects per group) and the subjects who are randomized to 1 mg q4w/1 mg q8w/placebo groups with the ratio of 1:1:1 after the amendment (142 subjects per group).
(MT-5547 1 mg q4w group: 182 subjects; MT-5547 1 mg q8w group: 142 subjects; placebo group: 182 subjects)

In addition, 57 patients each were enrolled in the fasinumab 3 mg q4w and 6 mg q8w groups prior to the protocol amendment (Ver. 04.00.00000) and were discontinued from study drug based on the recommendations from the IDMC. Thus, enrollment of 563 subjects is planned for this study in total.

9 Study Period
[redacted]

10 Test/Observation Schedule

(1) Test/Observation Schedule from informed consent to Week 48 of treatment period (if a joint replacement procedure is not going to be performed)

				Treatment period									Treatment period						
Visit times (visit window)	Informed consent	Screening[17] Day -37 ～ -8	Pre-treatment of observation period Day -7 ～-1 (±3)	Day1 Baseline	Week1 Day 8 (±3)	Week2 Day 15 (±3)	Week4 Day 29 (±7)	Week8 Day 57 (±7)	Week12 Day85 (±7)	Week16 Day 113 (±7)	Week 20 Day 141 (±7)	Week 24 Day 169 (±7)	Week 28 Day 197 (±7)	Week 32 Day 225 (±7)	Week 36 Day 253 (±7)	Week 40 Day 281 (±7)	Week 44 Day 309 (±7)	Week 48 Day 337 (±7)	At withdrawal[16]
Visit Number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Written informed consent	X																		
Eligibility confirmed		X	X	X															
Demographics		X		X															
Randomization[1]				X															
Study drug SC administration[2]				X			X	X	X	X	X	X	X	X	X	X	X		
Administration of naproxen										←								→	
Delivery of naproxen										X	X	X	X	X	X	X	X		
Return of naproxen											X	X	X	X	X	X	X	X	X
Delivery of acetaminophen			X	X		X	X	X	X	X	X	X	X	X	X	X	X		
Return of acetaminophen/check of amount taken[3]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[Efficacy]																			
NRS (average daily pain)[4]			X	←						→									
WOMAC[5]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA of OA		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36				X			X	X		X		X		X		X		X	X
EQ-5D-5L				X			X	X		X		X		X		X		X	X
[Safety]																			
Body weight (height: only at screening)		X								X								X	X
Vital signs[6]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X																X	X
Physical examination		X										X		X				X	X
Orthostatic blood pressure		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site assessment (30 minutes after administration)				X			X	X	X	X	X	X	X	X	X	X	X		
Joint Pain Questionnaire		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Autonomic Nerve Questionnaire		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological evaluation		X		X (brief version)		X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X	X
Radiology (bilateral knees, hips, shoulders)[7]		X								X								X	X
MRI testing (evaluated joint, contralateral joint, knee or hip joints with K-L ≥ 3)[7]		X																	
MRI testing (joint of joint replacement surgery)																			X
Adverse events		←																→	X
At joint pain worsening (imaging [X-ray, MRI] assessments)[8]					←													→	X
JOA Score[9]																			X
Laboratory testing[10]		X		X			X	X	X	X		X		X		X		X	X
Pregnancy test (for WOCBP)[11]		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Bone density[12]		X	X															X	X
Urinalysis		X		X						X		X						X	X
[Pharmacokinetics]																			
PK measurements				X[15]	X	X	X[15]	X[15]	X[15]	X[15]		X[15]		X[15]		X[15]	X[15]	X	X
ADA antibody				X[15]						X[15]		X[15]						X	X
[Other]																			
[redacted]				X															

(2) Test/Observation Schedule of post-treatment observation period (if a joint replacement procedure is not going to be performed)

	Post-treatment observation period (20 weeks)[14]					
	Week 52	Week 56	Week 60	Week 64	Week 68	At withdrawal[16]
Visit times (visit window)	Day 365 (±7)	Day 393 (±7)	Day 421 (±7)	Day 449 (±7)	Day 477 (±7)	
Visit Number	18	19	20	21	22	
Written informed consent						
Eligibility confirmed						
Demographics						
Randomization[1]						
Study drug SC administration[2]						
Administration of naproxen						
Delivery of naproxen						
Return of naproxen						
Delivery of acetaminophen						
Return of acetaminophen/check of amount taken[3]						
Concomitant medications	X	X	X	X	X	X
[Efficacy]						
NRS (average daily pain)[4]						
WOMAC[5]	X		X		X	X
PGA of OA	X		X		X	X
SF-36					X	X
EQ-5D-5L					X	X
[Safety]						
Body weight (height: only at screening)					X	X
Vital signs[6]	X				X	X
ECG						
Physical examination					X	X
Orthostatic blood pressure	X				X	X
Injection site assessment (30 minutes after administration)						
Joint Pain Questionnaire	X				X	X
Autonomic Nerve Questionnaire	X				X	X
Neurological evaluation	X (brief version)				X	X
Radiology (bilateral knees, hips, shoulders)[7]					X	X
MRI testing (evaluated joint, contralateral joint, knee or hip joints with K-L ≥ 3)[7]						
MRI testing (joint of joint replacement surgery)						X
Adverse events	←	—	—	—	→	X
At joint pain worsening (imaging [X-ray, MRI] assessments)[8]	←	—	—	—	→	X
JOA Score[9]						X
Laboratory testing[10]					X	X
Pregnancy test (for WOCBP)[11]	X				X	X
Bone density[12]						
Urinalysis					X	X
[Pharmacokinetics]						
PK measurements	X	X			X	X
ADA antibody					X	X
[Other]						
[redacted]						
[redacted]						

1) Subjects will be randomized (enrolled at the start of the treatment period) after all of the assessments through the pre-treatment observation period have been completed.
2) Investigational drug or comparative drug will be administered subcutaneously after all of the safety assessments, efficacy assessments, and collection of blood samples for pharmacokinetic assessments have been completed, and subjects will be kept under supervision at the study site for 30 minutes after the administration of the study drug.
3) The dose of acetaminophen taken will be checked based on the treatment diary. Every night, subjects will record in their treatment diaries the amount (number of tablets) of acetaminophen they took that day.
4) Every night (and as a rule at the same time) from the start of the pre-treatment observation period until Week 16, subjects will use the IVRS to report the mean pain on walking for the previous 24 hours (NRS data). Subjects will receive instruction in how to use the IVRS on the day of the visit at the start of the pre-treatment observation period.
5) The WOMAC score at screening will be assessed for the right knee joint, the left knee joint, the right hip joint, and the left hip joint, and the evaluated joint will be determined based on the WOMAC pain subscale scores. At the other time points, the WOMAC score will be assessed for the evaluated joint only.
6) If the pulse is less than 45 bpm at an assessment time point after investigational drug or comparative drug administration, electrocardiography will be performed and the patient carefully examined for cardiac function abnormalities.
7) Screening:
The following imaging tests will be performed for subjects who meet the study eligibility criteria, and the images will be submitted to a central laboratory. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted.
   - X- ray tests: Both knee joints, both hip joints, both shoulder joints
   - MRI tests: The evaluated joint, the joint opposite the evaluated joint, and any knee or hip joints with a K-L grade of 3 or more

   MRI tests will be performed as needed by the (sub)investigator.
   A check will be performed by the day specified below to make sure that the results of the central assessments meet the study enrollment criteria.
   - X-ray tests: By the start of the pre-treatment observation period
   - MRI tests: By baseline

   If the results of the central assessments cannot be confirmed by the specified day, then re-screening will be performed.
   Baseline and after baseline:
   At week 16, 48 (or at the early termination of the treatment period) and at 68 weeks (or at the early termination of the post-treatment observation period), images will be submitted to the central laboratory.
   If the (sub)investigator determine that there is an abnormal finding compared to normal osteoarthritis, MRI tests will be performed as needed. The images will be submitted to a central laboratory. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted, and the images submitted to the central laboratory(for more detailed information, see in the text "9.2.4.1.11 Imaging Tests").
   Week 16:
   The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator. The (sub)investigator will check the X-ray images before administered the investigational drug or comparative drug to determine whether or not investigational drug or comparative drug should be administered. If any abnormalities are found, investigational drug or comparative drug administration will be postponed. If the central laboratory rules out adjudicated arthropathy, investigational drug or comparative drug administration will be resumed.
   Assessment at the early termination of the treatment period and the early termination of the post-treatment observation period
   The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator. The images will be submitted to a central laboratory. If more than 30 days have passed since the last images were taken, images will be taken again. If not more than 30 days have passed, imaging tests will be performed if the (sub)investigator determines that it is necessary.
   If joint replacement surgery is required, the MRI tests of the joint of surgery will be performed (for more detailed information, see in the text "9.2.4.1.13 Assessments if a Joint Replacement Procedure Is Scheduled").

8) If a subject experiences a sudden worsening of pain that would not occur in the normal course of osteoarthritis, the

(sub)investigator will postpone investigational drug or comparative drug administration, and perform imaging test (X-ray and MRI) of the affected joint. Imaging test (X-ray and MRI) of other joints will be performed as needed by the (sub)investigator. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted. All images will be submitted to the central laboratory. The results of the central assessment will be checked by the (sub)investigator. The investigational drug or comparative drug administration will be postponed until the central laboratory rules out adjudicated arthropathy. If the result of the central assessment is adjudicated arthropathy, then study treatment must be discontinued. If adjudicated arthropathy is ruled out by the central assessment, the (sub)investigator will determine whether or not study treatment should be continued.

9) Assessmets of the joint by JOA score at discontinuation will be performed for subjects who required joint replacement surgery during the study.

10) Hematology and blood biochemistry tests will be performed. HbA1c, HBs antigen, HBs antibody, HCV antibody, and HIV antibody will be measured only at screening.

11) At screening, the pregnancy test will be performed using serum. At all other time points, the pregnancy test will be performed using urine. Furthermore, pregnancy tests will not be performed for postmenopausal females who have been amenorrheic for at least 1 year or for females who have undergone a surgical hysterectomy or bilateral ovariectomy. If a positive result is obtained on a urine pregnancy test, a serum pregnancy test will be performed. If a negative result is obtained on a serum pregnancy test, the study can be continued for the patient. If the serum pregnancy test is also positive, study treatment will be discontinued.

12) Bone density will be measured only at those study sites that are capable of performing measurements using the DEXA method. If it can not be measured at screening priod, it may be measured during the pre-treatment observation period.

[redacted]

14) The Week 64 assessments may be performed by telephone.

15) The blood samples will be collected before the investigational drug or comparative drug is administered.

16) In the case of early termination of the treatment period, follow-up evaluation of the same item as at the time of visit of the corresponding completed subjects below is carried out 4, 8, 12, 16, 20 and 24 weeks after the last dose of the investigational drug or comparative drug. However, blood sample collection for pharmacokinetic evaluation is performed only 24 weeks after the last dose (blood sampl collection for PK measurement is not necessary 4, 8 and 12 weeks after the the last dose corresponding to treatment period 48, 52 and 56 weeks of the completed subjects). The visit window at each evaluation time point is plus or minus 7 days.

Early termination of the treatment period	4 weeks after the last dose	8 weeks after the last dose	12 weeks after the last dose	16 weeks after the last dose	20 weeks after the last dose	24 weeks after the last dose	the early termination of the post-treatment observation period
Completed of the treatment period	Week 48	Week 52 週	Week 56 週	Week 60 週	Week 64 週	Week 68 週	the early termination of the post-treatment observation period

When assessments at discontinuation is included in visit window of each assessment time point, the same ones as those normally assessed at discontinuation. After assessment at discontinuation, the same ones as those normally assessed at the last dose of investigational drug or comparative drug.

If more than 30 days have passed since the last images were taken, images will be taken again. If not more than 30 days have passed, imaging tests will be performed if the (sub)investigator determines that it is necessary.

The tests at discontinuation and post-joint replacement procedure test/observation will be performed for subjects who required joint replacement surgery during the study. The all images will be submitted to a central laboratory (for more detailed information, see "10 (3) Post-joint replacement procedure test/observation schedule). If the assessments at discontinuation are not performed before the joint replacement procedure is performed, then images from before the procedure will be obtained and sent to the central laboratory.

17) The screening period is from "the screening start date" to the day before "the pre-treatment of observation period start date", and the screening start date and the end date are defined along with the allowable range of "the pre-treatment of observation period" (for example, when the pre-treatment of observation period is 4 days, The maximum screening period is 30 days from Day - 34 to Day - 5, the pre-treatment of observation period is 10 days, the screening period is the maximum from Day - 40 to Day - 11).

At each study visit after the baseline date, the assessments that are performed by the subjects

themselves (WOMAC, PGA, joint pain survey, SF-36, EQ-5D-5L, survey of autonomic symptoms) will be performed before all of the other assessments (including the assessments that are performed by the (sub)investigator) (except for cases where imaging tests are performed on a different day).

(3) Post-joint replacement procedure test/observation schedule

Follow-up day (visit window)	After surgery[1]	Long-term[1]
	Follow-up survey, 4 weeks post-operative	Follow-up survey 2, 20 weeks post-operative
	29 days post-operative (±5 days)	141 days post-operative (±7 days)
Concomitant medications	X	X
[Safety]		
Vital signs	X	X
Joint Pain Questionnaire	X	X
JOA score[2]	X	X
Radiology (bilateral knees, hips, shoulders)	X	X
Adverse events	←	→
At joint pain worsening (imaging [X-ray, MRI] assessments)3	←	→

1) Information about the procedure, including prosthesis replacement and/or the extent of surgery wound healing, will be collected.
2) The condition of the joint following joint replacement surgery will be assessed using the JOAScore.
3) If a sudden worsening of pain that does not occur in the normal progression of osteoarthritis occurs, the (sub)investigator will perform imaging test (X-ray and MRI) of the affected joint. Imaging test (X-ray and MRI) of other joints will be performed as needed by the (sub)investigator. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted. All images will be submitted to the central laboratory.

1. Background for the Study Plan, and Other Background Information

(1) Target Disease and Therapies Therefor

Osteoarthritis is a progressive, chronic disease that occurs through the breakdown and loss of joint cartilage and that results in pain in the hip joints, knees, hands, feet, and spine. Osteoarthritis is characterized by the loss of joint cartilage in a synovial joint, and is associated with deformation of the subchondral bone, spur formation at the joint periphery, thickening of the joint capsule, and mild local synovitis. The incidence of symptoms and impairment increases with age,[1),2)] and in Japan osteoarthritis is the most common joint disease. Osteoarthritis of the knee is a typical locomotive syndrome disease that has been estimated to afflict around 25.3 million people, 8 million of whom are symptomatic.[3)] It is expected that the prevalence of osteoarthritis will continue to increase further in the future as the Japanese population becomes increasingly elderly overall.

In Japan, the Japanese Orthopaedic Association issued revised osteoarthritis of the knee guidelines in 2015,[4)] and revised osteoarthritis of the hip guidelines in 2016.[5)] These guidelines state that acetaminophen can be used as an oral painkiller in the treatment of mild to moderate osteoarthritis of the knee, and is affective for the short-term alleviation of the pain of OA of the hip. However, the guidelines state that if acetaminophen is insufficiently effective or if the pain and/or inflammation are severe, then consideration should be given to switching the patient to some other drug therapy, taking into account efficacy and the types of adverse drug reactions. In Japan, however, acetaminophen is not prescribed very frequently for OA: the prescribing rate is 4% (internal company IMS survey data).

In mild to moderate osteoarthritis, NSAIDs are a mainstay of therapy. Although there is sufficient evidence of their efficacy, it is also clear that their use is accompanied by safety risks.[6),7),8),9),10),11)] An increased risk of gastrointestinal bleeding and cardiovascular events are known risks of the long-term use of NSAIDs,[12),13)] and the routine use of NSAIDs is contraindicated in some patients, such as patients with hypertension or kidney or GI complications. The guidelines therefore specify that the minimum effective dose of NSAIDs should be used, and that long-term use should be avoided whenever possible.

If other drugs are ineffective or contraindicated, and the patient complains of severe pain, the use of a weak opioid may be considered. However, the limitation of opioids is that they result in many adverse events, and patients may experience acute or chronic adverse drug reactions, including nausea, constipation, dizziness, and vomiting. It has been pointed out, regarding the use of opioids in the elderly, that adverse events such as sleepiness, dizziness, gastrointestinal tolerance, and motor disequilibrium, which only have a minor impact on young patients, have the potential to have a major impact on elderly patients, and the opioid toleration profile is extremely important in the elderly.[14)] The guidelines state that because of these adverse events, although opioids are effective for pain relief in the short term, their use requires caution. The osteoarthritis of the knee guidelines state that strong opioids should not be used for pain relief except in special cases, and the osteoarthritis of the hip guidelines exclude opioids from their list of recommended drugs.[5)]

Although the recommendation levels of some drugs, such as hyaluronic acid and steroid intraarticular injections of the Western OARSI guidelines[15)] are different from those in the Japanese guidelines, the Japanese and overseas guidelines are generally consistent in their recommendations of the drugs and therapies that should be used.[16)]

Not only in the West, but in Japan as well, therapies that can be used in patients who cannot tolerate or receive inadequate pain relief from existing therapies, such as NSAIDs and opioids, and that have fewer adverse reactions and afford greater pain relief than existing therapies are

in great demand.

(2) Name and description of the investigational drug

MT-5547 (fasinumab) is a fully human antibody that was discovered by Regeneron (anti-human NGF antibody; Regeneron investigational ingredient code: REGN475) and that is being developed in the West for the treatment of chronic pain in patients with osteoarthritis or chronic low back pain. Mitsubishi Tanabe Pharma acquired the development rights in Japan for fasinumab from Regeneron, and is planning to develop MT-5547 for the pain of osteoarthritis and chronic low back pain.

Nerve growth factor (NGF) was originally identified as a factor that is essential for the development, growth, and maintenance of function of sensory and sympathetic nerves. In recent years, it has become clear that NGF is intimately involved with chronic pain (e.g., inflammatory/neurogenic pain).[17] Fasinumab is a fully human IgG4P monoclonal antibody that binds specifically to mature NGF and proNGF. In MT-5547, to stabilize the dimer formation, the serine residue of the IgG4 hinge sequence has been replaced with a proline residue (S228P), resulting in the same sequence as the IgG1 hinge sequence (CPPC),[18] which is therefore denoted as IgG4P. Fasinumab blocks NGF signaling mediated by tyrosine kinase type 1 receptors and p75 receptors. It is believed that by selectively blocking NGF fasinumab will be effective in patients who receive inadequate pain relief from existing analgesics and patients who either cannot tolerate or are not eligible for treatment with existing analgesics.

(3) Nonclinical study results and clinical results

[redacted]

1)

(a)

[redacted]

(b)

[redacted]

(c)

[redacted]

2) Clinical studies

To date, overseas, three phase 1 studies have been completed in healthy adults, a phase 2a study has been completed in patients with knee osteoarthritis, and a phase 2/3 study has been completed in patients with knee or hip osteoarthritis. In the phase 2/3 study in chronic low back pain dosing was terminated when the study was placed on partial clinical hold. A decision was made not to resume enrollment or dosing in this study. Rather, patients already enrolled in the study continued with study visits per the protocol but without further dosing in those patients who had not received all study doses at the time of the partial clinical hold. Three phase 3 study (R475-PN-1523 , R475-PN-1611 and R475-PN-1688) for pain of osteoarthritis of the knee or hip and a Phase 3 study (R475-PN-1612) for CLBP in patients who also have osteoarthritis of the knee or hip, are underway. Patients currently enrolled in study R475-PN-1612 will not have dosing resumed but will be encouraged to complete the study visits in the follow-up period. A list of the clinical studies is presented in Table 1.

In April 2018, the fasinumab IDMC recommended that high dose groups (the 3 mg q4w and 6 mg q8w groups) should be discontinued from all ongoing studies. The recommendation was based on their review of unblinded data from study R475-PN-1523, where they observed an imbalance in clinically relevant adverse events (AEs) including time to total joint replacement, peripheral edema, arthralgia and a trend towards early fractures. According to the recommendation, the sponsor for overseas studies (Regeneron) removed the 3 mg q4w and 6 mg q8w groups from ongoing studies and discontinued further study treatment to the subjects who were randomized to these groups. Also, the protocols for ongoing studies have been amended to increase the number of subjects on 1 mg q8w group (add new 1mg Q8W group in R475-OA-1611; increase number of subjects on 1 mg q8w/1 mg q4w/placebo groups in R475-PN-1523).

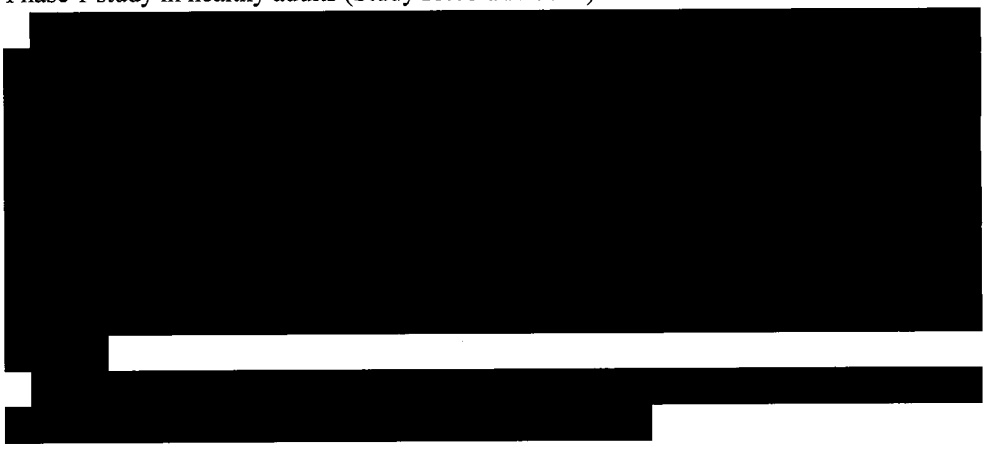
Table 1: List of Clinical Studies

Study	Phase Design	Dosing Regimen and Treatment Period	Number of Subjects	Objectives
Clinical Pharmacology Study REGN475-PN-0817 (US)	P1 Double-blind, placebo-controlled	[redacted]	[redacted]	[redacted]
Clinical Pharmacology Study TDU11480 (US)	P1b Double-blind, placebo-controlled	[redacted]	[redacted]	
Exploratory Study| R475-PN-0901 (US)	P2a Double-blind, placebo-controlled	IV: 0.03, 0 1, 0.3 mg/kg q8w, Placebo q8w, Treatment period: 8 weeks	Fasinumab: 160 Placebo: 55	Pharmacokinetics, safety, and efficacy against pain when repeated doses are administered to patients with knee osteoarthritis
Exploratory Study R475-PN-0908 (US)	P2a Double-blind, placebo-controlled	SC: 0.1, 0.3 mg/kg Placebo, single-dose	Fasinumab: 108 Placebo: 51	Pharmacokinetics, safety, and efficacy against pain when single doses are administered to patients with sciatic nerve pain
Exploratory Study ACT11308 (US)	P2a Double-blind, placebo-controlled	IV: 0.3 mg/kg Placebo, single-dose	Fasinumab: 21 Placebo: 20	Pharmacokinetics, safety, and efficacy against pain when single doses are administered to patients with spinal fractures
Exploratory Study ACT11286 (US)	P2a Double-blind, placebo-controlled	[redacted]	[redacted]	[redacted]
R475-PN-1227 (US)	P2/3 Double-blind, placebo-controlled	SC: 1, 3, 6, 9 mg q4w Placebo q4w Treatment period: 12 weeks	Fasinumab: 338 Placebo: 83	Pharmacokinetics, safety, and efficacy against pain when repeated doses are administered to patients with pain associated with knee or hip osteoarthritis
R475-PN-1516 (US)	P1b Double-blind, placebo-controlled	[redacted]	[redacted]	[redacted]
R475-PN-1523 [4] Ongoing (North America, South America, South Africa, Hong Kong, Europe)	P3 Double-blind, placebo-controlled	SC: 1 mg q8w, 1 mg q4w, 3 mg q4w [2], 6 mg q8w [2], Placebo q4w Treatment period: 48 weeks	7000 max (including around 1000 in an efficacy substudy)	Long-term safety in patients with pain associated with knee or hip osteoarthritis Trial contains a 1000 patient efficacy substudy in patients with OA of the knee or hip.
R475-PN-1524 [1]	P2/3 Double-blind, placebo-controlled	SC: 6, 9 mg q4w IV: 9 mg q8w Placebo q4w Treatment period: 12 weeks	Fasinumab: 422 Placebo: 141	Pharmacokinetics, safety and efficacy against pain when repeated doses are administered to patients with chronic low back pain
R475-PN-1611 On going (North America, Europe)	P3 Double-blind, naproxen-controlled, placebo-controlled	SC: 1 mg q4w, 1 mg q8w [5], 3 mg q4w [2], 6 mg q8w [2] Naproxen Placebo Treatment period: 48 weeks	Fasinumab: 2520 Naproxen: 840 Placebo: 280	Pharmacokinetics, safety and efficacy in patients with pain associated with knee or hip osteoarthritis
R475-PN-1688 On going (North America, Europe)	P3 Double-blind, diclofenac-controlled, celecoxib-controlled placebo-controlled	SC: 1 mg q4w 3 mg q4w [2], 6 mg q8w [2] Diclofenac Celecoxib Placebo Treatment period: 48 weeks	Fasinumab: 1800 Diclofenac: 300 Celecoxib: 300 Placebo: 300	Pharmacokinetics, safety and efficacy in patients with pain associated with knee or hip osteoarthritis
R475-PN- 1612 On going (North America, Europe)	P3 Double-blind, placebo-controlled	SC: 3 mg q4w [2] Placebo [3] Treatment period: 16 weeks	Fasinumab: 510 Placebo: 510	Pharmacokinetics, safety and efficacy against pain when repeated doses are administered to patients with non-radicular chronic low back pain and OA of the knee or hip

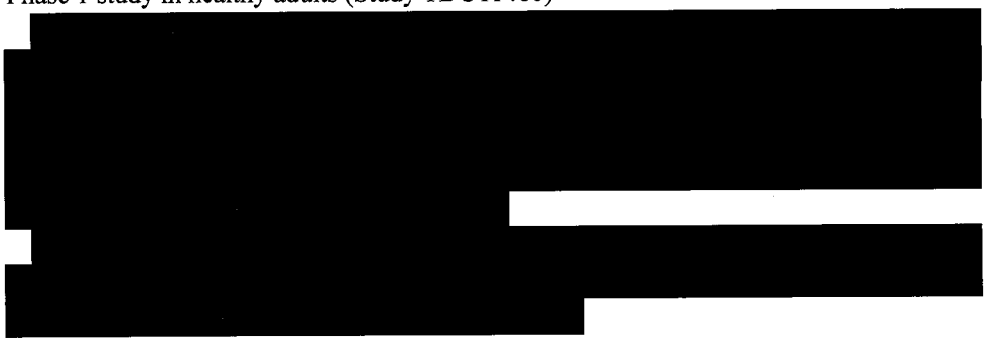
1) In October 2016, the FDA put a partial clinical hold on this study and all study treatments was terminated.
2) In May 2018, based on recommendations from the IDMC, the 3 mg q4w and 6 mg q8w groups were removed.
3) In the R475-OA-1612, all study treatments including 3 mg q4w and placebo were discontinued
4) In the R475-PN-1523, recruitment continued with increasing number of subjects on 1 mg q8w/1 mg q4w/placebo groups

5) In the R475-OA-1611, new 1mg Q8W group was added.

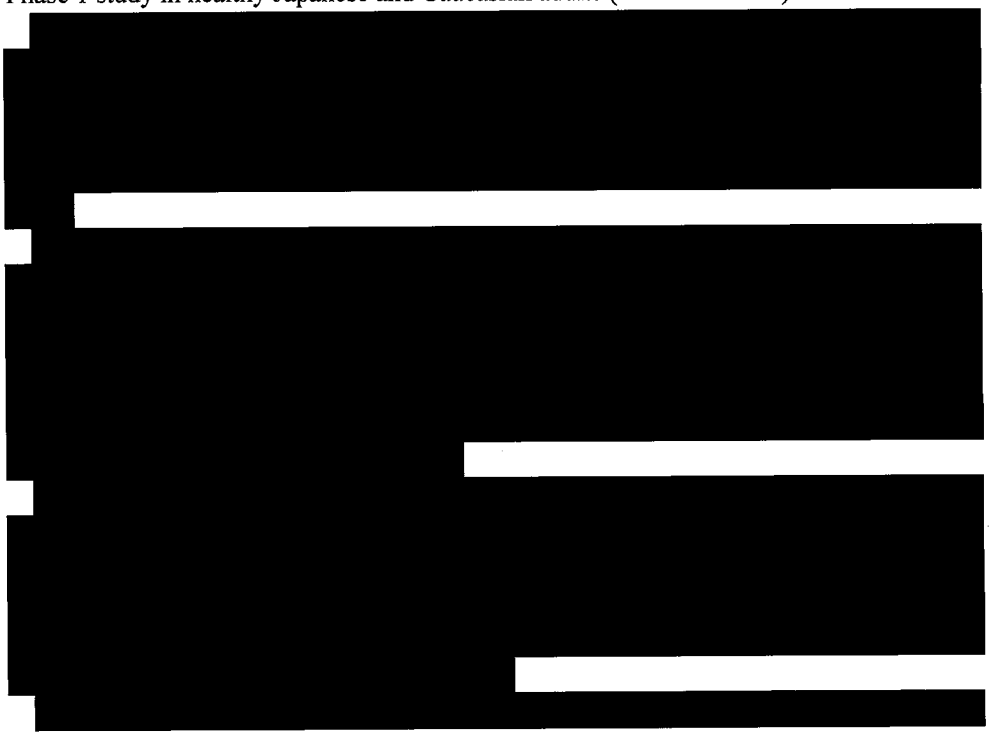
(a) Phase 1 study in healthy adults (Study R475-PN-0817)



(b) Phase 1 study in healthy adults (Study TDU11480)



(c) Phase 1 study in healthy Japanese and Caucasian adults (R475-PN-1516)



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(d) Phase 2a study in patients with knee osteoarthritis (Study R475-PN-0901)

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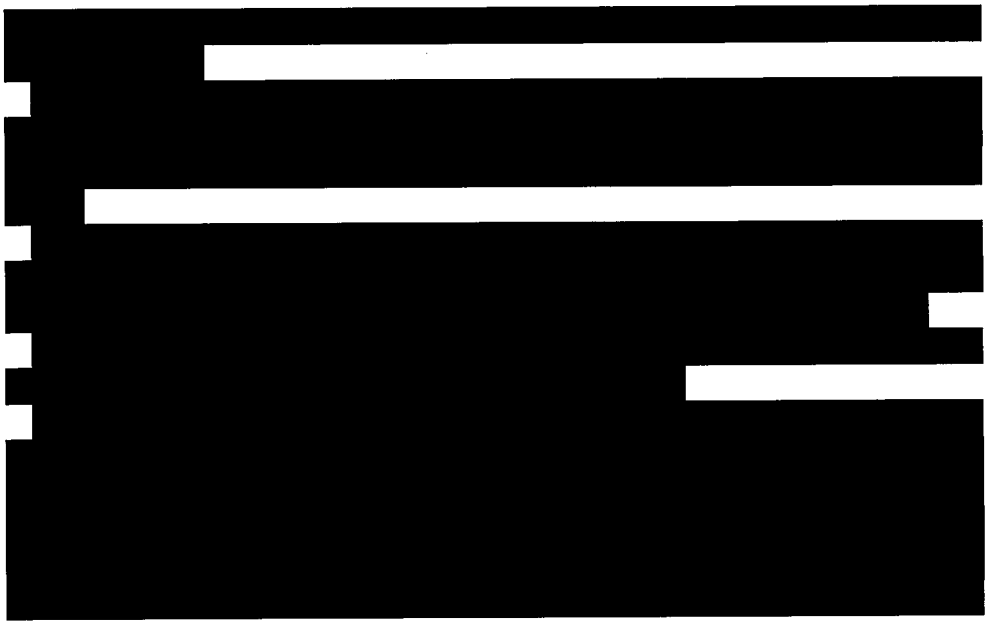
(e) Phase 2/3 study in knee osteoarthritis or hip arthrosis (Study R475-PN-1227)

[redacted]



(f) Study of long-term safety in knee osteoarthritis or hip arthrosis (Study R475-PN-1523)

In April 2018, the IDMC recommended discontinuation of the 3 mg q4w and 6 mg q8w groups from all ongoing studies. The recommendation was based on their review of unblinded data from study R475-PN-1523, where they observed an imbalance in clinically relevant adverse events (AEs) including time to total joint replacement, peripheral edema, arthralgia and a trend towards early fractures in the 6 mg q8w group. According to the recommendation, the 3 mg q4w and 6 mg q8w groups were removed. Then, the study increases number of subjects on 1 mg q8w/1 mg q4w/placebo groups.

(4) Plans for this study

Overseas, MT-5547 is being developed in osteoarthritis patients who receive insufficient pain relieve from existing analgesics, or who cannot tolerate or are ineligible for treatment with existing analgesics. In Japan as well, there is considerable unmet need in this patient population, and new therapies need to be developed. The applicant therefore decided to investigate the efficacy, safety, and pharmacokinetics of MT-5547 in Japanese osteoarthritis patients, and initiated this study with 1 mg q4w, 3 mg q4w, 6 mg q8w and placebo control groups.

The IDMC has been organized for this study, which has a role to make recommendation to the sponsor such as protocol amendment and/or study continuation/discontinuation. The IDMC will monitor not only this study but also all ongoing overseas studies including three studies in patients with osteoarthritis (R475-PN-1523, R475-OA-1611 and R475-OA-1688) and a study in patients with chronic low back pain (R475-PN-1612), and will make recommendations to the sponsor based on global data. As mentioned above, the IDMC was held in April 2018 and it recommended discontinuation of high dose regimens (3mg q4w and 6mg q8w) in all ongoing studies. According to the recommendation, the 3 mg q4w and 6 mg q8w groups were removed from this study. Also, a new 1 mg q8w group was added to investigate minimum effective dose in Japanese subjects (Protocol Ver 04.00.00000).

2. Study Objectives

The objective of this study is to verify the superiority of 16 weeks of MT-5547 treatment to placebo, as evidenced by the WOMAC pain score (the efficacy outcome measure), in patients with osteoarthritis of the knee or hip. Additional objectives of the study are to investigate the efficacy, safety, and pharmacokinetics of MT-5547 in long-term use.

3. Target Patient Population

3.1 Target Patient Population

Patients with moderate to severe pain associated with osteoarthritis of the knee or hip

3.2 Inclusion Criteria

Patients who satisfy all of the following inclusion criteria and have the capacity to consent to study participation will be eligible to participate in the study.

Inclusion Criteria at the Start of Screening

(1) Patients who have received a thorough explanation of participation in this study and who have freely given their written consent to participate in the study.
(2) Outpatients
(3) Japanese patients ≥40 and ≤85 years of age at the time written informed consent is obtained. Japanese patients will be considered patients whose biological parents are both Japanese.
(4) Patients who have been diagnosed with osteoarthritis of the knee or hip based on the American College of Rheumatology (ACR) criteria*. (see Attachment 1, "Osteoarthritis Diagnosis Guidelines") * Confirmation diagnosis based on the ACR criteria may be carried out during the screening period.
(5) Use of existing drug therapy for OA for at least the past 3 months from the start of screening period.
(6) Regular use of oral analgesic medications for OA (taken an average of 4 days or more per week for 4 or more weeks prior to screening), including NSAIDs, opioids, acetaminophen, or combinations thereof.

Inclusion Criteria at the Start of the Pre-treatment Observation Period

Patients who were confirmed to be suitable for study participation during the screening period and who satisfy all of the following inclusion criteria at the start of the pre-treatment observation period.

(7) Patients with an evaluated joint* (knee or hip) with a K-L (Kellgren-Lawrence) score of ≥2 based on the X-ray test performed at screening (centralized assessment).

*Evaluated joint

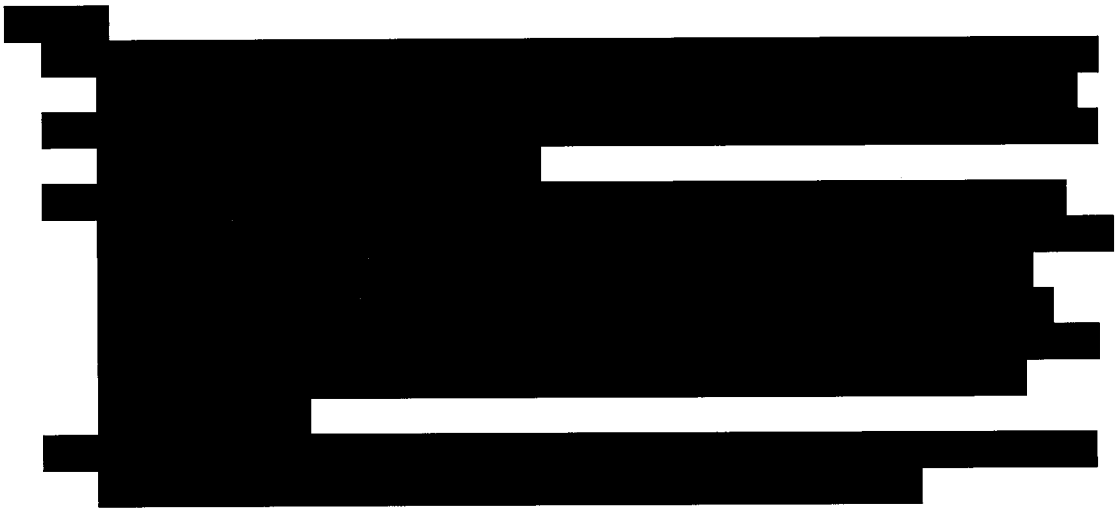
The evaluated joint will be a joint for which joint replacement or some other surgical procedure is not being performed (one of the right knee, left knee, right hip, or left hip). If the K-L score is ≥2 in more than 1 joint, the evaluated joint is the joint with the greater WOMAC pain score (average of the 5 items) at screening. If 2 or more joints have a K-L score of ≥2 and the same WOMAC pain score, the evaluated joint is the joint with the greater K-L score. If multiple joints have identical K-L grades and WOMAC pain scores, then the (sub)investigator will determine which joint should be evaluated.

(8) Moderate to severe pain in the evaluated joint, defined as a WOMAC pain score of ≥4 (mean of the 5 items), on the WOMAC assessments performed at screening

(9) Patients who satisfy both 1) and 2) below.
   1) Inadequate osteoarthritis pain relief from at least 1 oral NSAID.
   2) Intolerance to or inadequate osteoarthritis pain relief from at least 1 opioid (including combination drugs), or unwillingness to take opioid therapy
(10) Patients who agree to not change their current lifestyle (daily living activities and exercise) throughout the study.
(11) Patients who are able to complete post-operative follow-up for any joint replacement surgery that is performed during the study
(12) Body mass index at screening ≤39
(13) Patient who are able to understand and answer endpoint questions used in the study.

Inclusion Criteria at Baseline

(14) Moderate to severe pain in the evaluated joint, defined as a WOMAC pain score of ≥4 (mean of the 5 items), on the WOMAC assessments performed at baseline.



3.3 Exclusion Criteria

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

Exclusion Criteria at Screening

(1) Presence of symptoms of carpal tunnel syndrome within 6 months before screening.
(2) Any of the following intra-articular injections of hyaluronic acid.
   1) An intra-articular injection of sodium hyaluronate (average molecular weight 500,000 to 1,200,000; trade names: ARTZ, ARTZ Dispo; including generics) in any joint within 2 weeks prior to screening.
   2) An intra-articular injection of sodium hyaluronate (average molecular weight: 1,500,000 to 3,900,000; trade names: Suvenyl Dispo 25 mg, Suvenyl Vial 25 mg; including generics) in any joint within 4 weeks prior to screening.
   3) An intra-articular injection of sodium hyaluronate crosslinked polymer/sodium hyaluronate crosslinked polymer crosslinked with vinyl sulfone (trade name: Synvisc 2 mL) within 13 weeks prior to screening.
(3) Systemic (excluding topical, intranasal, ophthalmic, and inhaled formulations) corticosteroids within 4 weeks prior to screening.

(4) Use of a monoamine reuptake inhibitor (e.g., tricyclic antidepressant, SSRI, SNRI) for the treatment of pain within 4 weeks prior to screening.
(5) History of transient cerebral ischemic attack or cerebrovascular disorder within 12 months prior to screening, or history of myocardial infarction or acute coronary syndrome within 6 months prior to screening.
(6) New major illness diagnosed within 2 months prior to screening (Grade 3 in "Criteria for Seriousness of Adverse Reactions to Drugs, etc.").
(7) History of malignancy within 5 years prior to screening, except patients who have been treated successfully with no recurrence for ≥1 year of basal or squamous cell carcinoma of the skin or in situ cervical cancer.
(8) History of alcohol dependency, alcohol abuse, or drug or analgesic abuse within 5 years prior to screening.
(9) Participation in other studies and treatment with an investigational drug within 4 weeks or 5 half-lives of the investigational drug prior to the start of screening.
(10) MRI cannot be performed.
(11) Intolerance to naproxen.
(12) Presence of peptic ulcer or gastrointestinal bleed. History of peptic ulcer or gastrointestinal bleed and may recur during the study.
(13) Presence or history of aspirin asthma.
(14) History of hypersensitivity to oral NSAIDs.

Exclusion Criteria at the Start of the Pre-treatment Observation Period

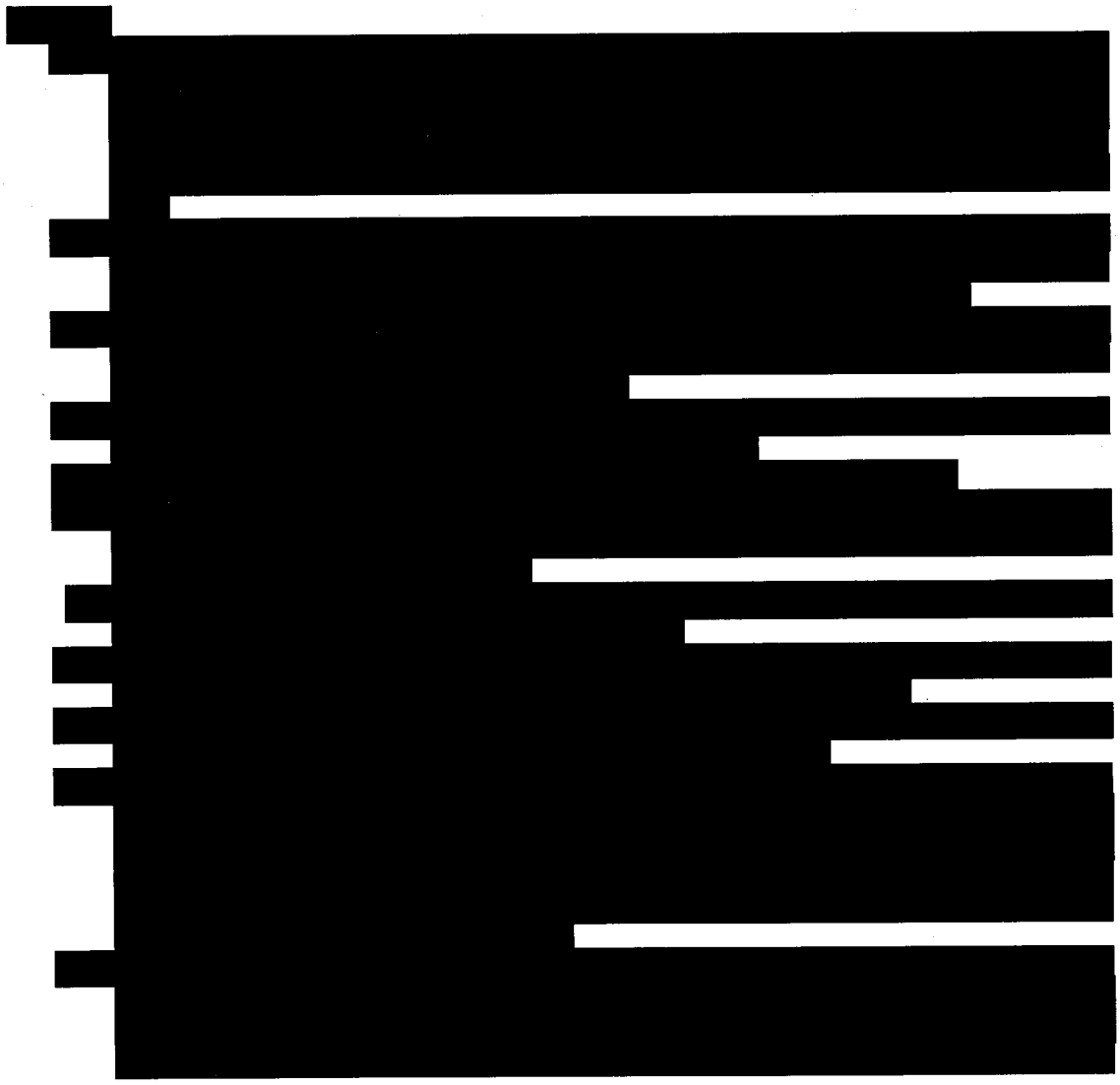
The subjects' eligibility for participation in the study will be checked during the screening period, and any patients meeting any of the following exclusion criteria at the start of the pre-treatment observation period will be excluded from the study. The check of eligibility will include a check of the results of the central assessments of the imaging tests (X-ray and MRI tests). However, if the MRI test results cannot be obtained by the start of the pre-treatment observation period, then the eligibility of the patient for the study will be confirmed by baseline (for details, see "9.1.1 Test/Observation Schedule" and "9.1.2 Re-screening").

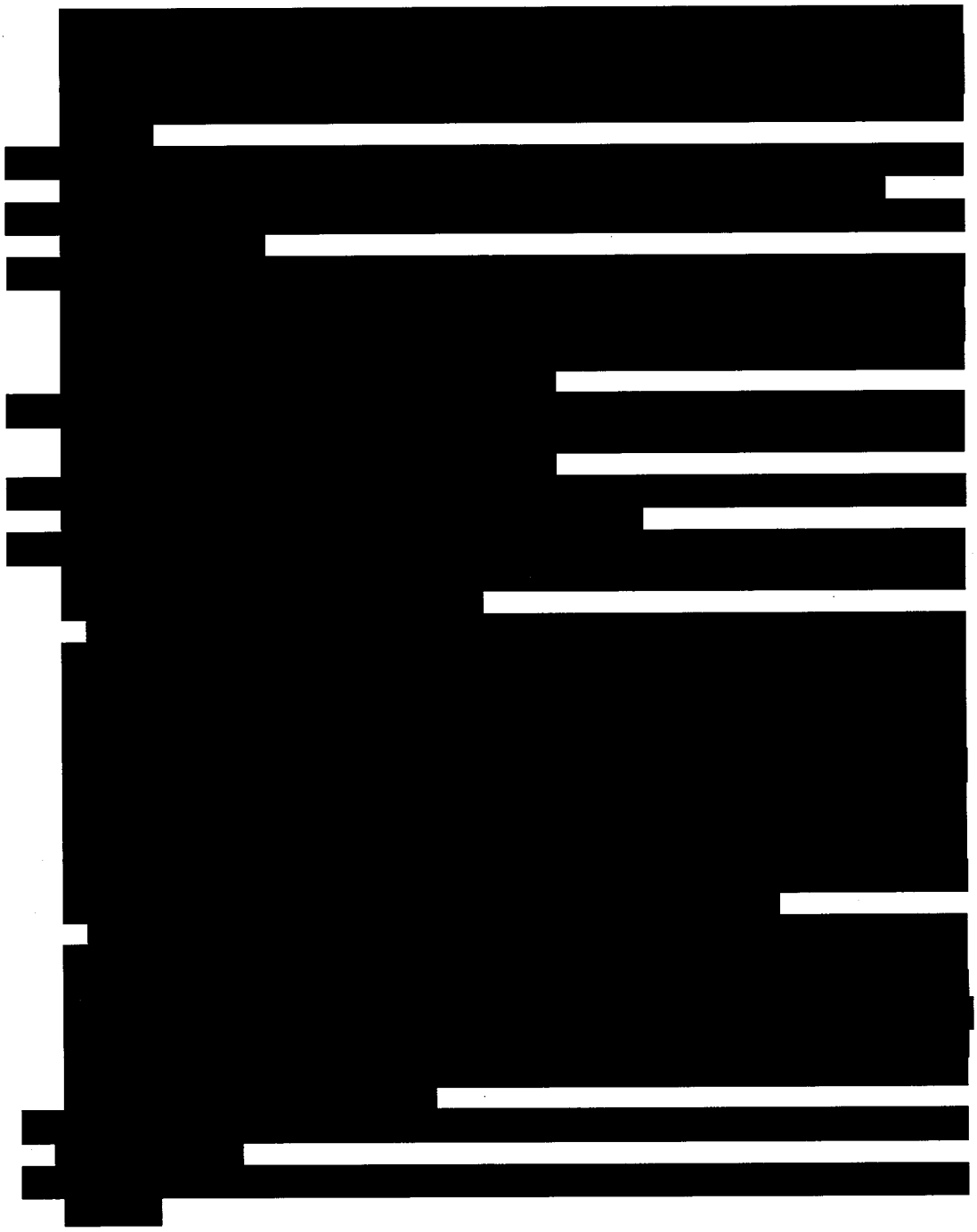
(15) Trauma to the evaluated joint within 3 months prior to screening (except for cases where no abnormal findings could be confirmed in images obtained at the time of the trauma).
(16) Presence or history of inflammatory joint diseases other than osteoarthritis (eg, rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, pseudogout, gout, spondyloarthropathy, joint infections within 5 years prior to screening), vertebral, pelvic, or femoral Paget's disease, multiple sclerosis, fibromyalgia, vertebral tumors or infections, or renal osteodystrophy.
(17) Presence or history, confirmed by imaging, of arthropathy (osteonecrosis, subchondral insufficiency fracture, rapidly progressive osteoarthritis type 1 or 2), neuropathic joint arthropathy, hip dislocation (except for artificial hip dislocation or developmental hip dislocation), knee dislocation (except for patella dislocation), extensive subchondral cyst, marked bone destruction or bone loss, or pathologic fractures.
(18) Need or desire for joint replacement surgery during the study.
(19) History of sickle cell disease, including S-C disease and S-β thalassemia.
(20) Regional pain caused by lumbar or cervical compression with radiculopathy or other moderate to severe pain that may confound assessments of the pain associated with OA.
(21) Presence or history of autonomic neuropathy, diabetic neuropathy, or other peripheral neuropathy such as reflex sympathetic dystrophy at screening.
(22) Presence or history of chronic familial dysautonomia (pure autonomic failure, multiple system atrophy [Shy-Drager syndrome]).

(23) Autonomic neuropathy diagnosed in the assessment of autonomic nerve symptoms performed at screening (for details, see "9.2.4.1.7 Autonomic Nerve Assessments").
(24) Presence or history of orthostatic hypotension at the orthostatic hypotension assessments performed at screening (for details, see "9.2.4.1.8 Standing Blood Pressure Assessment").
(25) Surgical procedure (including joint replacement) scheduled during the term of the study.
(26) History of acetaminophen intolerance or hypersensitivity.
(27) Allergy or hypersensitivity to doxycycline or related compounds, or monoclonal antibodies.
(28) Inability to undergo the scheduled tests.
(29) Intra-articular corticosteroids in the evaluated joint within 12 weeks prior to screening, or in any other joint within 4 weeks prior to screening.
(30) Patients for whom the use of the prohibited concomitant medications cannot be prohibited (see Attachment 4, "List of Prohibited Concomitant Medications").
(31) Resting heart rate of <50 bpm or >100 bpm at screening.
(32) Presence or history of 2nd or 3rd degree heart block, 1st degree heart block with abnormal QRS, or bifascicular block by ECG assessment at screening.
(33) Presence of poorly controlled hypertension:
    1) Systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg at screening
    2) Systolic blood pressure of 160 mmHg to 179 mmHg or diastolic blood pressure of 100 mmHg to 109 mmHg on the screening tests, AND a history of organ damage (i.e., left ventricular hypertrophy, heart failure, angina, myocardial infarction, stroke, transient ischemic attack, peripheral arterial disease and moderate to advanced retinopathy [hemorrhages or exudates, papilledema]).
(34) Congestive heart failure with New York Heart Association (NYHA, 1994) Classification of stage III or IV.
(35) Poorly controlled diabetes (HbA1c >9.0%).
(36) ALT or AST ≥2.5 times ULN at screening.
(37) Concomitant psychiatric, cardiac, renal, hepatic, neurological, endocrinological, metabolic, or lymphatic disease (Grade 2 in "Criteria for Seriousness of Adverse Reactions to Drugs, etc.") that, in the opinion of the (sub)investigator, would adversely affect the patient's participation in the study, or some other significant concomitant illness (Grade 3 in "Criteria for Seriousness of Adverse Reactions to Drugs, etc.") (including serious blood disorders).
(38) Presence or history of ophthalmic herpes simplex, herpes simplex virus (HSV) pneumonia, or HSV encephalitis.
(39) Presence or history of human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection, except that patients with a history of hepatitis B are eligible if negative for HBs antigen and positive for HBs antibodies, and patients with a history of hepatitis C are eligible if the hepatitis C virus RNA test results are negative.
(40) Use of an anti-NGF antibody in the past, or apparent hypersensitivity or intolerance to anti-NGF antibodies.
(41) Women who are pregnant, breastfeeding, or may be pregnant (positive serum pregnancy test) women of childbearing potential for whom pregnancy test results are not available, or women of childbearing potential, or men with female partners of childbearing potential, who are unwilling to use contraception during the study and for 20 weeks after the last dose of investigational drug or comparative drug.
(42) Patients otherwise judged by the (sub)investigator to be unsuitable for the study.

Exclusion Criteria at Baseline

(43) Autonomic neuropathy diagnosed in the assessment of autonomic nerve symptoms performed at baseline (for details, see "9.2.4.1.7 Autonomic Nerve Assessments").
(44) Orthostatic hypotension found at the orthostatic hypotension assessments performed at baseline (for details, see "9.2.4.1.8 Standing Blood Pressure Assessment").
(45) Resting heart rate of <50 bpm or >100 bpm at baseline.
(46) Use of a prohibited concomitant medication during the pre-treatment observation period (see Attachment 4, "List of Prohibited Concomitant Medications").
(47) Women who may be pregnant based on a positive urine pregnancy test result, and women of childbearing potential for whom no pregnancy test results are available.
(48) Presence of adjudicated arthropathy by the central rater based on the MRI tests performed at screening.
(49) Patients who forget to input their NRS data (average pain on walking in the evaluated joint over 1 day) 4 or more times during the IVRS training in the pre-treatment observation period.
(50) Patients otherwise judged by the (sub)investigator to be unsuitable for the study (a check will be performed of the exclusion criteria that were checked in the screening period and pre-treatment observation period as well to ensure that there has been no change to these findings).





4. Explanation and Consent

4.1 Informed Consent Form and Subject Explanation Sheet Preparation

The principal investigator will with the help of the study sponsor prepare an explanation sheet and informed consent form. The explanation sheet/informed consent form will be prepared as a single, unified document, and will be revised as needed.

The prepared or revised explanation sheet/informed consent form will be submitted to the study sponsor and approved by the institutional review board prior to the start of the study.

4.2 Information That Should be Included in the Explanation Sheet

The explanation sheet must include the following information at a minimum.

(1) The fact that the study has an experimental aspect.
(2) The objectives of the study.
(3) The names, job titles, and contact information for the principal investigators and subinvestigators.
(4) Study method (including the experimental aspects of the study, the subject inclusion criteria and, if randomization is being performed, the probabilities of the patient being assigned to each treatment)
(5) The expected clinical risks and benefits (If there are no expected benefits to the subject, then this must be explained to the subject.)
(6) If the subjects are going to be patients, then whether or not there are other therapies that are available to the patients, as well as the main benefits and risks of these therapies
(7) Because reproductive and developmental studies have revealed that toxicological changes are a concern, male subjects and female subjects of childbearing potential must practice contraception throughout the study.
(8) The planned term of participation in the study
(9) The fact that participation in the study is entirely up to the subject, and that the subject may refuse to participate in the study or withdraw from the study at any time, and that the subject will not be subject to any discriminatory treatment because of refusal to participate in or withdrawal from the study, nor will not participating in the study cause the subject to lose any benefits that the subject would have been expected to receive.
(10) The fact that the monitors, auditors, institutional review board, and regulatory authorities will be able to access the subject's medical records, and that in the case of said access the subject's privacy will be protected. Also, the fact that by signing or affixing the subject's personal seal to the informed consent form the subject consents to said access.
(11) The fact that the subject's privacy will be protected even if the results of the study are published.
(12) Whom the subject should contact at the study site if the subject wants to obtain information about the study or the subject's rights or to report any health injury that is related to the study.
(13) The compensation and treatment that the subject will be able to receive if the subject suffers any health injury related to the study.
(14) Information about the types of institutional review boards that will review, for example, the appropriateness of this study, what issues will be reviewed by each institutional review board, and other information about the institutional review boards that are involved in this study
(15) The planned sample size for the study.
(16) The fact that the subject will be notified promptly if any information that could affect the subject's willingness to continue participating in the study.
(17) The conditions or reasons that would cause the subject's participation in the study to be discontinued.
(18) If participating in the study will impose any financial burden on the subject, the exact nature thereof.
(19) If the subject will receive any financial compensation for participating in the study, the exact nature thereof (e.g., agreement on how the payments will be calculated).
(20) The rules the subject will be expected to follow.

4.3 Method of Obtaining Consent

(1) Before initiating the study, the (sub)investigator will provide the patient with an explanation sheet/informed consent form that has been approved by the institutional review board and explain its contents thoroughly to the patient. A study support staff member may also provide a supplemental explanation. The (sub)investigator will provide the explanation based on the explanation sheet using as simple language as possible to make sure that the patient understands, and must provide adequate responses to the patient's questions. The (sub)investigator will confirm that the patient has thoroughly understood the explanation before obtaining the patient's written consent to participate voluntarily in the study.

(2) Both the (sub)investigator who provided the explanation and the patient will sign (or print their names and affix their personal seals) and date the informed consent form. If a study support staff member provided a supplemental explanation, then this study support staff member will also sign (or print his or her name and affix his or her personal seal) and date the informed consent form as well.

(3) The (sub)investigator will, before the subject starts participating in the study, provide the signed and dated explanation sheet/informed consent form to the subject and store the original informed consent form properly, in accordance with the rules of the study site.

(4) The date of informed consent acquisition will be recorded on the case report form.

4.4 Informed Consent Form/Subject Explanation Sheet Revision

(1) If new, important information is obtained that could pertain to subject consent, the (sub)investigator will promptly convey this information orally to each subject who is already participating in the study and check whether or not they will continue participating in the study, and will record the results in the subjects' medical records.

(2) The principal investigator will promptly determine based on this information whether or not the informed consent form/explanation sheet needs to be revised.

(3) If the principal investigator determines that the informed consent form/explanation sheet needs to be revised, the principal investigator will do so promptly, and must then once again have it approved by the institutional review board.

(4) The (sub)investigator will provide all of the subjects who are already participating in the study with an explanation using the informed consent form/explanation sheet that has been newly approved by the institutional review board, and will obtain the subjects' written consent to voluntarily continue participating in the study.

(5) Similar to when consent is initially obtained, the (sub)investigator who provided the explanation and the subject will date and sign or affix their personal seals to the revised informed consent form/explanation sheet. If a study support staff member has provided a supplemental explanation, then this staff member will also date and sign or affix his/her personal seal to the revised informed consent form/explanation sheet.

(6) The (sub)investigator will give the subject the signed and dated informed consent form/explanation sheet, and will retain the original of the informed consent form properly, in accordance with the rules of the study site.

[redacted]

4.6 Informed Consent Form/Subject Explanation Sheet for Self-Injection

Before administration by self-injection starts in Week 24, the (sub)investigator will with the help of the study sponsor prepare an autoinjection informed consent form/explanation sheet. The (sub)investigator will give this informed consent form/explanation sheet to those subjects whom the (sub)investigator has determined are capable of performing self-infections and will thoroughly explain its contents to said subjects. A study support staff member may also provide a supplemental explanation. Subjects' consent to self-injection will be obtained in writing by the start of self-injections on Week 24. The (sub)investigator who provided the explanation and the subject himself or herself will sign (or print their names and affix their personal seals to) and date the form. If a study support staff member has provided a supplemental explanation, this study support staff member will also sign (or print his or her name and affix his or her seal to) and date the form. Subjects who have consented to self-inject will be provided with appropriate instruction by the (sub)investigator in accordance with the separately prepared "Self-Injection Guidance" guidelines, and will then administer study drug by self-injection at the study site.

5. Study Design

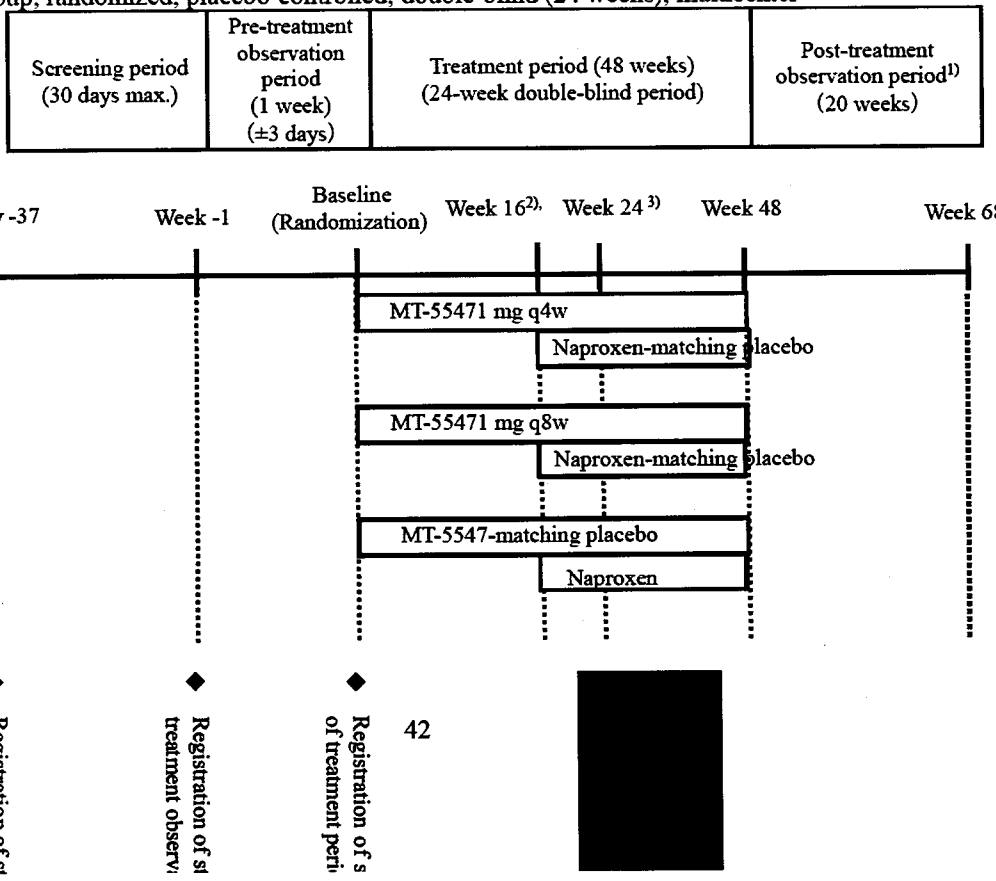
5.1 Study Phase and Type

Study Phase : Phase 2/3
Type of Study : Confirmatory study

5.2 Study Design

Based on recommendations from the IDMC, the 3 mg q4w and 6 mg q8w groups were removed and the 1 mg q8w group was newly added. The revised study is the following 3-arm design (Protocol Ver 04.00.00000).

Parallel group, randomized, placebo-controlled, double-blind (24 weeks), multicenter



◆ Primary endpoint time point
Database of all patients is locked

All patients who were randomized to 3 mg q4w or 6 mg q8w group and were discontinued from study drug based on IDMC recommendation will move onto the post-treatment observation period and will continue all tests/observations in the period (ref. 9.1.1 Test/Observation Schedule (2)).

1) The post-treatment observation period will be the 20 weeks from the day after the day of the 48-week treatment period. Furthermore, for subjects discontinued from the study, the post-treatment observation period will be the 24 weeks from the administration of MT-5547 or MT-5547 placebo. If a joint replacement procedure is going to be performed, the postoperative test observation period will be the period from the day after the day of discontinuation until 20 weeks after the joint replacement procedure is performed.
2) From Week 16 to Week 48, the placebo group will receive an additional dose of naproxen tablets to reduce the dropout rate in the placebo group. The MT-5547 group will receive an additional dose of naproxen placebo tablets.
   For each subject, the data for up through Week 16 will be fixed prior to the Week 20 visit, and the fixed data will be prepared.
3) The blind will be maintained, including for the study sponsor, until the key code is opened after the data have been fixed for all subjects in Week 24. In addition, in order to eliminate any bias that could affect the study assessments, to the extent possible, the blind will be maintained with respect to the study site and the subject even after the opening of the study sponsor key code.

[redacted]

5.3 Methods of Blinding and Randomization

5.3.1 Method of Blinding

[redacted]

5.3.2 Randomization and Allocation Methods

[redacted]

5.4 Endpoints

5.4.1 Efficacy Endpoints

(1) Primary efficacy endpoint
WOMAC pain score (change from baseline at Week 16)

(2) Key secondary efficacy endpoint
WOMAC physical function score (change from baseline at Week 16)

(3) Secondary efficacy endpoints

1) Patient global assessment (PGA) (change from baseline at each assessment time point)
2) WOMAC pain score (change from baseline at each assessment time point)
3) WOMAC physical function score (change from baseline at each assessment time point)
4) WOMAC stiffness score (change from baseline at each assessment time point)
5) WOMAC total score (change from baseline at each assessment time point)
6) Proportions of subjects with 30% and 50% improvements in their WOMAC pain scores compared to baseline (Weeks 16 and 24)
7) Proportions of subjects with 30% and 50% improvements in their WOMAC physical function scores compared to baseline (Weeks 16 and 24)
8) Numerical Rating Scale (NRS) score for the mean pain on walking in the evaluated joint (change from baseline at each assessment time point)
9) SF-36 (change from baseline at each assessment time point)
10) EQ-5D-5L (change from baseline at each assessment time point)
11) Improvement rate based on the Outcome Measures in Rheumatology Arthritis Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria (at Weeks 16 and 24)
12) Amount of rescue medication used (number of days on which rescue medication was used, and amount [number of tablets] used)

[redacted]

5.4.2 Safety Endpoints

(1) Adverse events and adverse reactions (for details, see "9.2.4.2. Adverse Events")
(clinically significant adverse events were identified as being adjudicated arthropathy, sympathetic nervous system disorders and altered peripheral sensation)
(2) General clinical laboratory tests
(3) Body weight
(4) Vital signs
(5) ECG
(6) Physical examination
(7) Joint pain questionnaire
(8) Survey of autonomic symptoms
(9) Standing blood pressure
(10) Neurological assessments
(11) Bone density
(12) Imaging Tests
(13) Injection site assessments
(14) Assessments of subjects undergoing joint replacement

[redacted]

5.4.3 Pharmacokinetic Endpoints

(15) Serum MT-5547 concentration
(16) Anti-fasinumab antibodies

[redacted]

5.4.4 Other

(1) [redacted]

(2)

6. Target Sample Size and Term of the Study

6.1 Target Sample Size

The original target sample size is 568 treated subjects (142 subjects per group)
(MT-5547 1 mg q4w group: 142 subjects; MT-5547 3 mg q4w group: 142 subjects; MT-5547 6 mg q8w group: 142 subjects; placebo group: 142 subjects)

After initiation of this study, based on the recommendations from the IDMC, the 3 mg q4w and 6 mg q8w groups were removed and 1 mg q8w group was newly added to the treatment groups.
The amended target sample size is 506 treated subjects, in total of the subjects who were randomized to 1 mg q4w/placebo groups before the amendment (approximately 40 subjects per group) and the subjects who are randomized to 1 mg q4w/1 mg q8w/placebo groups with the ratio of 1:1:1 after the amendment (142 subjects per group).
(MT-5547 1 mg q4w group: 182 subjects; MT-5547 1 mg q8w group: 142 subjects; placebo group: 182 subjects)

In addition, 57 patients each were enrolled in the fasinumab 3 mg q4w and 6 mg q8w groups prior to the protocol amendment (Ver. 04.00.00000) and were discontinued from study drug based on the recommendations from the IDMC. Thus, enrollment of 563 subjects is planned for this study in total.

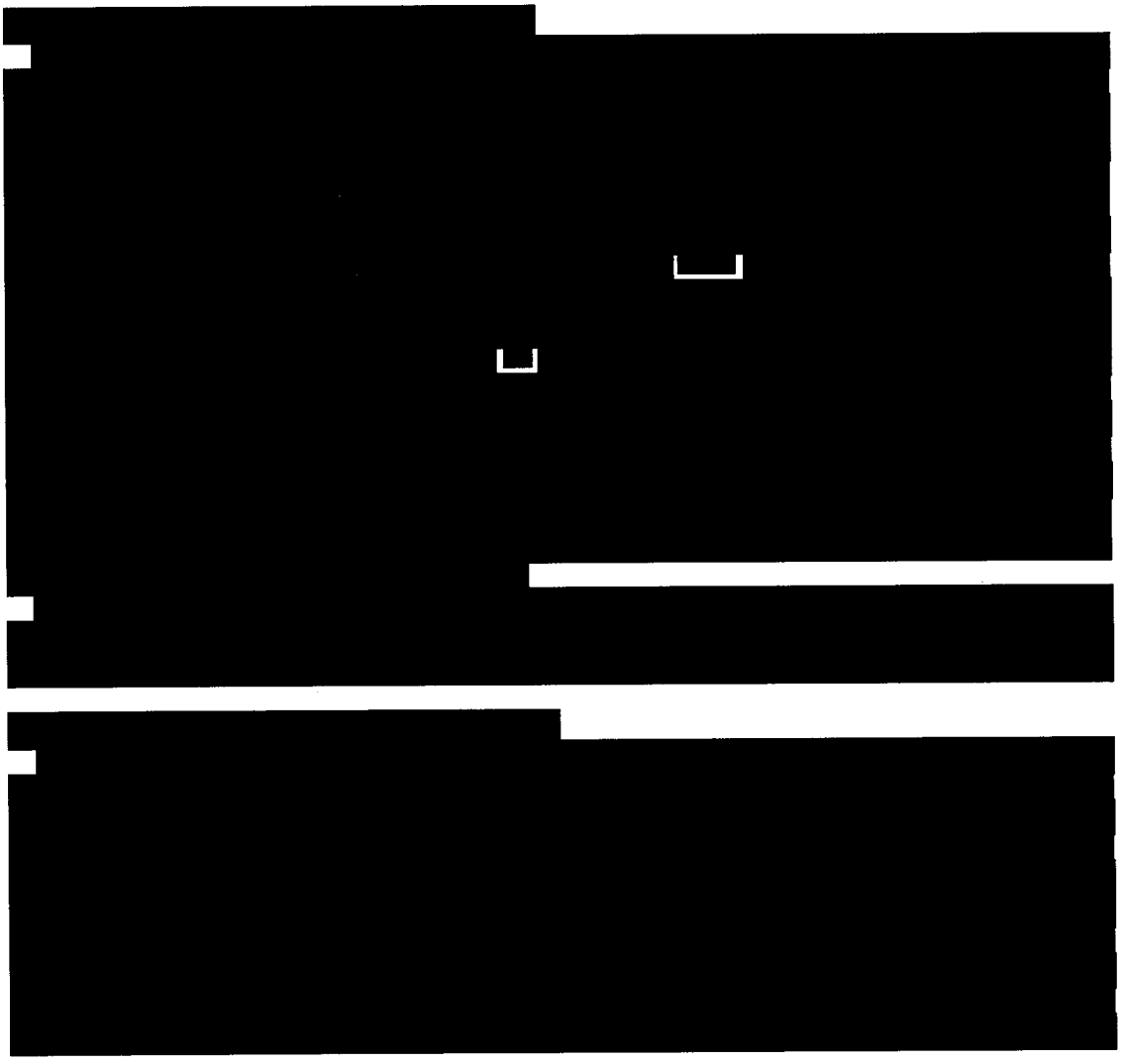


Table 6-1-1Change From Baseline at Week 16 in the WOMAC Pain and Physical Function Scores

	REGN Study R475-PN-1227					REGN Study R475-PN-0901			
	Placebo (N=83)	MT-5547 1 mg (N=85)	MT-5547 3 mg (N=84)	MT-5547 6mg (N=85)	MT-5547 9 mg (N=84)	Placebo (N=55)	MT-5547 0.03 mg/kg (N=53)	MT-5547 0.1 mg/kg (N=53)	MT-5547 0.3 mg/kg (N=54)
Change from baseline in WOMAC pain score									
Baseline	6.43	6.33	6.35	6.10	6.53	5.9	5.7	6.1	6.4
n[1)] Mean[1)] (SD)[1)]	71 -2.43 (2.38)	75 -3.49 (2.06)	78 -3.39 (2.44)	77 -3.07 (2.34)	79 -3.81 (2.49)	44 -2.4 (2.18)	47 -2.7 (1.89)	44 -3.4 (2.53)	41 -3.2 (2.24)
LSM[2)]	-2.25	-3.35	-3.33	-3.03	-3.65	-	-	-	-
Diff. vs. Pbo[3)]	-	-1.10	-1.08	-0.78	-1.40	-	-0.6	-1.1	-0.8
P value	-	0.0025	0.0029	0.0304	0.0001	-	0.1486	0.0090	0.0488
Change from baseline in WOMAC physical function score									
Baseline	6.15	6.11	6.09	5.94	6.20	5.9	5.9	6.2	6.2
n[1)] Mean[1)] (SD)[1)]	70 -2.12 (2.26)	75 -3.21 (2.23)	78 -3.28 (2.29)	76 -2.97 (2.45)	80 -3.51 (2.50)	44 -2.3 (2.30)	47 -2.9 (1.78)	44 -3.4 (2.28)	41 -3.1 (2.18)
LSM[2)]	-1.98	-3.08	-3.27	-3.03	-3.41	-	-	-	-
Diff. vs. Pbo[3)]	-	-1.10	-1.29	-1.06	-1.43	-	-0.8	-1.1	-0.9
P value	-	0.0019	0.0003	0.0029	< 0.0001	-	0.0693	0.0071	0.0245

1) n: number of subjects at Week 16; mean: arithmetic mean at Week 16; SD: standard deviation at Week 16. However, in REGN Study R475-PN-1227, the n includes WOMAC data from after treatment discontinuation.
2) LSM: MMRM least squares mean
3) Diff. vs. Pbo: Difference for each group relative to the placebo group in the MMRM least squares mean

6.2 Term of the Study

[redacted]

7. Study Drugs

7.1 Names of Study Drugs

(1) Investigational drug

Name: MT-5547

Generic name: Fasinumab

Dosage form and strength:

MT-5547 1 mg: Contains 0.5 mL of 1 mg fasinumab per prefilled syringe (2 mg/mL).

The pre-filled syringe to use in this clinical study corresponds to non-certification medical equipment in Japan.

(2) Comparative drug

Name: MT-5547 placebos

Dosage form and strength:

MT-5547 placebo: A prefilled syringe that does not contain any fasinumab, and that contains 0.5 mL of a placebo that is externally indistinguishable from MT-5547.

(3) Control drugs

Names: Naproxen tablets and naproxen placebo tablets

Dosage forms and contents:

Naproxen 100 mg tablets: Each tablet contains 100 mg of naproxen.

Naproxen placebo tablets: Placebo tablets those are externally indistinguishable from naproxen 100 mg tablets

7.2 Study Drug Packaging and Labeling

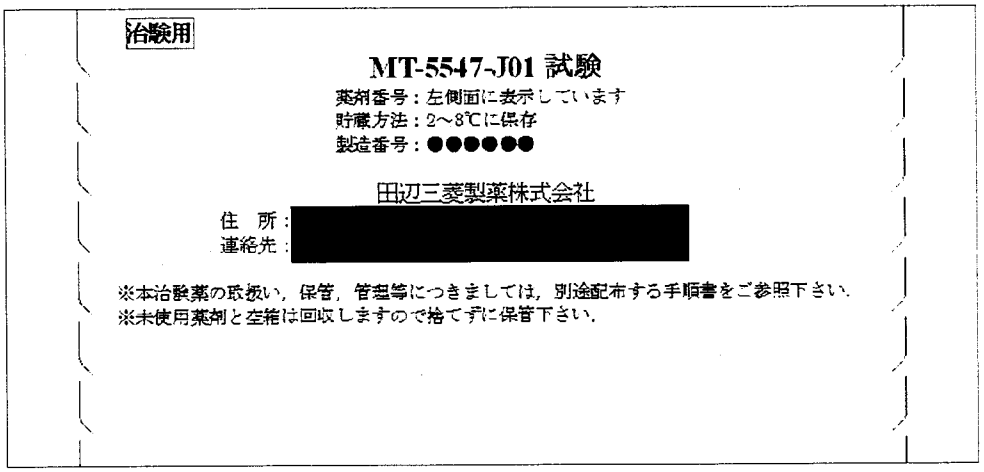
7.2.1 Investigational Drugs (MT-5547 and MT-5547 placebo)

(1) Packaging

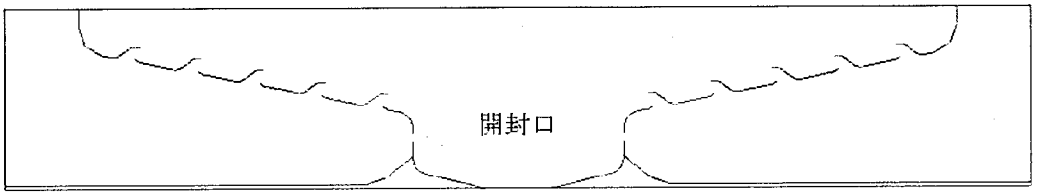
A single syringe will be placed into a holder, and the holder into which the syringe has been placed will be placed into an individual carton, and the individual carton will be sealed shut with a label.

(2) Label

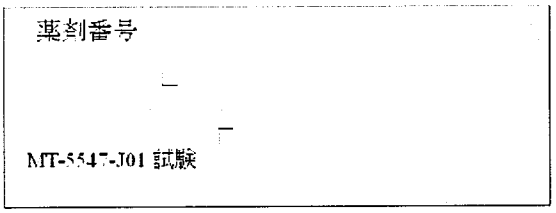
Top of Carton



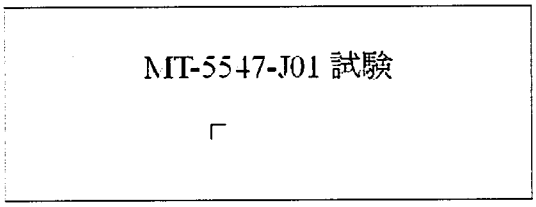
Front (Opening Side) of Carton



Left Side of Carton



Right Side of Carton



7.2.2 Control Drugs (naproxen tablets and naproxen placebo tablets)

(1) Packaging

Ppackage 10 tablets in PTP and package 10 pieces of PTP packaging in pillow. Pack 1 piece of pillow packing in individual box and seal with hot melt. Attach a drug number seal to sealed individual packaging box. Pack 10 pieces of packages in a cellective box, seal with a seal label and attach a drug number seal.

(2) Label

Individual packaging box (Opening Side of Carton)

MT-5547 治験用　　薬剤番号：右側面に表示しています

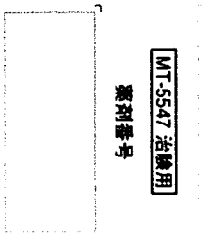
ナプロキセン錠 100mg

製造番号：17P060
貯蔵方法：室温保存

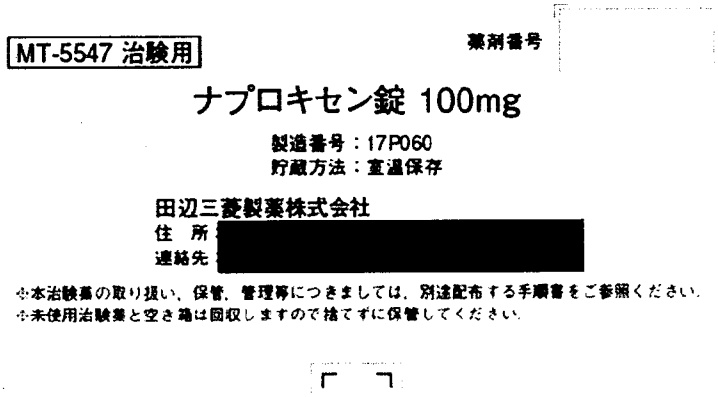
田辺三菱製薬株式会社
住　所：[redacted]
連絡先：

※本治験薬の取り扱い、保管、管理等につきましては、別途配布する手順書をご参照ください。
※未使用治験薬と空き箱は回収しますので捨てずに保管してください。

Individual packaging box (Top of Carton)



Cellective box (Top of Carton)



7.3 Storage

Investigational Drugs (MT-5547 and MT-5547 placebo):Refrigerated storage (2-8°C)

Control Drugs (naproxen tablets and naproxen placebo tablets):Room temperature. Keep shading storage after opening

7.4 Study Drug Handling, Storage, and Control

The study sponsor will deliver the study drugs once the contract with the study site has been concluded. The study drug controller will store and control the study drug in accordance with the "Study Drug Control Written Procedures" and the "IWRS Operating Manual" established by the study sponsor, and will return all unused study drug and empty cartons to the monitor once the study has ended.

Furthermore, study drug must not be used for any purpose other than those described in this study protocol (e.g., for other clinical studies, animal studies, basic research).

7.5 Emergency Unblinding Procedures

8. Subject Study Methods

8.1 Subject Screening and Preparation of an Enrollment Registry and ID Code List

The principal investigator will prepare a list of all subjects who have been screened (subjects who have received consent explanations), and will prepare a subject screening registry. The principal investigator will assign ID codes to subjects who have consented to participate in the study, and will prepare a subject ID code list. When doing so, the principal investigator will note the information that will serve as the key when referencing the subject's medical records. Furthermore, if re-screening is performed after a subject has been registered at the start of screening, after a subject has been registered at the start of the pre-treatment observation period, or after it has been determined at the start of the treatment period that the subject is ineligible for study enrollment, then this subject will be assigned a new subject ID code and a new subject ID code list will be prepared.

The principal investigator will also prepare a subject registry that lists the sex, date of consent, subject ID codes, etc. of the subjects who have been enrolled in the study (including the subjects whose study treatments have been temporarily or permanently discontinued).

8.2 Subject Registration

Subjects will be registered by the MT-5547-J01 registration center (IWRS) in accordance with the subject registration procedures (see Attachment 3, "Study Procedures Flow Chart"), and the registration center will also handle subject randomization, drug number assignment, and visit and discontinuation requests.

8.2.1 Consent Registration

- (Sub)investigators will select patients who appear to be suitable for study participation, and will obtain their written consent to study participation in accordance with "4. Subject Explanation and Consent." For all subjects from whom consent has been obtained, (sub)investigators will enter the information into the IWRS to complete consent registration.
- After the receipt of registration, (sub)investigators will use the IWRS to check the results of the assessment. In addition, the results of the assessments will be sent by e-mail to both the (sub)investigators and the study sponsor.
- Furthermore, IWRS consent registration may be performed by a study support staff member provided that it is approved by a (sub)investigator and that the necessary consent registration information is entered by a (sub)investigator in, for example, the medical records.

8.2.2 Registration of the Start of Screening

- The (sub)investigator will check the suitability of the subject for study participation at the start of screening, and will enter the information in the IWRS to register the start of screening.
- After the receipt of registration of the start of screening, (sub)investigators will use the IWRS to check the results of the assessment. In addition, the results of the assessments will be sent by e-mail to both the (sub)investigators and the study sponsor.

- If registration is discontinued because, for example, the subject does not satisfy the conditions for the start of screening, the (sub)investigator will nevertheless enter the required information into the IWRS and provide notification that the subject is unsuitable for screening to start.
- If the subject discontinues from the study after consent has been registered but before the start of screening has been registered, the (sub)investigator will provide notification of the discontinuation of the subject from registration of the start of screening.
- Furthermore, a study support staff member may register the start of screening using the IWRS provided that approval is obtained from the (sub)investigator and that the information required to register the start of screening has been recorded by the (sub)investigator in, for example, the medical records.

8.2.3 Registration of the Start of the Pre-treatment Observation Period

- The (sub)investigator will check the suitability of the subject for study participation at the start of the pre-treatment observation period, and will enter the information in the IWRS to register the start of the pre-treatment observation period.
- After the receipt of registration of the start of the pre-treatment observation period, (sub)investigators will use the IWRS to check the results of the assessment. In addition, the results of the assessments will be sent by e-mail to both the (sub)investigators and the study sponsor.
- If registration is discontinued because, for example, the subject does not satisfy the conditions for the start of the pre-treatment observation period, the (sub)investigator will nevertheless enter the required information into the IWRS and provide notification that the subject is unsuitable for the pre-treatment observation period to start.
- If the subject discontinues from the study after the start of screening has been registered but before the start of the pre-treatment observation period has been registered, the (sub)investigator will provide notification of the discontinuation of the subject from registration of the start of screening.
- Furthermore, a study support staff member may register the start of the pre-treatment observation period using the IWRS provided that the information required to register the start of the pre-treatment observation period has been recorded by the (sub)investigator in, for example, the medical records, and with the (sub)investigator's consent.
- If the patient is found to be suitable for study participation as a result of the assessment of the registration of the start of the pre-treatment observation period, the (sub)investigator will prescribe the rescue drug (acetaminophen). In addition, the (sub)investigator or a study support staff member will instruct [the subject] to record the quantity of the rescue drug (acetaminophen) taken in the treatment diary, and to report the NRS data for the average pain on walking in the evaluated joint each day via the IVRS. Subjects for whom NRS have not been reported for 4 or more days during the pre-treatment observation period will be considered unsuitable to progress to the start of the treatment period.
- If no actions (e.g., washout) are taken towards study participation for 1 month from the date consent was obtained, then the subject's willingness to participate in the study will be checked once again.

8.2.4 Registration of the Start of the Treatment Period

- The (sub)investigator will check the suitability of the subject for study participation once more at baseline, and will enter the information in the IWRS to register the start of the treatment period.
- After the request for the registration of the start of the treatment period has been accepted, the (sub)investigator will use the IWRS to check the results of the assessment (if the subject is considered suitable for study participation, a randomization number and a drug number will be assigned). In addition, the results of the assessments will be sent by e-mail to both the (sub)investigators and the study sponsor.
- If registration is discontinued because, for example, the subject does not satisfy the start of the treatment period, the (sub)investigator will nevertheless enter the required information into the IWRS and provide notification that the subject is unsuitable for registration of the start of the treatment period.
- If the subject discontinues from the study after the start of the pre-treatment observation period has been registered but before the start of the treatment period has been registered, the (sub)investigator will provide notification of the discontinuation of the subject from registration of the start of the treatment period.
- Furthermore, a study support staff member may register the start of the treatment period using the IWRS provided that the (sub)investigator's approval is obtained and that the information required to for allocation notification has been recorded by the (sub)investigator in, for example, the medical records.

8.2.5 Visit Reception (Presence or Absence of Subject Visits and Study Treatments From Week 4 to Week 44)

- At each scheduled visit from Week 4 to Week 44 after treatment initiation, the (sub)investigator will input into the IWRS whether or not the subject came in for the visit and whether or not the subject received study drug (MT-5547 drug number assignment or treatment interruption), and will perform the visit reception procedures. The assignment of the drug numbers for the naproxen 100 mg tablets will be done at Week 16.
- The results of the reception (whether or not the patient came in for the visit and whether or not the patient received study drug) will be sent by e-mail to both the (sub)investigators and the study sponsor.
- Furthermore, the IWRS visit reception procedures may be performed by a study support staff member provided that the approval of the (sub)investigator is obtained and that the (sub)investigator has entered the necessary visit reception information into, for example, the medical records.
-

8.2.6 Discontinuation Reception (during the treatment period from baseline to Week 48)

- If the (sub)investigator is going to discontinue the subject from the study during the treatment period, the (sub)investigator will enter the information in the IWRS to perform the discontinuation reception procedures.
- After the discontinuation reception procedures have been performed, the (sub)investigator will use the IWRS to check the results of the reception. In addition, the results of the reception will be sent by e-mail to both the (sub)investigators and the study sponsor.

- Furthermore, a study support staff member may perform the discontinuation reception procedures using the IWRS provided that the (sub)investigator's approval is obtained and that the information required for discontinuation has been recorded by the (sub)investigator in, for example, the medical records.

8.3 Dosage and Administration

(1) MT-5547 and MT-5547 placebos

Assigned investigational drug or comparative drug will be administered subcutaneously every 4 weeks between Week 0 and Week 44*.

MT-5547 1 mg q4w group: MT-5547 1 mg q4w from Week 0 to Week 44
MT-5547 1 mg q8w group: MT-5547 1 mg q8w on Weeks 0, 8, 16, 24, 32, and 40, and MT-5547 placebo q8w on Weeks 4, 12, 20, 28, 36, and 44
MT-5547 placebo group: MT-5547 placebo q4w from Week 0 to Week 44

* All patients previously randomized to 3 mg q4w or 6 mg q8w group under the previous versions of this protocol (up to Ver. 03.00.00000) will be discontinued from study drug immediately and will continue all tests/observations in the post-treatment observation period (ref. 9.1.1 Test/Observation Schedule (2)).

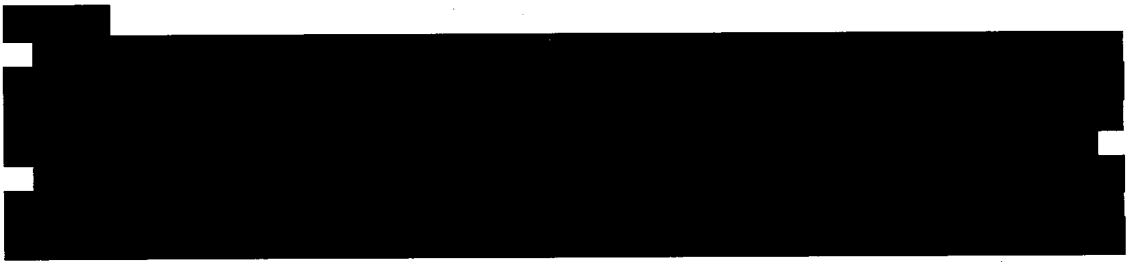
The entire contents of a single prefilled syringe will be injected subcutaneously into the abdomen, thigh or upper arm for each dose. Subjects will be monitored at the study site for 30 minutes after the administration of the investigational drug or comparative drug. The investigational drug or comparative drug study drug will be administered at the scheduled administration days plus or minus 7 days. If the investigational drug or comparative drug cannot be administered during this time window, then the dose will be skipped and study drug will not be administered until the next scheduled treatment date. The investigational drug or comparativedrug will be administered after all of the procedures planned for the day of the study visit have been completed.

Furthermore, for subjects who consent to self-inject, the study drug will be administered by self-injection subcutaneously at the study site from Week 24 on. The injection site of self-inject subcutaneously should be the abdomen or thigh, not injected on upper arm.

Precautions Related to the Dosage and Administration

Treatment will be initiated by the baseline day, after all of the tests and observations have been completed, it has been confirmed based on the IWRS that the subject is eligible to participate in the study, and a drug number has been assigned. The investigational drug or comparative drug will be administered once all of the planned procedures on the visit day have been completed.

Emergency instruments and therapeutic medications for treating hypersensitivity/anaphylaxis (e.g., antihistamines, corticosteroids, acetaminophen, and/or epinephrine) will be prepared at the study site so that they can be used immediately. Subjects must be monitored closely for the emergence of events that could be associated with hypersensitivity/anaphylaxis.



[redacted]

(2) Naproxen tablets and naproxen tablet placebos:

Naproxen tablets or naproxen placebo tablets 3 to 6 tablets (300 to 600 mg/day) will be administered 2 to 3 times a day by mouth with water from the morning of the day after the Week 16 assessment day until the end of the Week 48 assessments. At each visit, the dosage and administration may be changed at the discretion of the (sub)investigator. Administration will be by mouth, with administration in a fasted condition avoided whenever possible. The (sub)investigator instructs the examinee to keep the naproxen tablets or naproxen placebo tablet in a shading bag.

[redacted]

[redacted]

8.4 Treatment Period

Treatment Period: 48 weeks in total

[redacted]

8.5 Concomitant Drugs/Therapies

8.5.1 Prohibited Concomitant Medications and Therapies

The coadministration of the drug products/therapies (including over-the-counter medications) shown below will be prohibited throughout the following period.

(1) For 60 weeks from the start of the pre-treatment observation period or until 16 weeks after the final dose of investigational drug or comparative drug
NSAIDs (including oral, injectable, topical, or ophthalmic dosage forms), except in the following cases

1) Up to 100 mg/day of aspirin taken for thrombus/embolism prophylaxis in patients with cardiovascular and cerebrovascular disease
2) Temporary use of combination cold medicines that contain NSAIDs
3) From the morning of the day after the Week 16 assessment day until the end of the Week 48 assessments. Control drug (naproxen)

About following NSAIDs which has a long half-life, prohibit comcomitant period will be set, respectively.

1) For 60 weeks starting from 12 days before baseline, or until 16 weeks after the final dose of investigational drug or comparative drug
Oxaprozin, Piroxicam (including oral and topical dosage forms)

2) For 60 weeks starting from 10 days before baseline, or until 16 weeks after the final dose of investigational drug or comparative drug
Ampiroxicam

3) For 60 weeks starting from 7 days before baseline, or until 16 weeks after the final dose of investigational drug or comparative drug
Meloxicam

(2) For 48 weeks from 2 weeks before the start of screening, or until discontinuation
Sodium hyaluronate (average molecular weight 500,000 to 1,200,000; brand name: Artz® Joint Injection, Artz Disposable® Joint Injection, including generics)

(3) For 48 weeks from 4 weeks before the start of screening, or until discontinuation

1) Sodium hyaluronate (average molecular weight 1,500,000 to 3,900,000; brand name: Suvenyl® Disposable Joint Injection 25 mg and Suvenyl® Vial Joint Injection 25 mg, including generics)
2) Corticosteroid (excluding topical, intranasal, ophthalmic, and inhaled dosage forms, and intraarticular injections into the evaluated joint).
3) Monoamine reuptake inhibitor used for analgesic effect (tricyclic antidepressant, SSRI, SNRI, etc.)

(4) For 48 weeks from 12 weeks before the start of screening, or until discontinuation

Intraarticular injections of corticosteroids into the evaluated joint

(5) For 48 weeks from 13 weeks before the start of screening, or until discontinuation

Sodium hyaluronate crosslinked polymer/sodium hyaluronate crosslinked polymer crosslinked with vinyl sulfone (brand name: Synvisc Disposable® Joint Injection 2 mL)

(6) For 16 weeks from the starting day of the pre-treatment observation period, or until discontinuation

1) Glucosamine
2) Chondroitin

(7) For 48 weeks from the starting day of the pre-treatment observation period, or until discontinuation

1) Opioids (including combination drugs)
2) Tizanidine
3) Drugs intended for analgesic effects (pregabalin, etc.)
4) Nerve block therapy and trigger point injections
5) Physical therapy (such as non-pharmacological transcutaneous electrical nerve stimulation, acupuncture, and exercise therapy)

However, concomitant therapy will be permitted if the patient has been receiving stable physical therapy on an ongoing basis since before screening and the extent and frequency is changed as little as possible during the study period.

6) Chinese herbal medicines that are indicated for osteoarthritis

(8) From the start of the pre-treatment observation period until the end of the post-treatment observation period

1) Immunosuppressants (e.g., cyclosporine, azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, tofacitinib)
2) Biological drug products (e.g., anti-TNF antibodies, IL-1 inhibitors, IL-6 inhibitors, abatacept, rituximab, denosumab)

(9) From the earliest day of 4 weeks before the start of screening, or 5 half-lives of the investigational drug until the end of the post-treatment observation period

All investigational drugs other than this investigational drug

[redacted]

8.5.2 Restricted Concomitant Medications

The coadministration of the following drugs (including over-the-counter medications) will be restricted (or caution must be exercised when using the following drugs) throughout the following periods.

(1) For 48 weeks from the starting day of the pre-treatment observation period, or until discontinuation

1) Acetaminophen (the rescue medication)

The concomitant use of acetaminophen will be permitted as the rescue medication in this study.

Until the Week 48 visit, if relief from pain associated with osteoarthritis is inadequate, acetaminophen 300-1000 mg will be taken orally as needed every 4 to 6 hours, or more, as the rescue medication. This dose may be adjusted depending on the age and symptoms of the subject. The combined OA-pain and non-OA pain should not exceed 4000 mg in a single day. In addition, administration in a fasted state should be avoided. For 48 weeks starting from screening, or until treatment period discontinuation, acetaminophen may not be used from 48 hours before each scheduled visit until after the efficacy assessments have been completed in order to minimize the effects of the rescue drug on the efficacy outcome measure.

2) Acetaminophen (the use for the acute-phase therapy of conditions other than osteoarthritis)

Acetaminophen can also be used for acute treatment of non-OA pain, and will be reported as concomitant medication. The combined OA-pain and non-OA pain should not exceed 4000 mg in a single day. For 48 weeks starting from screening, or until treatment period discontinuation, acetaminophen may not be used from 48 hours before each scheduled visit until after the efficacy assessments have been completed in order to minimize the effects of the rescue drug on the efficacy outcome measure.

(2) For 60 weeks from the start of the pre-treatment observation period, or until 16 weeks after the final dose of investigational drug or comparative drug

The following NSAIDs

1) Low-dose aspirin

The concomitant use of aspirin will be permitted at doses of up to 100 mg when it is being used to prevent thrombosis/embolism in cardiovascular or cerebrovascular diseases.

2) Combination cold medicines that contain NSAIDs

The temporary use of combination cold medicines that contain NSAIDs will be permitted if the subjects have colds. The use of such medicines will be restricted to 3 days in a row, and as a rule at least 1 month must be allowed to pass before such medicines are used again. The use of such medicines will not be permitted from 48 hours before each scheduled visit until

after the efficacy assessments have been completed.

(3) For 48 weeks from the start of the pre-treatment observation period, or until discontinuation
Monoamine reuptake inhibitors used other than for analgesic effect (such as tricyclic antidepressants, SSRIs, and SNRIss).

The concomitant use of these drugs will be permitted provided that as a rule, the subject has been continuing to take them since at least 8 weeks before the start of screening, and that they are taken using a fixed dosage starting from at least 4 weeks before the start of screening and continuing during the planned period of participation in this study.

(4) From Week 16 until Week 48 or discontinuation
The following drugs, which need to be used carefully when being coadministered with naproxen

1) Hydantoin anticonvulsants (phenytoin)
2) Sulfonyl urea hypoglycemic agents (e.g., chlorpropamide, tolbutamide, glivenclamide)
3) Anticoagulants (e.g., warfarin, dabigatran etexilate)
4) Anti-platelet agents (e.g., clopidogrel)
5) Probenecid
6) Methotrexate
7) Antihypertensive agents (e.g., beta blockers, diuretics, ACE inhibitors, A-II receptor blockers) : Especially, when patients take combination of diuretics with ACE-I or ARB, the (sub)investigator should be careful to monitor renal function.
8) Lithium preparations (lithium carbonate)
9) Zidovudine
10) New quinolone antibacterial agents
11) Iguratimod
12) Low-dose aspirin

There are no particular restrictions on drugs or therapies other than the ones listed above.
Furthermore, because naproxen will be administered concomitantly from Week 16 on, the concomitant use of H2 blocker, misoprostol or a proton pump inhibitor etc. to protect the gastrointestinal tract may be considered, at the discretion of the (sub)investigator.

[redacted]

(1)

(2)

(3)

(4) [redacted]

8.5.3 Records of Concomitant Drugs and Therapies

The (sub)investigator or a study support staff member will record in the concomitant drugs and therapies section of the case report form the following information about the drugs and therapies that were concomitantly administered from the start of screening until the final assessment time point in the post-treatment observation period or 20 weeks after joint replacement, whichever comes later. However, normal saline solutions used to reconstitute injectable drugs, disinfectants for wound healing, etc. will not be recorded.

(1) Concomitant drugs: Drug name, daily dose, route of administration, treatment period, objective of use
(2) Concomitant therapies: Therapy name, period administered, frequency, objective of use

8.6 Subject Management

The (sub)investigator or a study support staff member will perform subject management duties paying attention to the following issues. Furthermore, the (sub)investigator or study support staff member will during the study solicit from the subject the following information about the subject's condition and treatment compliance.

8.6.1 Lifestyle Guidance

The (sub)investigator or a study support staff member will provide the subject with the following instructions.

(1) Subjects are expected to undergo the observations/tests on the scheduled days. If a subject cannot come in to the study site on the scheduled day, the subject must notify the (sub)investigator or a study support staff member and follow his or her instructions.
(2) The subject must carry around a clinical study participation card and present it when being examined at another hospital or department. In addition, if the subject uses any drugs that have been prescribed by a doctor outside of this study, or even any drugs that have been purchased by the subject at a drug store, the subject must be sure to inform the (sub)investigator or a study support staff member. Also, if the subject is going to use a new drug during the study, the subject must notify the (sub)investigator or a study support staff member in advance.
(3) The (sub)investigator or a study support staff member will instruct the subject not to change their current lifestyle (daily living activities and exercise) as a general rule.
(4) If a subject notices a physical problem, such as signs of an infection (even if it is just a minor cold), the subject must inform the (sub)investigator or a study support staff member promptly and confirm whether or not an examination is necessary.

8.6.2 Contraception

The (sub)investigator or a study support staff member will instruct the subject to use a reliable means of contraception,* as defined in 1) or 2) below, from the day of consent until 20 weeks after the final study treatment. The calendar method, ovulation method, sympto-thermal method, post-ovulation method, and withdrawal method are not reliable methods of contraception. Furthermore, postmenopausal females who have been amenorrheic for at least 1 year and females who have undergone surgical hysterectomies or bilateral ovariectomies are excluded.

*Reliable methods of contraception

1) Abstaining from sexual intercourse
2) The use of 2 effective methods of contraception. The use of a barrier method (a diaphragm or latex condom) in combination with a more effective method of contraception (oral contraceptive drugs, intrauterine ring, tubal ligation, vasectomy, etc.) is recommended.

8.6.3 Rescue Drug/Treatment Diary

Acetaminophen will be prescribed by the (sub) investigator at participating study sites from the day of the visit at the start of the pre-treatment observation period through Week 44. At each scheduled visit, the remaining acetaminophen will be collected, and new acetaminophen prescribed.

The (sub)investigator or a study support staff member will instruct the subject to every night record in the treatment diary the amount of acetaminophen (the number of tablets) that the subject took that day. Furthermore, the subject will record separately in the treatment diary the amount (number of tablets) of acetaminophen that was taken because of osteoarthritis and the amount (number of tablets) that was taken for the acute-phase treatment of pain not associated with osteoarthritis. The (sub)investigator or a study support staff member will record the amount (number of tablets) of acetaminophen that was taken for pain associated with osteoarthritis in the case report form.

The (sub)investigator or a study support staff member will instruct the subject to at every visit bring in remaining rescue drug (acetaminophen) as well as the treatment diary to the study site. The (sub)investigator or a study support staff member will check the amount of remaining drug that is recovered. However, the subject will be instructed that, in order to minimize the effects of acetaminophen on the efficacy assessments, the rescue drug may not be used from 48 hours before each schedule visit of efficacy assessments until the end of the efficacy assessments.

8.6.4 IVRS

The (sub)investigator or a study support staff member will instruct the subject in how to use the IVRS on the day of the visit at the start of the pre-treatment observation period. The subject will use the IVRS every night from the start of the pre-treatment observation period until the day before Week 16 to report the average pain on walking (NRS score) in the evaluated joint each day. The (sub)investigator or a study support staff member will confirm that the subject is reporting the information using the IVRS correctly.

9. Tests/Observations

9.1 Test/Observation Schedule

9.1.1 Test/Observation Schedule

(1) Test/Observation Schedule from informed consent to Week 48 of treatment period (if a joint replacement procedure is not going to be performed)

				Treatment period									Treatment period						
	Informed consent	Screening	Pre-treatment of observation period	Day1 Baseline	Week1	Week2	Week4	Week8	Week12	Week16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	At withdrawal[16]
Visit times (visit window)		Day -37 ~ -8	Day -7 ~ -1 (±3)		Day 8 (±3)	Day 15 (±3)	Day 29 (±7)	Day 57 (±7)	Day85 (±7)	Day 113 (±7)	Day 141 (±7)	Day 169 (±7)	Day 197 (±7)	Day 225 (±7)	Day 253 (±7)	Day 281 (±7)	Day 309 (±7)	Day 337 (±7)	
Visit Number		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
Written informed consent	X																		
Eligibility confirmed		X	X	X															
Demographics		X		X															
Randomization[1]				X															
Study drug SC administration[2]				X			X	X	X	X	X	X	X	X	X	X	X		
Administration of naproxen										←								→	
Delivery of naproxen										X	X	X	X	X	X	X	X		
Return of naproxen											X	X	X	X	X	X	X	X	X
Delivery of acetaminophen			X	X		X	X	X	X	X	X	X	X	X	X	X	X		
Return of acetaminophen/check of amount taken[3]				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[Efficacy]																			
NRS (average daily pain)[4]			X	←						→									
WOMAC[5]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PGA of OA		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SF-36				X			X	X		X		X		X		X		X	X
EQ-5D-5L				X			X	X		X		X		X		X		X	X
[Safety]																			
Body weight (height: only at screening)		X								X								X	X
Vital signs[6]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG		X																X	X
Physical examination		X										X		X				X	X
Orthostatic blood pressure		X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Injection site assessment (30 minutes after administration)				X			X	X	X	X	X	X	X	X	X	X	X		
Joint Pain Questionnaire		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Autonomic Nerve Questionnaire		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Neurological evaluation		X		X (brief version)		X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X (brief version)	X	X
Radiology (bilateral knees, hips, shoulders)[7]		X								X								X	X
MRI testing (evaluated joint, contralateral joint, knee or hip joints with K-L ≥ 3)[7]		X																	
MRI testing (joint of joint replacement surgery)																			X
Adverse events		←																→	X
At joint pain worsening (imaging [X-ray, MRI] assessments)[8]					←													→	X
JOA Score[9]																			X
Laboratory testing[10]		X		X			X	X	X	X		X		X		X		X	X
Pregnancy test (for WOCBP)[11]		X		X			X	X	X	X	X	X	X	X	X	X	X	X	X
Bone density[12]		X																X	X
Urinalysis		X		X						X		X						X	X
[Pharmacokinetics]																			
PK measurements				X[15]	X	X	X[15]	X[15]	X[15]	X[15]		X[15]		X[15]		X[15]	X[15]	X	X
ADA antibody				X[15]						X[15]		X[15]						X	X
[Other]																			
[redacted]				X															

(2) Test/Observation Schedule of post-treatment observation period (if a joint replacement procedure is not going to be performed)

	Post-treatment observation period (20 weeks)[14]					
	Week 52	Week 56	Week 60	Week 64	Week 68	At withdrawal
Visit times (visit window)	Day 365 (±7)	Day 393 (±7)	Day 421 (±7)	Day 449 (±7)	Day 477 (±7)	
Visit Number	18	19	20	21	22	
Written informed consent						
Eligibility confirmed						
Demographics						
Randomization[1]						
Study drug SC administration[2]						
Administration of naproxen						
Delivery of naproxen						
Return of naproxen						
Delivery of acetaminophen						
Return of acetaminophen/check of amount taken[3]						
Concomitant medications	X	X	X	X	X	X
[Efficacy]						
NRS (average daily pain)[4]						
WOMAC[5]	X		X		X	X
PGA of OA	X		X		X	X
SF-36					X	X
EQ-5D-5L					X	X
[Safety]						
Body weight (height: only at screening)					X	X
Vital signs[6]	X				X	X
ECG						
Physical examination					X	X
Orthostatic blood pressure	X				X	X
Injection site assessment (30 minutes after administration)						
Joint Pain Questionnaire	X				X	X
Autonomic Nerve Questionnaire	X				X	X
Neurological evaluation	X (brief version)				X	X
Radiology (bilateral knees, hips, shoulders)[7]					X	X
MRI testing (evaluated joint, contralateral joint, knee or hip joints with K-L ≥ 3)[7]						
MRI testing (joint of joint replacement surgery)						X
Adverse events	←				→	X
At joint pain worsening (imaging [X-ray, MRI] assessments)[8]	←				→	X
JOA Score[9]						X
Laboratory testing[10]					X	X
Pregnancy test (for WOCBP)[11]	X				X	X
Bone density[12]						
Urinalysis					X	X
[Pharmacokinetics]						
PK measurements	X	X			X	X
ADA antibody					X	X
[Other]						
[redacted]						
[redacted]						

1) Subjects will be randomized (enrolled at the start of the treatment period) after all of the assessments through the pre-treatment observation period have been completed.
2) Investigational drug or comparative drug will be administered subcutaneously after all of the safety assessments, efficacy assessments, and collection of blood samples for pharmacokinetic assessments have been completed, and subjects will be kept under supervision at the study site for 30 minutes after the administration of the study drug.
3) The dose of acetaminophen taken will be checked based on the treatment diary. Every night, subjects will record in their treatment diaries the amount (number of tablets) of acetaminophen they took that day.
4) Every night (and as a rule at the same time) from the start of the pre-treatment observation period until Week 16, subjects will use the IVRS to report the mean pain on walking for the previous 24 hours (NRS data). Subjects will receive instruction in how to use the IVRS on the day of the visit at the start of the pre-treatment observation period.
5) The WOMAC score at screening will be assessed for the right knee joint, the left knee joint, the right hip joint, and the left hip joint, and the evaluated joint will be determined based on the WOMAC pain subscale scores. At the other time points, the WOMAC score will be assessed for the evaluated joint only.
6) If the pulse is less than 45 bpm at an assessment time point after investigational drug or comparative drug administration, electrocardiography will be performed and the patient carefully examined for cardiac function abnormalities.
7) Screening:
   The following imaging tests will be performed for subjects who meet the study eligibility criteria, and the images will be submitted to a central laboratory. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted.
   - X- ray tests: Both knee joints, both hip joints, both shoulder joints
   - MRI tests: The evaluated joint, the joint opposite the evaluated joint, and any knee or hip joints with a K-L grade of 3 or more

   MRI tests will be performed as needed by the (sub)investigator.
   A check will be performed by the day specified below to make sure that the results of the central assessments meet the study enrollment criteria.
   - X-ray tests: By the start of the pre-treatment observation period
   - MRI tests: By baseline

   If the results of the central assessments cannot be confirmed by the specified day, then re-screening will be performed.
   Baseline and after baseline:
   At week 16, 48 (or at the early termination of the treatment period) and at 68 weeks (or at the early termination of the post-treatment observation period), images will be submitted to the central laboratory.
   If the (sub)investigator determine that there is an abnormal finding compared to normal osteoarthritis, MRI tests will be performed as needed. The images will be submitted to a central laboratory. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted, and the images submitted to the central laboratory(for more detailed information, see in the text "9.2.4.1.11 Imaging Tests").
   Week 16:
   The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator. The (sub)investigator will check the X-ray images before administered the investigational drug or comparative drug to determine whether or not investigational drug or comparative drug should be administered. If any abnormalities are found, investigational drug or comparative drug administration will be postponed. If the central laboratory rules out adjudicated arthropathy, investigational drug or comparative drug administration will be resumed.
   Assessment at the early termination of the treatment period and the early termination of the post-treatment observation period
   The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator. The images will be submitted to a central laboratory. If more than 30 days have passed since the last images were taken, images will be taken again. If not more than 30 days have passed, imaging tests will be performed if the (sub)investigator determines that it is necessary.
   If joint replacement surgery is required, the MRI tests of the joint of surgery will be performed (for more detailed information, see in the text "9.2.4.1.13 Assessments if a Joint Replacement Procedure Is Scheduled").

8) If a subject experiences a sudden worsening of pain that would not occur in the normal course of osteoarthritis, the

(sub)investigator will postpone investigational drug or comparative drug administration, and perform imaging test (X-ray and MRI) of the affected joint. Imaging test (X-ray and MRI) of other joints will be performed as needed by the (sub)investigator. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted. All images will be submitted to the central laboratory. The results of the central assessment will be checked by the (sub)investigator. The investigational drug or comparative drug administration will be postponed until the central laboratory rules out adjudicated arthropathy. If the result of the central assessment is adjudicated arthropathy, then study treatment must be discontinued. If adjudicated arthropathy is ruled out by the central assessment, the (sub)investigator will determine whether or not study treatment should be continued.

9) Assessmets of the joint by JOA score at discontinuation will be performed for subjects who required joint replacement surgery during the study.
10) Hematology and blood biochemistry tests will be performed. HbA1c, HBs antigen, HBs antibody, HCV antibody, and HIV antibody will be measured only at screening.
11) At screening, the pregnancy test will be performed using serum. At all other time points, the pregnancy test will be performed using urine. Furthermore, pregnancy tests will not be performed for postmenopausal females who have been amenorrheic for at least 1 year or for females who have undergone a surgical hysterectomy or bilateral ovariectomy. If a positive result is obtained on a urine pregnancy test, a serum pregnancy test will be performed. If a negative result is obtained on a serum pregnancy test, the study can be continued for the patient. If the serum pregnancy test is also positive, study treatment will be discontinued.
12) Bone density will be measured only at those study sites that are capable of performing measurements using the DEXA method. If it can not be measured at screening priod, it may be measured during the pre-treatment observation period.
13) [redacted]
14) The Week 64 assessments may be performed by telephone.
15) The blood samples will be collected before the investigational drug or comparative drug is administered.
16) In the case of early termination of the treatment period, follow-up evaluation of the same item as at the time of visit of the corresponding completed subjects below is carried out 4, 8, 12, 16, 20 and 24 weeks after the last dose of the investigational drug or comparative drug. However, blood sample collection for pharmacokinetic evaluation is performed only 24 weeks after the last dose (blood sampl collection for PK measurement is not necessary 4, 8 and 12 weeks after the the last dose corresponding to treatment period 48, 52 and 56 weeks of the completed subjects). The visit window at each evaluation time point is plus or minus 7 days.

Early termination of the treatment period	4 weeks after the last dose	8 weeks after the last dose	12 weeks after the last dose	16 weeks after the last dose	20 weeks after the last dose	24 weeks after the last dose	the early termination of the post-treatment observation period
Completed of the treatment period	Week 48	Week 52 週	Week 56 週	Week 60 週	Week 64 週	Week 68 週	the early termination of the post-treatment observation period

When assessments at discontinuation is included in visit window of each assessment time point, the same ones as those normally assessed at discontinuation. After assessment at discontinuation, the same ones as those normally assessed at the last dose of investigational drug or comparative drug.
If more than 30 days have passed since the last images were taken, images will be taken again. If not more than 30 days have passed, imaging tests will be performed if the (sub)investigator determines that it is necessary.
The tests at discontinuation and post-joint replacement procedure test/observation will be performed for subjects who required joint replacement surgery during the study. The all images will be submitted to a central laboratory (for more detailed information, see "10 (3) Post-joint replacement procedure test/observation schedule). If the assessments at discontinuation are not performed before the joint replacement procedure is performed, then images from before the procedure will be obtained and sent to the central laboratory.

17) The screening period is from "the screening start date" to the day before "the pre-treatment of observation period start date", and the screening start date and the end date are defined along with the allowable range of "the pre-treatment of observation period" (for example, when the pre-treatment of observation period is 4 days, The maximum screening period is 30 days from Day - 34 to Day - 5, the pre-treatment of observation period is 10 days, the screening period is the maximum from Day - 40 to Day - 11).

At each study visit after the baseline date, the assessments that are performed by the subjects

themselves (WOMAC, PGA, joint pain survey, SF-36, EQ-5D-5L, survey of autonomic symptoms) will be performed before all of the other assessments (including the assessments that are performed by the (sub)investigator) (except for cases where imaging tests are performed on a different day).

[redacted]

(3) Post-joint replacement procedure test/observation schedule

Follow-up day (visit window)	After surgery[1]	Long-term[1]
	Follow-up survey, 4 weeks post-operative	Follow-up survey 2, 20 weeks post-operative
	29 days post-operative (±5 days)	141 days post-operative (±7 days)
Concomitant medications	X	X
[Safety]		
Vital signs	X	X
Joint Pain Questionnaire	X	X
JOA score[2]	X	X
Radiology (bilateral knees, hips, shoulders)	X	X
Adverse events	←	→
At joint pain worsening (imaging [X-ray, MRI] assessments)3	←	→

1) Information about the procedure, including prosthesis replacement and/or the extent of surgery wound healing, will be collected.
2) The condition of the joint following joint replacement surgery will be assessed using the JOAScore.
3) If a sudden worsening of pain that does not occur in the normal progression of osteoarthritis occurs, the (sub)investigator will perform imaging test (X-ray and MRI) of the affected joint. Imaging test (X-ray and MRI) of other joints will be performed as needed by the (sub)investigator. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted. All images will be submitted to the central laboratory.

9.1.2 Re-screening

If re-screening is going to be performed after registration at the start of screening, after registration at the start of the pre-treatment observation period, or after registration at the start of the treatment period, then the study sponsor will be consulted in advance, written consent will be obtained again, and all of the endpoints, except for the imaging tests, will be assessed.

The imaging tests will not need to be redone if imaging test results are available from not more than 60 days after screening or the imaging day in the pre-treatment observation period.

9.2 Test/Observation Parameters and Time Points

9.2.1 Patient Characteristics

The (sub)investigator will investigate the following patient characteristics and inclusion/exclusion criteria between registration at the start of screening and baseline and record the results in the case report form. The (sub)investigator or a study support staff member will instruct the subject in how to use the IVRS (NRS score for the average pain on walking in the evaluated joint each day) and the treatment diary (amount of rescue drug used) starting in the pre-treatment observation period, and will check to make sure that the subject is reporting this information properly (see Attachment 4, "Rescue Drug Treatment Diary"). If an adverse event occurs after the start of screening, it will be recorded in the case report form. The date of the end of the 48-week treatment period will be recorded in the case report form.

Information Collected at the Start of Screening

(1) Sex
(2) Date of birth (Western calendar)
(3) Diagnosis
(4) Time of osteoarthritis diagnosis (the first diagnosis time)
(5) Pain location of osteoarthritis onset
(6) Concomitant drugs
(7) Concurrent illness(es)
(8) Alcohol, drug, and pain killer abuse status
(9) Previous therapeutic drug (Drug for osteoarthritis pain within 4 weeks before the start of screeing)
(10) Effect of treatment with the past-analgesic (Effect of NSAIDs, acetaminophen, and opioid. Reason in the case of intolerance them)

Information Collected During Screening

(1) Anatomical location of evaluated joint
(2) K-L grade
(3) WOMAC score (both knees and both hips evaluated)
(4) PGA
(5) Joint pain questionnaire
(6) Vital signs
(7) ECG
(8) Physical examination
(9) Standing blood pressure
(10) Survey of autonomic symptoms
(11) Neurological assessments
(12) Imaging assessments
X-ray test: both knees, both hips, both shoulders
MRI test: Evaluated joint, joint opposite the evaluated joint, and any knee or hip joint with a K-L grade of 3 or above
(13) General clinical laboratory tests
(14) Whether or not the subject is a female of childbearing potential and if not, then the reason thereof; and a pregnancy test (serum)
(15) Concomitant drugs
(16) Concomitant Therapies (Physical therapies)
(17) Height
(18) Weight

(19) Bone density

Information Collected at Baseline

(1) Amount of rescue drug taken
(2) NRS score for the average pain on walking in the evaluated joint
(3) All WOMAC items (only for the evaluated joint)
(4) PGA
(5) SF-36
(6) EQ-5D-5L
(7) Imaging assessments (MRI; if not confirmed during the screening period)
(8) Vital signs
(9) Standing blood pressure
(10) Joint pain questionnaire
(11) Survey of autonomic symptoms
(12) Neurological assessments (simplified version)
(13) Concomitant drugs
(14) Concomitant Therapies (Physical therapies)
(15) General clinical laboratory tests
(16) Pregnancy test (urine)
(17) Collection of blood samples for the pharmacokinetic assessments
(18) [redacted]
(19) [redacted]

9.2.2 Treatment Compliance

9.2.2.1 Investigational drug and comparative drug (MT-5547 and MT-5547 placebos)

The stipulated dosage and administration, treatment period, and administration method of the investigational drug or comparative drug will not change. The (sub)investigator will administer the investigational drug or comparative drug subcutaneously at the study site at each scheduled subject visit. Subjects will be monitored closely at the study site for 30 minutes after the administration of the investigational drug. The (sub)investigator or a study support staff member will record in the case report form the date and time of administration and location of administration at each subject visit from baseline on.

The administration of the investigational drug by the subject by self-injection will be done at the study site. The (sub)investigator will make sure that the subject properly administers the investigational drug subcutaneously, and the (sub)investigator or a study support staff member will record the date and time and location of administration of the self-injection in the case report form.

9.2.2.2 Control Drugs (Naproxen Tablets and Naproxen Placebo Tablets)

The (sub)investigator or a study support staff member will at each visit during the control drug treatment period check the subject's treatment compliance by questioning the subject and checking the amount of remaining drug. The (sub)investigator or a study support staff member will record in the case report form the dosing regimen of the control drug.

9.2.2.3 Rescue Drug

The dose of the rescue drug (acetaminophen) may not exceed the maximum permitted dose. The (sub)investigator or study support staff member will record the number of days the rescue drug was taken and the amount of rescue drug taken (number of tablets) in the case report form based on the treatment diary (see Attachment 4, "Rescue Drug Treatment Diary"). The (sub)investigator or a study support staff

member will recover the remaining drugs at baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and at treatment period discontinuation and will investigate the subject's treatment compliance and instruct the patient in how to take the rescue drug appropriately and in how to record the information appropriately in the treatment diary.

9.2.3 Efficacy Endpoints

9.2.3.1 Efficacy Assessment Procedures

As much as possible, the efficacy endpoints will be assessed each time in the same order and at the same location.

9.2.3.1.1 WOMAC

The (sub)investigator or study support staff member will ask the subject to complete Attachment 5, "WOMAC," at screening, baseline, Weeks 1, 2, 4, 8, 12, 16, 20, 28, 32, 36, 40, 44, 48, 52, 60, and 68, and at treatment period discontinuation or post-treatment observation period discontinuation, and will recover Attachment 5 from the subject after the subject has filled it out. The (sub)investigator or a study support staff member will check the information that has been filled out by the subject and if any revisions have been made will confirm the revisions that have been made by the subject and then enter the information in the case report form.

The WOMAC is a scale that is used to assess the activities of daily living in osteoporosis over the past 48 hours, and that comprises a total of 24 items, consisting of 5 pain subscale items, 17 physical functioning subscale items, and 2 stiffness subscale items. Each item is assessed using an 11-level scale.

The WOMAC will be used at screening to assess the right knee joint, the left knee joint, the right hip joint, and the left hip joint, and the evaluated joint* will be determined based on the WOMAC pain subscale scores. The WOMAC scores for the other time points will be assessed only for the evaluated joint.

* Determination of evaluated joint

The evaluated joint will be a joint (one of the right knee joint, the left knee joint, the right hip joint, and the left hip joint) for which joint replacement or some other surgical procedure is not being performed. If the K-L score is ≥2 in more than 1 joint, the evaluated joint will be the joint with the greater WOMAC pain score (average of 5 items) at screening. If 2 or more joints have a K-L score of ≥2 and the same WOMAC pain score, the evaluated joint will be the joint with the greater K-L score. If multiple joints have identical K-L grades and WOMAC pain scores, then the (sub)investigator will determine which joint should be evaluated.

9.2.3.1.2 Patient's Global Assessment (PGA) of Osteoarthritis

The (sub)investigator or a study support staff member will ask the subject to complete Attachment 6, "PGA," at screening, baseline, Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 60, and 68, and at treatment period discontinuation or post-treatment period discontinuation, and will recover Attachment 6 from the subject once the subject has filled it out. The (sub)investigator or a study support staff member will check the information, and if any revisions have been made will confirm the revisions that have been made by the subject and then enter the information in the case report form.

The patient's global assessment is a measure whereby the patient assesses global improvement in osteoarthritis using the following 5-level scale.

1. Much improved
2. Improved
3. No change
4. Worse
5. Much worse

9.2.3.1.3 NRS (Average Daily Pain in the Evaluated Joint)

The (sub)investigator or a study support staff member will instruct the subject to use the IVRS every night between the start of the pre-treatment observation period and the day before Week 16 to report, using an 11-level NRS score (0 is no pain, to 10 is worst pain that is no longer thought about), the average pain on walking in the evaluated joint each day. Subjects who fail to report NRS data on 4 or more days during IVRS training in the pre-treatment observation period will not be allowed to advance to the treatment period (they will be considered ineligible to start the treatment period).

The (sub)investigator or a study support staff member will confirm that the subject is reporting the information using the IVRS correctly.

9.2.3.1.4 SF-36

The (sub)investigator or a study support staff member will ask the subject to fill out Attachment 7, "SF-36," at baseline, Weeks 4, 8, 16, 24, 32, 40, 48, and 68, and at treatment period discontinuation or post-treatment period observation period discontinuation, and will then collect Attachment 7 once the subject has filled it out. The (sub)investigator or a study support staff member will check the contents and if any revisions have been made will check the revisions that have been made by the subject and then enter the information in the case report form.

9.2.3.1.5 EQ-5D-5L

The (sub)investigator or a study support staff member will ask the subject to fill out Attachment 8, "EQ-5D-5L," at baseline, Weeks 4, 8, 16, 24, 32, 40, 48, and 68, and at treatment period discontinuation or post-treatment period observation period discontinuation, and will then collect Attachment 8 once the subject has filled it out. The (sub)investigator or a study support staff member will check the contents and if any revisions have been made will check the revisions that have been made by the subject and then enter the information in the case report form.

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol group in order to provide a simple, generic measure of health for clinical and economical appraisal. The EQ-5D-5L descriptive system comprises the following 5 dimensions as measures of QOL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels, shown below.

1. No problems
2. Slight problems
3. Moderate problems
4. Severe problems
5. Unable/extreme

The respondent's overall health status is represented by a 5-digit number. The patient's health status as defined by these 5 parameters can be converted into a single numerical value that serves as the 5Q-5D-5L index score. A score of 1 indicates full health, and 0 means dead.

9.2.3.1.6 OMERACT-OARSI

The WOMAC pain subscore and physical function subscore and the PGA will be used to calculate the improvement rate based on the OMERACT-OARSI criteria.

9.2.4 Safety Endpoints

9.2.4.1 Objective Findings

9.2.4.1.1 General Clinical Laboratory Tests

The (sub)investigator will collect blood samples for clinical laboratory tests at screening, baseline, Weeks 4, 8, 12, 16, 24, 32, 40, 48, and 68, and at treatment period discontinuation or post-treatment period discontinuation, and will collect urine samples at screening, baseline, Weeks 16, 24, 48, and 68, and at treatment period discontinuation or post-treatment period discontinuation, and the following clinical laboratory test parameters will be measured at the central organization being commissioned to perform the clinical laboratory tests. The organization being commissioned to perform the clinical laboratory tests will be responsible for recovering the samples. The test slips provided by the organization being commissioned to perform the clinical laboratory tests will be stored by the study sites and the study sponsor. The (sub)investigator or a study support staff member will enter the dates of blood and urine samples collection and the results of the urine pregnancy tests in the case report form.

The (sub)investigator will enter the date of confirmation day and results (clinical significance) about the clinical laboratory tests in the source documents.

(1) Hematology tests:
RBC count, hemoglobin, hematocrit, MCHC, WBC count, platelet count, blood cell differential count (neutrophils, lymphocytes, monocytes, basophils, eosinophils)

(2) Blood biochemistry tests:
AST (GOT), ALT (GPT), ALP, LDH, gamma-GTP, total protein, albumin, total cholesterol, total bilirubin, BUN, serum creatinine, eGFR, serum electrolytes (Na, K, Cl, Ca, HCO_3^-), uric acid, triglycerides, BAP, inorganic phosphorus, CPK, CRP

(3) Urinalysis (qualitative):
Glucose, protein, occult blood, pH, bilirubin, nitrites, WBC count, specific gravity, urinary sediment (white blood cells, hyaline casts, epithelial cells, bacteria, yeast), ketones

(4) Urine electrolytes
Creatinine, phosphorus

(5) HbA1c (test at screening)

(6) Pregnancy test (only females of childbearing potential)
Serum test (test performed at screening), urinalysis (after baseline). Female subjects meeting the following criteria will be excluded from the pregnancy test requirements.
1) Postmenopausal women who have been amenorrheic for at least 1 year
2) Women who have undergone a surgical hysterectomy or bilateral ovariectomy

(7) Immune serum tests (tests performed at screening)
HBs antigen, HBs antibody, HCV antibody, HIV antibody
Furthermore, if a patient has a past history of hepatitis C, then an HCV-RNA test will be performed.

(8) Inflammation reaction test
ESR (This test will be performed by the study site, etc. if it is necessary to diagnose hip osteoarthritis based on the ACR criteria)

9.2.4.1.2 Height/Weight

The (sub)investigator will measure the subject's height at screening and will measure the subject's weight at screening, at Weeks 16, 48, and 68, and at treatment period discontinuation or post-treatment observation period discontinuation. The (sub)investigator or a study support staff member will enter this information in the case report form.

9.2.4.1.3 Vital Signs

The (sub)investigator will measure the subject's vital signs (body temperature, sitting blood pressure, and pulse rate) at screening, baseline, Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 68, and at treatment period discontinuation or post-treatment observation period discontinuation. The (sub)investigator or a study support staff member will record this information in the case report form. If the subject's pulse rate is less than 45 bpm at the time of the assessments performed following the administration of the investigational drug or comparative drug, then an ECG will be performed to check the subject's heart rate and rhythm. Furthermore, if the day of the assessment is a day on which investigational drug or comparative drug is to be administered, then the vital signs will be measured prior to investigational drug or comparative drug administration.

9.2.4.1.4 ECG

The (sub)investigator will perform a standard 12-lead ECG for approximately 5 minutes with the subject in a recumbent position prior to blood sample collection at screening, Weeks 48, and at treatment period discontinuation. The (sub)investigator or a study support staff member will record the subject's heart rate, RR, PR, QRS, and QT in the case report form. The (sub)investigator will check the information for the presence of any abnormal findings. ECGs will be taken at each of the vital sign measurement time points following the administration of the investigational drug or comparative drug whenever the pulse rate is less than 45 bpm, as well.

9.2.4.1.5 Physical examination

The (sub)investigator will assess the physical examination at screening, baseline, Weeks 24, 32, 48, 68, and at treatment period discontinuation and post-treatment observation perios discontinuation. The (sub)investigator or a study support staff member will enter this information in the case report form.

The physical examination will be assessed subject's overall impression and each part of the body (neurological, eyes, ear/nose/throat, cardiovascular, respiratory, abdominal, hepatic, gastrointestinal, musculoskeletal, and dermatological) using the following 3 categories.

- Normal
- Abnormal, Not Clinically Significant
- Abnormal, Clinically Significant

9.2.4.1.6 Joint Pain Questionnaire

The (sub)investigator or a study support staff member will ask the subject to fill out Attachment 9, "Joint Pain Questionnaire," at screening, baseline, Weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 68, and at treatment period discontinuation and post-treatment observation period discontinuation. The subject will record whether or not he or she experienced pain in the knee joints, hip joints, or shoulder joints, and the (sub)investigator or a study support staff member will check these entries after collection and if any revisions have been made will check the revisions that have been made by the subject and record the information in the case report form.

9.2.4.1.7 Assessment of Autonomic Nervous Symptoms

The (sub)investigator or a study support staff member will ask the subject to fill out Attachment 11, "Survey of Autonomic Symptoms," at screening, baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 68, and at treatment period discontinuation or post-treatment observation period discontinuation, and will recover said attachment after it has been filled out by the subject. The (sub)investigator will use the survey of autonomic symptoms that has been filled out by the subject to assess the subject's signs and symptoms of autonomic nervous disorders and will record the subject's symptom score and impact score in the case report form.

The symptom scores will be assessed using the following 2 categories (12 items for males and 11 items for females).

1. Yes
2. No

The impact scores will be assessed using the following 5 categories.

1. Not at all
2. A little
3. Some
4. A moderate amount
5. A lot

If the total symptom score at screening and at baseline is 4 or more or the total impact score at screening is 12 or more, the (sub)investigator will evaluate the autonomic symptoms of the subject and determine whether or not the subject should participate in the study ("3.3 Exclusion Criteria, (24)). After the start of investigational drug administration, the (sub)investigator will assess the signs, symptoms, and worsening in the subject's autonomic symptoms, and will, taking into account other outcome measures, confirm whether or not the subject has a sympathetic nervous disorder (see "11.2.2 Monitoring of Sympathetic Nerve Disorders").

These assessments should be performed by the same (sub)investigator throughout the term of the study. If the (sub)investigator determines that a specialist (a neurologist or a circulatory medicine specialist) needs to perform the sympathetic nervous disorder assessment, then the (sub)investigator will consult a specialist.

9.2.4.1.8 Standing Blood Pressure Assessments

The (sub)investigator or a study support staff member will measure the subject's standing blood pressure at screening, during the pre-treatment observation period, at baseline, at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, and 68, and at treatment period discontinuation or post-treatment observation period discontinuation. After the subject has been lying down in a supine position for at least 10 minutes, the subject's blood pressure and pulse rate will be measured twice, and the results recorded in the case report form for the purpose of diagnosing orthostatic hypotension. If the two measurements are substantially different and the (sub)investigator determines that an additional measurement is needed, then up to 2 more measurements may be performed (for a total of 4 measurements), and 2 stable measurement values will be recorded in the case report form. The (sub)investigator or a study support staff member will then measure the subject's blood pressure and pulse rate 1 and 3 minutes after the subject stands up from a lying down position for the purpose of diagnosing orthostatic hypotension, and will record the results in the case report form. The (sub)investigator or a study support staff member will check the reason why, and enter this information in the case report form if the subject was not able to remain standing. A detailed description of the procedures will be described separately, in the "Standing Blood Pressure Assessment Procedures." Furthermore, and automated manometer will be used for the blood pressure and pulse rate measurements.

(1) If any of the following criteria 1) to 3) are met, as in (2), additional tests will be performed. As in (4), additional tests will not be performed and the subject will be given a diagnosis of postural hypotension. In addition, investigational drug and comparative drug administration will be temporarily postponed.

1) Mean supine systolic blood pressure < 160 mmHg

If the systolic blood pressure 1 or 3 minutes after standing up decreases by 20 mmHg or more compared to that in a supine position, or if the diastolic blood pressure 1 or 3 minutes after standing up decreases by 10 mmHg or more compared to that in a supine position

2) Mean supine systolic blood pressure ≥ 160 mmHg

If the systolic blood pressure 1 or 3 minutes after standing up decreases by 30 mmHg or

more compared to that in a supine position, or the diastolic blood pressure 1 or 3 minutes after standing up decreases by 15 mmHg or more compared to that in a supine position

3) If the pulse rate 1 or 3 minutes after standing increases by 30 beats per minute or more compared to the pulse rate in a supine position
4) If the subject cannot remain standing during the standing blood pressure measurement because of dizziness or lightheadedness

(2) If any of the criteria of (1), 1) to 3) are met

Additional measurements will be performed a maximum of 2 times (for 3 measurements in total) for parameters that satisfied the criteria (blood pressure and/or pulse rate). If 2 of these 3 measurements meet any of the criteria listed in (1) 1) to 3), then the subject will be considered to have postural hypotension, and this will be treated as an adverse event. In addition, investigational drug and aomparative drug administration will be temporarily postponed.

If the subject is given a diagnosis of postural hypotension, another assessment will be performed in accordance with "11.2.2 Monitoring of Sympathetic Nervous System Disorders."

9.2.4.1.9 Neurological Tests

The (sub)investigator will perform neurological assessments at screening, Weeks 48 and 68, and at treatment period discontinuation or post-treatment observation period discontinuation, and will perform neurological assessments (simplified version) at baseline, Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 52.

The (sub)investigator will comprehensively assess the test findings for each of the cranial nerves, motor system, sensory system, reflexes, and coordination/balance, and make the assessment using the 3-level scale below, and record the result in the case report form. If an assessment is judged to be a clinically significant abnormality, then this abnormal finding will be recorded in the case report form.

In addition, whether or not the subject has symptoms of carpal tunnel syndrome will be recorded in the case report form.

1. Normal
2. Clinically insignificant abnormality
3. Clinically significant abnormality

Table 9.2-1: Neurological Test Parameters

	Full Version	Simplified Version
Cranial nerves	Papillary light reflex, eye movement, nystagmus, facial sensory/lower facial muscle movement, upper facial muscle movement, hearing, palate movement, head rotation, tongue movement	Papillary light reflex
Motor system	Shoulder abduction, elbow extension, elbow flexion, wrist dorsal flexion, wrist palmar flexion, finger extension, finger flexion, finger abduction	Finger extension, finger flexion, finger abduction
Sensory system	Pain, sense of position (articular sensation), sense of vibration	Pain, sense of position (articular sensation), sense of vibration
Reflexes	Biceps brachii, triceps brachii, patellar tendon, Achilles tendon	Patellar tendon, Achilles tendon

Coordination/balance	Finger-nose test, finger tapping movement, diadochokinesis (hand pronation/supination test), Romberg's test, walking	Finger-nose test, finger tapping movement, diadochokinesis (hand pronation/supination test), Romberg's test, walking

Neurological findings at screening that do not cause the subject to be excluded from the study will be recorded in the concurrent illnesses column. In the assessments of the findings after baseline, the (sub)investigator will record in the case report form details about any clinically significant abnormalities, and if there is a change from a "normal" finding or a clinically insignificant abnormality to a clinically significant abnormality, then this will be handled as an adverse event.

Detailed procedures are described separately in the "Neurological Test Procedures."

To the extent possible, the same (sub)investigator will perform the neurological tests throughout the study.

If the (sub)investigator determines that a specialist's opinion is needed for a subject who exhibits persistent or worsening neurological symptoms on the neurological tests, then a neurologist will be consulted. The additional neurological assessments performed as neede by a neurology specialist. In addition, if the (sub)investigator judges the additional neurological assessments necessary, consideration will be given to temporarily postponing the administration of the investigational drug and comparative drug.

If carpal tunnel syndrome is newly discovered, or if a worsening of symptoms pointing to carpal tunnel syndrome is found, then the subject will be discontinued from the study drug administration (see "12.1 Study drug administration discontinuation criteria").

9.2.4.1.10 Bone Density

The (sub)investigator will measure bone density by means of DEXA at screening, Week 48, and treatment period discontinuation. Furthermore, bone density measurements will be taken only at those study sites that are capable of taking such measurements. The locations of measurement will be the lumbar vertebra (L2-L4), the femoral head, and the total hip. These assessments of femur should be performed the same location throughout the term of the study. The (sub)investigator or a study support staff member will record the bone density (lumbar vertebra L2-L4, femoral head, and total hip) and the young adult mean (YAM) in the case report form.

9.2.4.1.11 Imaging Tests

The (sub)investigator will perform X-ray tests at screening, Weeks 16, 48, and 68, and at treatment period discontinuation or post-treatment observation period discontinuation, and will perform MRI tests at screening. The additional imaging tests (X-ray and MRI) performed as neede by the (sub)investigator throughout the term of the study. All images (both X-ray and MRI images) will be submitted to a central laboratory, and assessed centrally. The (sub)investigator or a study support staff member will record the imaging test dates in the case report form. Detailed descriptions of the tests are presented in the reference manual for this study.

(1) Screening

The following imaging tests will be performed for subjects who meet the eligibility criteria, and the images will be submitted to the central laboratory. These tests will also be performed if the central laboratory requests their conduction.

1) X-ray tests: Both knee joints, both hip joints, both shoulder joints

Anteroposterior images will be taken of both knees in a weight-bearing (standing), semiflexed position, and anteroposterior images will also be taken of both hip joints and both

shoulder joints.

The X-ray images will be centrally classified/assessed based on the K-L classification criteria (K-L grade ≥ 2) to ensure that there is no adjudicated arthropathy or anything else that would cause the patient to be excluded from the study.

2) MRI tests: The evaluated joint, the joint contralateral to the evaluated joint, and any knee or hip joint with a K-L grade of 3 or above

MRI images will also be taken by the (sub)investigator if X-ray images reveal any findings that need to be evaluated more carefully. In addition, MRI tests will be performed as needed by the (sub)investigator. The MRI images will be assessed centrally to make sure that there is no Adjudicated arthropathyor anything else that would cause the patient to be excluded from the study.

The (sub)investigator will perform checks before the following specified days to make sure that the results of the central assessments meet the study eligibility criteria.

- X-ray tests: By the start of the pre-treatment observation period
- MRI tests: By baseline

If the results of the centralized assessments cannot be checked by each scheduled day, then re-screening will be performed.

(2) Baseline and after baseline: at Weeks 16, 48, and 68, and at treatment period discontinuation or post-treatment observation period discontinuation

The imaging tests will be performed for the subjects, and the images will be submitted to a central laboratory.

If the (sub)investigator or the central laboratory determine that there is an abnormal finding compared to normal osteoarthritis, and requests that an MRI be performed, an MRI will be performed, and the images submitted to the central laboratory.

1) Week 16

The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator. The (sub)investigator will check the X-ray images before administered the investigational drug or comparative drug whether or not investigational drug or comparative drug should be administered. If an abnormality is found, administration will be postponed. If the central assessments rule out adjudicated arthropathy, then investigational drug administration may be resumed.

2) Week 48

The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator.

3) Treatment period discontinuation

The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator. The images will be submitted to a central laboratory. If more than 30 days have passed since the last images were taken, images will be taken again. If not more than 30 days have passed, imaging tests will be performed if the (sub)investigator determines that it is necessary.

If joint replacement surgery is required, the MRI tests of the joint of surgery will be

performed (for more detailed information, see "9.2.4.1.13 Assessments if a Joint Replacement Procedure Is Scheduled").

4) Week 68

The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator.

5) Post-Treatment observation period discontinuation

The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed by the (sub)investigator. The images will be submitted to a central laboratory.

If joint replacement surgery is required, the MRI tests of the joint of surgery will be performed (for more detailed information, see "9.2.4.1.13 Assessments if a Joint Replacement Procedure Is Scheduled").

(3) If a sudden worsening of pain occurs

The (sub)investigator will postpone investigational drug or comparative drug administration, and perform imaging test (X-ray and MRI) of the affected joint. Imaging test (X-ray and MRI) of other joints will be performed as needed by the (sub)investigator. maging tests will also be performed if the central laboratory requests that additional tests be conducted. All images will be submitted to the central laboratory. The results of the central assessment will be checked by the (sub)investigator. The investigational drug or comparative drug administration will be postponed until the central laboratory rules out adjudicated arthropathy. If the central assessment result is adjudicated arthropathy, then study treatment must be discontinued. If adjudicated arthropathy is ruled out by the central assessment, then the (sub)investigator will determine whether or not treatment should be continued.

9.2.4.1.12 Injection Site Assessments

The injection site will be confirmed at baseline, Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. If a clinically significant abnormality is found, this abnormality will be recorded in the case report form.

9.2.4.1.13 Assessments if a Joint Replacement Procedure Is Scheduled

If a subject who has undergone a joint replacement procedure during the study for a reason other than adjudicated arthropathy does not have a worsening of joint pain, then administration of the investigational drug and comparative drug may be continued until the joint replacement procedure is performed.

Follow-up will be performed in accordance with the procedures described in the Schedule of Assessments at Discontinuation and Post-joint replacement procedure test/observation schedule (4 and 8 weeks after the procedure) for all subjects who undergo a joint replacement procedure during the study (9.1 (3) Post-joint replacement procedure test/observation schedule).

The assessments at discontinuation (imaging tests) will be performed if more than 30 days have passed since the last imaging tests were performed. They will also be performed even if fewer than 30 days have passed if the (sub)investigator judges it necessary.

- X- ray tests: Both knee joints, both hip joints, both shoulder joints
- MRI tests: Joint of joint replacement surgery

MRI test of other joints will be performed as needed by the (sub)investigator. If the assessments at discontinuation cannot be performed, then images taken before the joint replacement procedure is performed. All images will be submitted to the central laboratory. If the assessments at discontinuation

cannot be performed before the joint replacement procedure is performed, images of normal examination will be submitted to the central laboratory. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted.

The X-ray tests (both knee joints, both hip joints, both shoulder joints) will be performed at 4, 20 weeks after the procedure

The (sub)investigator will measure the subject's vital signs, join pain questionnaire (Attachment 9, "Joint Pain Questionnaire"), JOA score (Attachment 11, "JOA score"), X-ray test (both knee joints, both hip joints, both shoulder joints), adverse event, and concomitant drugs. The (sub)investigator or a study support staff member will record the information in the case report form.

If a sudden worsening of pain that does not occur in the normal progression of osteoarthritis occurs during the post-joint replacement procedure test/observation period, the (sub)investigator will perform imaging test (X-ray and MRI) of the affected joint. Imaging test (X-ray and MRI) of other joints will be performed as needed by the (sub)investigator. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted. All images will be submitted to the central laboratory.

JOA Score (The Japanese Orthopaedic Association Score)

The (sub)investigator will assess the condition of the affected joints using the JOA score (Attachment 11, "JOA Score") at discontinuation and at 4 and 20 weeks after the procedure. The (sub)investigator or a study support staff member will record the information in the case report form. JOA Score is recorded by the (sub)investigator to assess a condition before and after the procedure. As much as possible, the same investigator will be responsible for completing this questionnaire throughout the study.

9.2.4.2 Adverse Events

An adverse event is any clinically undesirable or unintended sign (including clinically significant test value abnormalities), symptom, or disease that occurs during the safety assessment period following the start of screening, regardless of whether or not it is causally related to the study drug. Adverse events include worsenings of existing symptoms (clinically significant worsening in the frequency or severity) that are temporally related to study drug administration.

The (sub)investigator will inform the study sponsor of any adverse events that occur in a subject between the start of screening and the end of post-treatment observation peiod and that meet the definition of a "serious adverse event" in accordance with "11.1 Handling of Serious Adverse Events."

(1) Symptoms or disease

The (sub)investigator will check for the presence or absence of adverse events by questioning and examining the subject.

(2) Objective findings

The (sub)investigator will handle as an adverse event any event that is judged to be a clinically significant abnormality.*

*: A "clinically significant abnormality" will be determined based on the following criteria.

- When there is a relationship to a clinical sign or symptom

  However, if these symptoms or signs have been reported as separate adverse events, then there is no need to handle this test value abnormality as an adverse event.
- When a medical or surgical treatment has been administered for the test value abnormality
- when the study drug administration method has been changed (e.g., a change in the dose, treatment interruption, treatment discontinuation) because of the test value abnormality
- When the (sub)investigator determines for some other reason that the finding is a clinically significant abnormality

(3) Adverse event assessment and criteria

1) Day of onset

The day of onset will be the day on which the symptom is observed or the day on which the clinical test value abnormality was observed.

2) Severity

Adverse event severity will be classified using the following categories.

1. Mild: No effect on the subject's normal activities
2. Moderate: The event has some impact on the subject's normal activities
3. Severe: The event prevents the subject from engaging in the subject's normal activities

3) Seriousness

The seriousness of adverse events will be classified using the following categories.

1. Not serious: Anything other than 2 below
2. Serious: Any of a) through f) below

a) The event results in death.

b) The event is life-threatening (here, "life-threatening" indicates a situation in which the patient is placed at risk of death at the time of onset of the event, not that the subject might have died had the event been more severe).

c) The event results in hospitalization or the prolongation of a hospital stay for treatment (this does not include hospitalization for monitoring or social reasons or hospitalization associated with the subject's personal circumstances).

d) The event results in permanent or marked disability or dysfunction (the essential elimination of the ability to perform a normal vital function).

e) The event results in a congenital anomaly or defect.

f) The event is some other event or reaction that is determined to be medically significant

(Important medical events that could place the patient in danger and that require medical treatment or intervention to prevent a result such as those meeting the above definitions, even if they are not immediately life-threatening or result in death or hospitalization, should be classified as serious, and whether or not they constitute a serious adverse event should be judged based on the medical and scientific evidence. Examples of such events include allergic bronchospasm requiring intensive care, either at home or in an emergency room, blood dyscrasias or seizures, even if they do not result in hospitalization, and drug dependence or abuse.)

4) Causal relationship to the investigational drug or comparative drug

The (sub)investigator will assess whether or not it is "logically possible" that the study drug caused the adverse event. This assessment will be made taking into account non-study-drug factors, such as the underlying disease, the natural course of the underlying disease (e.g., complications), the concomitant therapies, and other risk factors, as well as the temporal relationship between the event and study drug administration (e.g., recurrence after re-administration, resolution after treatment discontinuation). Furthermore, adverse events for which the causal relationship to the study drug is classified as being "logically possible" will be considered adverse reactions.

1. A relationship is logically possible
2. A relationship is not logically possible

5) Outcome

The outcomes of adverse events will be classified using the following 6 categories.

1. Recovered
2. Improved
3. Did not recover
4. Recovered, but with sequelae
5. Death
6. Unknown

6) Day of outcome

The day of outcome will be classified according to the following criteria.

Recovered: The day on which the subject recovered from the event. However, if the day on which the subject recovered cannot be identified, then the day of outcome will be the day on which the outcome was confirmed or determined.

Improved: The day on which the improvement was confirmed or determined.

Did not recover: The day on which it was confirmed or determined that the subject did not recover.

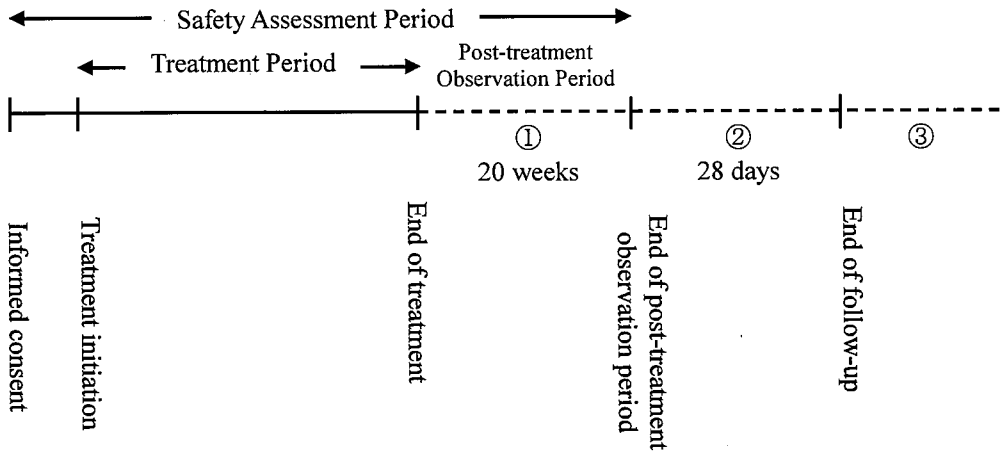
Recovered, but with sequelae: The day on which the presence of sequelae was confirmed or determined.

Death: The day of death. However, if the day of death cannot be determined, then this will be the day on which the death was confirmed or determined.

Unknown: If the outcome is unknown because the subject dies due to a cause other than the adverse event, then this will be the day of death. Otherwise, this will be the day on which the outcome was confirmed or determined.

Follow-up

<u>When a joint replacement procedure is not going to be performed:</u>

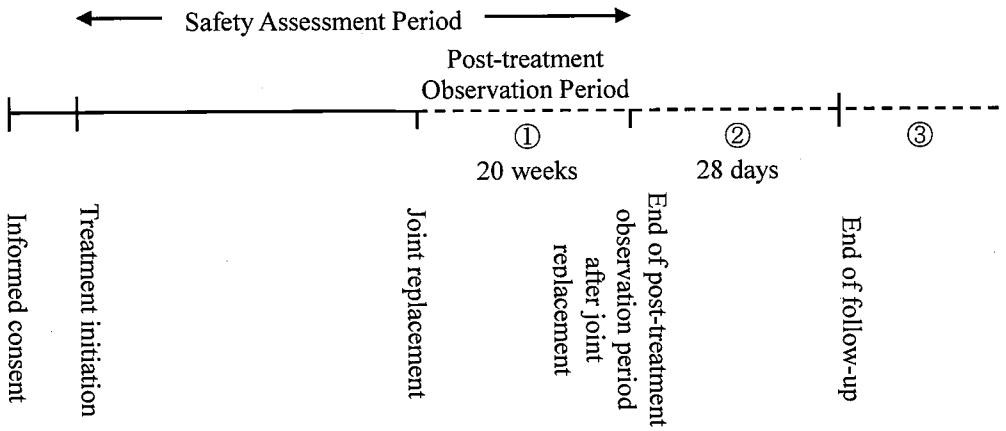


- The period indicated by ① that comes after the end of the treatment period (the post-treatment observation period) lasts for 20 weeks from the day after the day of the 48-week treatment period. For subjects discontinuing from the study, the 24 weeks after the last dose of MT-5547

or MT-5547 placebo will be considered the post-treatment observation period, during which time subjects will be monitored for the emergence of adverse events.

- The duration of Period ② after the end of the post-treatment observation period will be 28 days; during this time, follow-up will be performed for the adverse events that occurred during the assessment period (the treatment period + Period ①).
- The subjects who discontinue prior to study treatment initiation do not go into the post-treatment observation period (Period ①) but follow-up (Period ②) will be performed for the adverse events that occurred during the period from screening to discontinuation.
- The courses of the adverse events for which follow-up has been performed during Period ② after the end of the post-treatment observation period will be recorded in the cases report form.
- The outcome date that is entered into the case report form for an adverse event for which the outcome is improved or did not recover will be the date of the last observation during Period ② after the end of the post-treatment observation period.
- For adverse reactions for which the outcome was improved or did not recover at the end of Period ② after the end of the post-treatment observation period, the subsequent course (③) will be investigated.
- If there is a valid reason for cutting short the investigation after the end of the assessment period (after the end of Period ①), then this reason will be recorded in the source documents, and the follow-up investigation will be concluded.

<u>When a joint replacement procedure is going to be performed:</u>



- Follow-up will be performed for joint replacement procedures conducted during the treatment period + 20 weeks (the safety assessment period for "When a joint replacement procedure is not going to be performed").
- The duration of Period ① after the end of the treatment period (the post-treatment observation period) will be 20 weeks from the day after the joint replacement procedure is performed; during this period, the subject will be monitored for adverse events.
- The post-treatment observation period ② after the end of the post-treatment observation period will be 28 days, during which follow up will be performed for the adverse events that occurred during the assessment period (from treatment initiation until the end of the post-treatment observation period after the joint replacement procedure was performed).

- The courses of the adverse events for which follow-up is performed during the post-treatment observation period ② after the end of the post-treatment observation period will be recorded in the case report form.
- The outcome day that is recorded in the case report form for an adverse event for which the outcome is improved or did not recover will be the day of the last observation during Period ② after the end of the post-treatment observation period.
- For adverse reactions for which the outcome was improved or did not recover at the end of the post-treatment observation period ② after the end of the post-treatment observation period, the subsequent course (③) will be investigated.
- If there is a valid reason for cutting short the investigation after the end of the post-treatment observation period after the joint replacement procedure is performed, then this reason will be recorded in the source documents, and the follow-up investigation will be concluded.

(4) Information recorded in the case report form

If an adverse event occurs, the (sub)investigator will record the adverse event term,* date of onset, severity, seriousness, causal relationship to study drug, action taken with respect to study drug, non-study-drug-related actions, outcome, and the date of the outcome in the adverse event column of the case report form.

*: The adverse event terms will conform to the following criteria.

- As a rule, the diagnosis term will be used.
- If the diagnosis term is unclear, the symptom name will be used.
- If multiple symptoms emerge, if they indicate a single diagnosis term, then this diagnosis term will be used.
- Surgical procedures, etc. will not be considered adverse events; if an illness and/or symptom requiring a surgical procedure, etc. is confirmed, then this will be considered an adverse event.

9.2.5 Pharmacokinetic Parameters

At the measurement time points, the (sub)investigator or a study support staff member will collect blood samples for the purpose of measuring the serum MT-5547 concentration and anti-MT-5547 antibodies. The dates and times of blood sample collection will be recorded in the case report form.

The measurement results will be stored by the drug concentration measurement organization until unblinding, and will not be divulged to any third party.

(1) Serum MT-5547 concentration measurements

1) Blood sample collection times and volumes collected

(a) Blood sample collection times

- Before the administration of investigational drug or comparative drug on the visits at baseline, and Weeks 4, 8, 12, 16, 24, 32, 40, and 44
- On the visits at Weeks 1, 2, 48, 52, 56, and 68
- Subjects discontinuing from the study: At discontinuation and at 24 weeks after the last dose of investigational drug or comparative drug

(b) Number of blood samples collected: 15

(c) Volume of blood collected: [redacted]

2) Blood processing

The collected blood will be allowed to stand at room temperature for 30 minutes and then subjected to centrifugal separation for 15 minutes at 1200 g. Within 30 minutes after centrifugal separation, the serum will be divided equally into 2 tubes and frozen and stored at a temperature not greater than -20°C.

The frozen and stored serum samples will be collected from the study site by the organization being commissioned to perform the clinical laboratory tests and stored frozen at a temperature of -70°C. The organization being commissioned to perform the clinical laboratory tests will send the test samples (MT-5547 group only) to the drug concentration measurement organization in accordance with the materials list. When shipping the samples, they will be shipped with a sufficient quantity of dry ice.

3) Information recorded in the case report form

The following information will be recorded in the case report form.

- Day 1 and Weeks 1, 4, 8, 12, 16, 20, 24, 32, 40, and 44: The date and time of investigational drug or comparative drug administration on the day of blood sample collection, and the date and time of blood sample collection
- Visits at Weeks 2, 48, 52, 56, and 68, at discontinuation, and at 24 weeks after the last dose of investigational drug or comparative drug: date and time of blood sample collection

(2) Serum anti-MT-5547 antibody measurement

If the sample is positive for anti-MT-5547 antibodies, the sample will also be tested for neutralizing antibodies.

1) Blood sample collection time points, and volumes collected

(a) Blood sample collection times

- Before investigational drug or comparative drug administration at baseline and Weeks 16 and 24
- At the subject visits at Weeks 48 and 68
- Subjects of discontinuation; at discontinuation, Week 24 after the end of treatment.

(b) Number of blood samples collected: 5

(c) Volume of blood collected: [redacted]

2) Blood processing

The collected blood will be allowed to stand at room temperature for 30 minutes and then subjected to centrifugal separation for 15 minutes at 1200 g. Within 30 minutes after centrifugal separation, the serum will be divided equally into 2 tubes and frozen and stored at a temperature not greater than -20°C.

The frozen and stored serum samples will be collected from the study site by the organization being commissioned to perform the clinical laboratory tests and stored frozen at a temperature of -70°C. The organization being commissioned to perform the clinical laboratory tests will send the samples (all samples) to the drug concentration measurement organization. When shipping the samples, they will be shipped with a sufficient quantity of dry ice.

3) Information recorded in the case report form

The following information will be recorded in the case report form.

- At baseline and Weeks 16 and 24: The date and time of investigational drug or comparative drug administration on the day of blood sample collection, and the date and time of blood sample collection
- Visits at Weeks 48 and 68, at discontinuation, and at 24 weeks after the last dose of investigational drug or comparative drug: date and time of blood sample collection

[redacted]

[redacted]

1)

(a)

(b)

(c)

2)

3)

[redacted]

10. Assessment Methods and Criteria

10.1 Efficacy

For details, see "9.2.3 Efficacy Endpoints."

(1) Primary efficacy endpoint
WOMAC pain score (change from baseline at Week 16)

(2) Key secondary efficacy endpoint
WOMAC physical function score (change from baseline at Week 16)

(3) Secondary efficacy endpoint

1) Patient Global Assessment (PGA) (change from baseline at each assessment time point)
2) WOMAC pain score (change from baseline at each assessment time point)
3) WOMAC physical function score (change from baseline at each assessment time point)
4) WOMAC stiffness score (change from baseline at each assessment time point)
5) WOMAC global score (change from baseline at each assessment time point)
6) Proportions of subjects exhibiting improvements of 30% and 50% in the WOMAC pain score compared to baseline (Weeks 16 and 24)

7) Proportions of subjects exhibiting improvements of 30% and 50% in the WOMAC physical function score compared to baseline (Weeks 16 and 24)
8) Numerical rating scale (NRS) score for the average pain on walking in the evaluated joint each day (change from baseline at each assessment time point)
9) SF-36 (change from baseline at each assessment time point)
10) EQ-5D-5L (change from baseline at each assessment time point)
11) Percent improvement based on the OMERACT-OARSI criteria (Weeks 16 and 24)
12) Rescue medication dose (number of days taken, and amount (number of tablets) taken)

10.2 Safety

(1) Adverse events and adverse reactions(for more detailed information, see "9.2.4.2. Adverse Events")
(Adjudicated arthropathy, sympathetic nerve disorders and altered peripheral sensation are defined as adverse events of special interest (AESI))
(2) General clinical laboratory tests
(3) Weight
(4) Vital Signs
(5) ECG
(6) Physical examination
(7) Joint pain questionnaire
(8) Survey of autonomic symptoms
(9) Standing blood pressure
(10) Neurological assessments
(11) Bone Density
(12) Imaging Tests
(13) Injection site assessments
(14) Assessments if a Joint Replacement Procedure Is Scheduled

10.3 Pharmacokinetics

(1) Serum MT-5547 concentration
(2) Anti-MT-5547 antibodies

Before starting to take the measurements, the drug concentration measurement organization will prepare a separate study protocol for the serum MT-5547 concentration and anti-fasinumab antibody measurements, The drug concentration measurement organization will prepare a measurement results report detailing the measurement results.

10.4 Other

(1) [redacted]

(2)

11. Ensuring Subject Safety

11.1 Handling of Serious Adverse Events

If serious adverse events occur between the start of screening and the final assessment time point in the post-treatment observation period, the (sub)investigator will immediately provide the subject with appropriate treatment irrespective of the presence or absence of a causal relationship to the study drug.

The (sub)investigator will immediately report to the monitor any serious adverse events that occur, and will use the form shown in Attachment 12 (Serious Adverse Event Report Form / Device Failure Report Form) to provide the study sponsor with a detailed report, including the causal relationship to the study drug, within 7 days after receiving the report. In addition, the principal investigator will report the following serious adverse events to the director of the study site.

Also, if device failures on pre-filled syringe that may cause serious adverse events occure, the (sub)investigator will immediately report to the monitor the device failures, and will use the form shown in Attachment 12 (Serious Adverse Event Report Form / Device Failure Report Form) to provide the study sponsor with a detailed report. In addition, the principal investigator will report the device failures to the director of the study site.

Serious Adverse Event Definition

The level of seriousness of adverse events will be classified as described below.

1. Not serious: Any adverse event not meeting the criteria listed in 2 below.
2. Serious: Any of a) through f) below
   a) Adverse event resulting in death
   b) Life-threatening adverse event (Here, a "life-threatening adverse event" refers to any situation where the patient is placed at risk of death at the time of onset of the event; it does not refer to a situation where the patient could have died if the event had been more severe.)
   c) An event that requires the patient to be hospitalized or to remain in the hospital for a longer period for treatment (except for situations in which the patient is hospitalized for management or societal reasons, or because the patient wants to be hospitalized)
   d) An event that results in permanent or marked impairment or disability (fundamental loss of the ability to perform normal daily activities).
   e) An event that results in a congenital anomaly or defect.
   f) Any other event or reaction that is judged to be medically significant (Major medical events that, even if they are not life-threatening or result in death or hospitalization immediately, could put the patient in danger or that require action or treatment to ensure that they do not result in an outcome such as that described above should be considered serious events. Whether or not this describes the event in question must be decided based on medical and scientific evidence. Examples of such events are allergic bronchospasm requiring intensive therapy in the ICU or at home, blood disorders or convulsions, even if they do not result in hospitalization, and drug dependency or drug abuse.)

11.2 Handling of Adverse Events of Special Interest

Adjudicated arthropathy, sympathetic nerve disorders and altered peripheral sensation are defined as adverse events of special interest (AESI) for the sake of investigating the safety profile of MT-5547.

If an adverse event of special interest occurs between the start of investigational drug or comparative administration at baseline and the last assessment time point in the post-treatment observation period, the (sub)investigator will immediately administer appropriate treatment to the subject, regardless of whether or not there is a causal relationship to the study drug.

If a clinically significant adverse event occurs and it is judged to constitute adjudicated arthropathy on the basis of central assessment of imaging tests, or if a specialist (neurologist or circulatory specialist) finds that the event constitutes a sympathetic nervous system disorder, or the (sub)investigator due to the findings of "9.2.4.1.9 Neurological examinations", physicians recognized altered peripheral sensation judged to require inquiries to specialists in neurologist, or altered peripheral sensation continuing for more than 2 months, the (sub)investigator will notify the monitor immediately, and will use the form provided in Attachment to supply the study sponsor with detailed information about the event, including the causal relationship to the study drug, within 7 days of reporting the event to the monitor.

11.2.1 Monitoring of Adjudicated Arthropathy

The (sub)investigator will at each visit day perform a comprehensive assessment of the subject's pain and other clinical symptoms and imaging (including pre-operative imaging test) assess whether or not the subject has arthropathy.

- Primary Osteonecrosis
- SIF
- RPOA Type 1
- RPOA Type 2
- DA

If a clinically significant worsening of joint pain* is found at any joint, the (sub)investigator will postpone the administration of the investigational drug or comparative drug, perform imaging test (X-ray and MRI) of the affected joint. Imaging test (X-ray and MRI) of other joints will be performed as needed by the (sub)investigator. Imaging tests will also be performed if the central laboratory requests that additional tests be conducted. All images will be submitted to the central laboratory. The (sub)investigator or a study support staff member will record the results of the assessment in the case report form (for more detailed information, see "9.2.4.1 Objective Findings, (11) Imaging Tests").

The investigational drug or comparative drug administration will be postponed until the central laboratory rules out adjudicated arthropathy. If adjudicated arthropathy is ruled out by the central assessment, the (sub)investigator will determine whether or not study treatment should be continued. If the result of the central assessment is adjudicated arthropathy, then study treatment must be discontinued, and appropriate actions taken (see "12.1 Study Drug Administration Discontinuation Criteria"). If a joint replacement procedure is required, all of the assessments that are to be performed at discontinuation will be completed as much as possible before the procedure is performed (for more detailed information, see "9.2.4.1 Objective Findings, (13) Assessments if a Joint Replacement Procedure Is Scheduled").

*: Worsening of arthralgia

When the (sub)investigator concludes that there is a sudden worsening of pain that would not be seen in the normal progression of osteoarthritis is persisting (for 2 weeks as a rule, but in less than 2 weeks at the (sub)investigator's discretion).

11.2.2 Monitoring of Sympathetic Nerve Disorders

Sympathetic nerve disorders will be assessed based on adverse event reports, standing blood pressure assessments, and autonomic nerve symptom assessments. The (sub)investigator will assess whether or not signs or symptoms of autonomic nerve disorders have appeared or worsened. Sympathetic nerve disorders will be confirmed only after an examination performed by a specialist (a neurologist or a circulatory medicine specialist).

11.2.2.1 If orthostatic hypotension is diagnosed

If the (sub)investigator reaches a diagnosis of orthostatic hypotension based on "9.2.4.1.7 Standing Blood Pressure Assessment," the subject will come in for another visit at between 1 and 10 days after the day of this diagnosis for a reassessment of the orthostatic hypotension. The (sub)investigator or a study support staff member will enter the dates of the assessment and the test results in the case report form.

If orthostatic hypotension is not diagnosed at the reassessment, then investigational drug

administration may be resumed.

If orthostatic hypotension is diagnosed at the reassessment, then the subject will be referred to a specialist (neurologist or circulatory medicine specialist) for an assessment of whether or not sympathetic nervous system dysfunction is present. If the presence of a sympathetic nerve disorder is not suggested, as shown below, based on the results of the specialist's assessment, or if another cause is identified (e.g., if a new drug therapy that is known to cause hypotension has been initiated), then the administration of investigational drug may be resumed.

(1) Bradycardia (lightheadedness)
(2) Orthostatic hypotension (lightheadedness on standing)
(3) Syncope
(4) Abnormal sweating (e.g., sweating not observed even in condition in which it would be expected)

Post-Orthostatic Hypotension Diagnosis Procedures (Figure 11.2-1: Algorithm Following a Diagnosis of Orthostatic Hypotension)

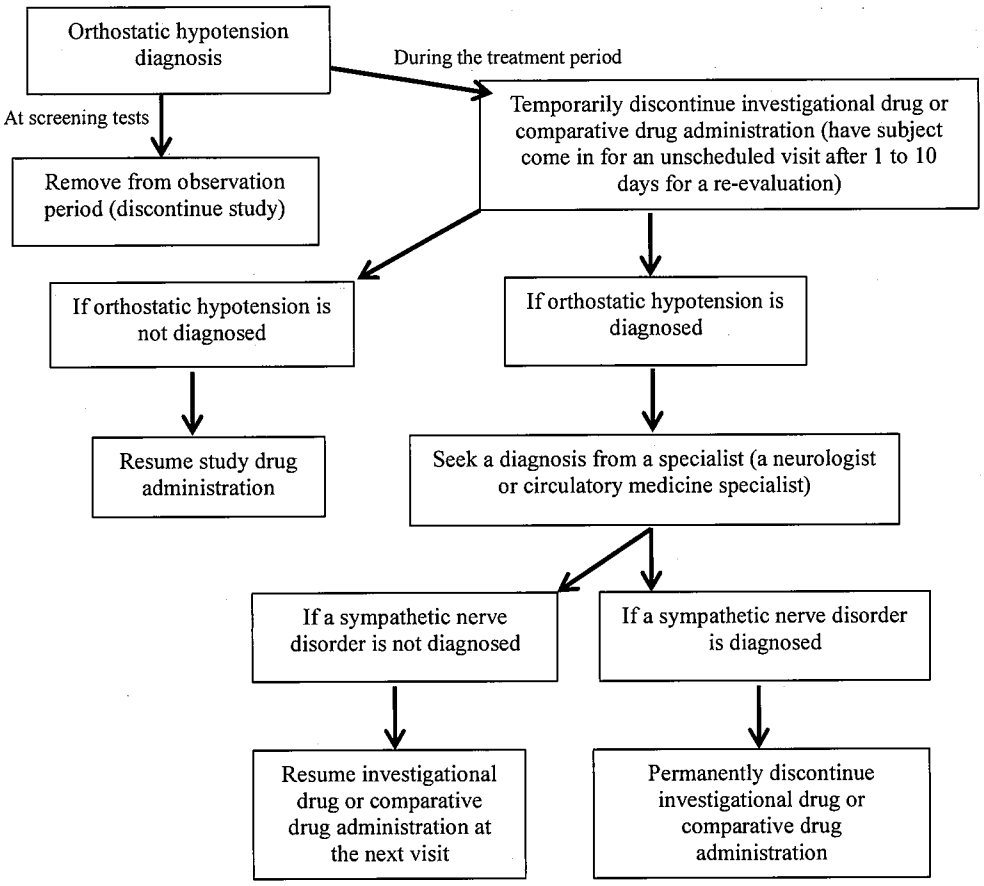


Figure 11.2-1: Procedure Following a Diagnosis of Orthostatic Hypotension

If the specialist determines that sympathetic nervous system dysfunction is present, the investigational drug will not be administered (see "12.1 Subject Study Discontinuation Criteria").

The (sub)investigator will enter the event as sympathetic nervous system dysfunction in the case report form only if it is diagnosed by a specialist as being sympathetic nervous system dysfunction.

11.2.2.2 If the sympathetic nervous system dysfunction is suspected or worsen

If symptoms that are suggestive of moderate to severe, or as determined by the (sub)investigator clinically significant, sympathetic nervous system dysfunction emerge or worsen, and do not resolve or return to a baseline level within 2 weeks (or less, at the discretion of the (sub)investigator), then the administration of the investigational drug and comparative drug will be temporarily postponed, and a specialist will be consulted.

If the specialist determines that sympathetic nervous system dysfunction is present, the investigational drug will not be administered (see "12.1 Subject Study Discontinuation Criteria"). However, if sympathetic nervous system dysfunction is ruled out, investigational drug administration may be resumed.

The (sub)investigator will enter the event as sympathetic nervous system dysfunction in the case report form only if it is diagnosed by a specialist as being sympathetic nervous system dysfunction.

11.2.3 Monitoring of Altered Peripheral Sensation

Altered Peripheral Sensation (eg, Paraesthesias and Dysaethesias) are important identified risk in fassinumab and other anti-NGF antibody (see INVESTIGATOR'S BROCHURE).

The (sub)investigator due to the findings of "9.2.4.1.9 Neurological examinations", physicians

recognized altered peripheral sensation judged to require inquiries to specialists in neurologist, or altered peripheral sensation continuing for more than 2 months, the (sub)investigator will record in the case report as adverse events of special interest (AESI).

11.3 Reporting of Pregnancies

The (sub)investigator will notify the monitor immediately if it is learned that the embryo or fetus of a female subject (or the female partner of a male subject) may have been exposed to the investigational drug or comparative drug prior to the end of the contraception period (from the day of consent until 20 weeks after the final dose), and will within 7 days of reporting the pregnancy to the monitor use the pregnancy reporting form in Attachment 14 to inform the study sponsor. If a female subject (or the female partner of a male subject) wants to give birth, the (sub)investigator will to the extent possible perform follow-up until the birth and investigate whether or not the study drug had any effects on the newborn, and will use the pregnancy reporting form in Attachment 14 to inform the study sponsor of the results of this investigation.

11.4 Informing the Subject's Other Doctors

The (sub)investigator will check whether or not the subject is being treated outside the context of this study both before the start of the during the study. If a subject is being treated by another doctor, this doctor will be informed, with the subject's consent, of the subject's participation in this study. In addition, the (sub)investigator of a study support staff member will give the subject a study participation card or the like and instruct the subject to present it to other hospitals or departments to inform other doctors of the subject's participation in the study.

11.5 Independent Data Monitoring Board

An independent data monitoring board will periodically assess unblinded data, and will make recommendations to the study sponsor regarding the appropriateness of continuing the study and about the need for protocol amendments.

The independent data monitoring board will include independent statistical and medical experts. For more details, the overseas independent data monitoring committee procedures (DMC Charter) will be followed.

12. Subject Study Discontinuation Criteria and Procedures

12.1 Study Drug Administration Discontinuation Criteria

If any of the following discontinuation criteria are met, the study drug administration will be discontinued.

(1) If the subject asks to be discontinued from the study
(2) If it is discovered that the subject is clearly unsuitable for study participation
(3) If the (sub)investigator determines that it would be difficult to continue the study because of the emergence of, for example, an adverse event
(4) If the (sub)investigator determines that it would not be appropriate to continue the study because of a worsening of the subject's underlying disease
(5) If it becomes necessary to continue to administer one of the prohibited concomitant drugs or one of the prohibited concomitant therapies listed in "8.5.1 Prohibited Concomitant Drugs/Therapies"
(6) If a joint replacement procedure is performed
(7) If a clinically significant adverse event, as defined below, occurs.

1) Adjudicated arthropathy
2) Sympathetic nervous system disorder

(8) If carpal tunnel syndrome is newly discovered, or if a worsening of symptoms pointing to carpal tunnel syndrome is observed

(9) If it is discovered that the subject is pregnant

(10) If the (sub)investigator determines that the study should be discontinued for some other reason.

[redacted]

12.2 Study Discontinuation Criteria

If any of the following discontinuation criteria are met, the (sub)investigator will discontinue the study for that subject.

(1) If the subject requests discontinuation.

(2) If it is determined that, for example, given the subject's circumstances, the study cannot be continued.

(3) If notification is received from the study sponsor that the entire study is being discontinued.

(4) If the (sub)investigator otherwise determines that the study should be discontinued.

[redacted]

12.3 Discontinuation Procedures

If a subject is discontinued from the study between the day consent is obtained and the start of the treatment period, the (sub)investigator will initiate appropriate therapeutic actions for the subject and will register the discontinuation of the study before the start of the treatment period using the IWRS, in accordance with "8.2 Subject Registration," sections 8.2.2 through 8.2.4.

If a subject is discontinued from the study during the treatment period, the (sub)investigator will initiate appropriate therapeutic actions for the subject and will inform the monitor promptly that the subject is being discontinued, and will register the discontinuation using the IWRS in accordance with "8.2 Subject Registration, section 8.2.6 Discontinuation Reception". The (sub)investigator will also instruct the subject to come in to the study site promptly so that the tests and observations that are stipulated should be performed at discontinuation may be performed (see "9.1.1 Test/Observation Schedule").

If a subject is discontinued from the study during the post-treatment observation period, the (sub)investigator will initiate appropriate therapeutic actions for the subject and will inform the monitor promptly that the subject is being discontinued. The (sub)investigator will also instruct the subject to come in to the study site promptly so that the tests and observations that are stipulated should be performed at discontinuation may be performed (see "9.1.1 Test/Observation Schedule"). Furthermore, the tests that are to be performed at discontinuation should be performed prior to joint replacement procedures for subjects who are going to undergo such procedures.

The (sub)investigator will record in the case report form the date of discontinuation, the reason for discontinuation,* the details of discontinuation, the background leading to discontinuation, the actions that have been taken, etc. Furthermore, the date of discontinuation will be the date on which the assessments at discontinuation are performed (the assessment date); however, if no assessments are performed at discontinuation, then the date of discontinuation will be the date on which the decision was made to discontinue the study. As a rule, all assessments at discontinuation will be perfoemed within 2

weeks.

For subjects for whom the observations/tests stipulated at discontinuation could not be performed or who failed to come in for visits following discontinuation, follow-up investigations will be performed by written correspondence, telephone calls, etc. to determine the reasons why as well as the subsequent courses, etc. of the subjects.

The (sub)investigator or a study support staff member will to the extent possible recover the treatment diaries of subjects who failed to come in for site visits.

*As the "reason for discontinuation," one of the following reasons will be selected.

1. Adverse event
2. Death
3. Worsening of underlying disease
4. Insufficient efficacy
5. Unable to continue the study (the study cannot be continued because, for example, the subject moved due to personal circumstances)
6. The subject is clearly unsuitable for study participation
7. The subject dropped out of the observation period
8. The (sub)investigator determined that the study should be discontinued
9. Deviation from study protocol
10. Pregnancy
11. Technical problem
12. Request from the subject for discontinuation
13. Discontinuation of the study at the study site by the study sponsor
14. Discontinuation of the entire study by the study sponsor
15. Other reason

13. Statistical Analysis

This chapter will only include that information about the method of statistical analysis that is needed to achieve the primary objectives of this study; a more detailed, technical explanation of the statistical analysis methodology will be included in the statistical analysis plan (SAP), which is being prepared separately.

In this study, For the data obtaind from screening to Week 16, from screening to Week 24 and from screeining to post-treatment observation period of Week 20 after the end of the treatment period, a statistical analysis will be respectively performed. Statistical analysis plans will be prepared for each of these analyses, and these statistical analysis plans will be finalized before each data lock (data lock will be performed 3 times).

In addition, a comparison of the doses administered by (sub)investigator up through Treatment Week 24 and the self-injections performed after Treatment Week 24 and a comparison of the doses administered by (sub)investigator after Treatment Week 24 and the self-injections performed after Treatment Week 24 in subjects who received at least one self-injection after Treatment Week 24 will be included in the statistical analysis of the efficacy and safety data obtained from screening through the post-treatment observation period 20 weeks after the end of treatment period.

In response to the protocol amendment (Ver. 04.00.00000) with removal of 3 mg q4w / 6 mg q8w groups and addition of 1 mg q8w, analysis will be performed as follows; For evaluation on 1 mg q4w, since subjects are randomized to 1 mg q4w / placebo at the same time with the same ratio of 1:1 regardless of pre- or post- amendment, analyses will be performed with pooled comparable data including pre- and post- amendment data on 1 mg q4w / placebo. For evaluation on 1 mg q8w, analyses will be performed with only the post-amendment data.

13.1 Analysis Sets

The analysis of efficacy will be performed in the full analysis set (FAS). The principal analysis set for efficacy will be the modified FAS (mFAS). Secondary analyses of the primary endpoint and key secondary endpoint will also be performed in the per-protocol set (PPS). The analysis of safety will be performed in the safety analysis set (SAF). The analysis of pharmacokinetics will be performed in the pharmacokinetic analysis set.

The analysis sets are defined below. Detailed rules about subject handling will be decided by the study sponsor before the data for each statistical analysis are fixed.

(1) Efficacy analysis sets

1) Randomized subjects (RAND)

2) FAS

The FAS will consist of all randomized subjects except for the following subjects.

- Subjects who have not received study drug even once
- Subjects with no WOMAC pain score (the primary endpoint) at baseline
- Subjects with no WOMAC pain score (the primary endpoint) at any time point after randomization

3) Modified FAS (mFAS)

The mFAS will consist of the FAS, except for the following subjects.

- Subjects who are randomized to 3 mg q4w group
- Subjects who are randomized to 6 mg q8w group

4) PPS (This set will be used for only statistical analysis for the data obtained from screening to Week 16)

The PPS will consist of the mFAS, except for the following subjects.

- Subjects who did not meet the inclusion criteria
- Subjects who met the exclusion criteria
- Subjects who did not comply with the rules on prohibited concomitant drugs/therapies
- Subjects who did not complete the period from study treatment initiation through the assessment of the WOMAC pain score (the primary endpoint) at Week 16

(2) SAF

The SAF will consist of all randomized subjects except for the following subjects

- Subjects who did not receive study drug even once
- Subjects for whom absolutely no post-randomization safety data are available

(3) Pharmacokinetic analysis set

The pharmacokinetic analysis set will consist of subjects who have received investigational drug at least once and for whom post-dose serum drug concentration data are available for at least one time point.

(4) Anti-drug antibody (ADA) analysis set

The ADA analysis set will consist of all treated subjects who received investigational drug or comparative drug at least once and who had at least 1 qualified (non-missing) post-dose ADA result.

13.2 Data Handling

Data handling will be performed as described below, except for issues that have been decided in the investigation of data handling pertaining to the assessment of drug concentrations or by the study sponsor's case handling committee. Details of the handling of the efficacy, safety, and drug concentration data will be provided in the statistical analysis plan or the clinical study report.

(1) Definition of baseline for the efficacy and safety endpoints

Unless otherwise specified, the baseline values for the endpoints will be the last data obtained prior to study treatment initiation.

(2) Handling of time point data in analyses performed by measurement time point

For the analyses performed for each measurement time point, the allowable range of handling for the analysis will be specified in the SAP, and data satisfying these rules will be used. No data replacement will be performed using data from outside the allowable range. If multiple values are available within the allowable range for the endpoint in question, then the most recent values will be used.

(3) Handling of reference values and indeterminate values for clinical laboratory test parameters

If a value is indeterminate or a reference value because of a problem with a test sample, then this value will be handled as a missing value.

(4) Handling of data for pharmacokinetic assessments

The allowable ranges for the collection of blood samples for the measurement of the serum drug concentrations are shown in "9.1.1 Test/Observation Schedule (1)." If it is necessary to investigate the data handling because of, for example, a protocol deviation (e.g., the blood collection time fell outside the allowable range, the serum drug concentration could not be measured, or the serum collection procedures were not followed), the study sponsor will decide on the data handling (e.g., whether or not to exclude the data from drug concentration data tabulation/analysis). Data handling investigations will be performed by the case review board or when the handling of pharmacokinetic and other data is investigated after the opening of the randomization key code.

13.3 Statistical Analysis Plan

For all of the variables analyzed, in the case of continuous data, the descriptive statistics (sample size, mean, SD, minimum, median, maximum) will be calculated, and in the case of categorical or ordered data, the frequency (%) will be calculated for each category.

The tests will be two-sided, with a significance level of 5%. The confidence intervals will be two-sided, with a confidence coefficient of 95%.

13.3.1 Investigation of Demographic and Other Baseline Characteristics

For the following demographic and other baseline characteristics, the descriptive statistics and frequency (%) will be calculated for each treatment group.

Parameter:
1) Sex
2) Age (at consent acquisition)
3) Time of osteoarthritis diagnosis
4) Anatomical location of osteoarthritis diagnosis
5) Anatomical location of evaluated joint
6) K-L grade
7) Height
8) Weight
9) BMI

Other parameters investigated will be described in the SAP.

13.3.2 Efficacy

(1) Analyses of the primary endpoint

The following analyses will be performed on the primary endpoint, the change in the WOMAC pain score from baseline to Week 16.

(a) Primary analysis

The mFAS will be used as the analysis set, and a mixed effect model for repeated measurement (MMRM) approach will be used for each cohort in which treatment group, measurement time point, treatment group and measurement time point interaction, stratification factor K-L grade (2-3 or 4), and stratification factor evaluated joint (knee or hip) will be factors, and the baseline and baseline—measurement time point interaction will be covariates. The within-subject correlation structure will be unstructured, and the denominator degrees of freedom for the test statistics of estimated parameters will be approximated using the Kenward-Roger method.

Evaluation on 1 mg q4w group

With pooling the data on 1 mg q4w and placebo obtained before and after the protocol amendment (Ver. 04.00.00000), the least square mean, standard error, P value, and 95% confidence interval of the difference between each of the MT-5547 1 mg q4w and the placebo group in the change in the WOMAC pain score from baseline to Week 16 will be calculated using the MMRM approach.

Evaluation on 1 mg q8w group

Using only the data obtained after the protocol amendment (Ver. 04.00.00000), the least square mean, standard error, P value, and 95% confidence interval of the difference between each of the MT-5547 1 mg q4w, MT-5547 1 mg q8w and the placebo groups in the change in the WOMAC pain score from baseline to Week 16 will be calculated using the MMRM approach.

MMRM that assumes that the missing mechanism is missing at random (MAR) is an analysis method in which missing values are not replaced. This model will be used to estimate the treatment effect in the FAS when subjects continue receiving treatment through Week 16.

(b) Sensitivity and supplementary analyses

Sensitivity analyses will be performed only at the time of the statistical analysis of the data from the double-blind period from screening through Week 16 after treatment initiation.

● Supplementary analysis with respect to the mFAS

The PPS will be analyzed using the same method as for the primary analysis to confirm the robustness of the results of the primary analysis for the effects of the analysis set.

● Sensitivity analysis with respect to the MAR missing mechanism

The robustness of the results of the primary analysis for the effect of the missing mechanism will be checked using a placebo multiple imputation method and a pattern mixing model (including a shift parameter analysis)[36] that assumes a missing not at random missing mechanism. A more detailed description of the analysis method will be presented in the SAP.

● Supplementary analysis with respect to the data pooling on 1 mg q4w and placebo

The data on 1 mg q4w and placebo obtained before and after the protocol amendment (Ver. 04.00.00000) will be analyzed using the same method as for the primary analysis to confirm the data homogeneity and the robustness of the results of the primary analysis. Also, homogeneity in demographic and other baseline characteristics [Section 13.3.1] between data obtained before and after the protocol amendment will be confirmed.

(2) Analysis of the key secondary efficacy endpoint

Analyses similar to those described in primary analysis (a) will be performed for the change in the WOMAC physical function score and the change in the PGA from baseline to Week 16, the key secondary efficacy endpoint.

Because this study is a confirmatory study, in order to keep the family wise type 1 error rate to a significance level of 5% (alpha), two-sided, in the tests of the following hypotheses regarding the primary endpoint and the key secondary efficacy endpoint, a gatekeeping method[37] based on a graphical approach will be used to perform multiplicity adjustment, as shown in Figure 13.3.2.1 to verify the hypotheses.

This multiplicity adjustment will only be performed for the statistical analyses of data from the double-blind period from screening to Week 16 after treatment initiation.

- Null hypothesis H01: The change from baseline in the WOMAC pain subscale at Week 16 in the 1 mg SC q4w group is the same as that in the placebo group
- Null hypothesis H02: The change from baseline in the WOMAC pain subscale at Week 16 in the 1 mg SC q8w group is the same as that in the placebo group
- Null hypothesis H03: The change from baseline in the WOMAC physical subscale at Week 16 in the 1 mg SC q4w group is the same as that in the placebo group
- Null hypothesis H04: The change from baseline in the WOMAC physical subscale at Week 16 in the 1 mg SC q8w group is the same as that in the placebo group

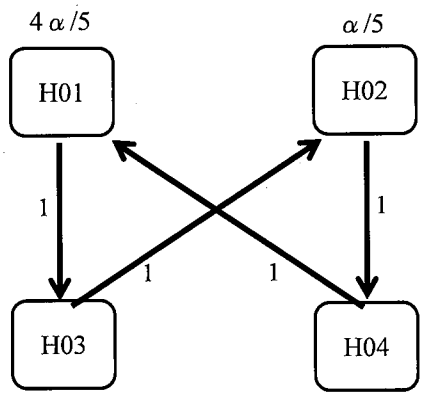


Figure 13.3.2-1: MT-5547 Multiple Test Procedure

(3) Analysis of Secondary Endpoints

The same method as that described in (a) Primary Analysis will be used to analyze the changes from baseline at each assessment time point in the WOMAC pain score, the WOMAC physical function score, the WOMAC stiffness score, the WOMAC total score, PGA, the NRS score for the average pain on walking in the evaluated joint over the past 24 hours, the SF-36, and the EQ-5D-5L.

A generalized linear mixed-effects model by logit type for response variable with baseline as a covariate and treatment group, K-L grade (2-3 or 4), and evaluated joint location (knee or hip) as factors will be used to evaluate the proportions of subjects achieving 30% and 50% improvements in their WOMAC pain scores at Weeks 16 and 24 compared to baseline as well as the OMERACT-OARSI response rate. A detailed description of this model is presented in the SAP.

The analysis methods used for the other secondary endpoints will be described in the SAP.

13.3.3 Safety

Adverse events that occur in the treatment period will be tabulated as treatment-emergent adverse events (TEAEs). TEAEs are defined as AEs that developed or worsened during the treatment period. The numbers and proportions of subjects with TEAEs, TEAEs that are causally related to study treatment, TEAEs that result in study treatment discontinuation, serious TEAEs, and TEAEs that are associated with adjudicated arthropathy or sympathetic nerve system disorders (Adverse Events of Special Interest: AESIs) will be calculated for each treatment group.

Summary statistics will be calculated for values at each measurement time point as well as the changes from baseline therein for each treatment group for the clinical laboratory test parameters, body weight, vital signs (body temperature, sitting blood pressure, pulse rate), ECG parameters (heart rate, RR, PR, QRS, QT), and bone density. For urinalysis parameters, shift tables will be prepared for each treatment group, measurement time point, and category.

The numbers and proportions of subjects will be calculated for each treatment group, measurement time point, and category for the presence or absence of pain, the survey of autonomic symptoms (SAS) symptom score (1 or 2) and impact score (1 to 5), and the 3-level assessments of the neurological evaluation (cranial nerves, motor system, sensory system, reflexes, and coordination/balance).

The analysis methods used for the other safety endpoints will be described in the SAP.

13.3.4 Pharmacokinetics

Summary statistics will be calculated for each time point for the serum MT-5547 concentration. In addition, summaries of the anti-fasinumab antibody data will be provided. Listings of ADA positivity and titers presented by patient, time point, and dose group will be provided.

Other pharmacokinetic parameters will be described in the SAP.

13.4 Statistical Analysis Plan Amendments

If the statistical analysis plan described in this section is going to be amended before data lock for each statistical analysis, the reason for the amendment will be described in the statistical analysis plan and the clinical study report. If the analysis method is going to be changed or an additional analysis performed after data lock, the reason thereof will be described in the statistical analysis plan and the clinical study report, and the results will be distinguished from the results of the analysis that had been planned.

14. Study Protocol Compliance, Deviations, and Changes

14.1 Agreement and Compliance With the Study Protocol

Before agreeing on the study protocol with the study sponsor, the principal investigator must hold discussions with the study sponsor based on the study protocol, the most recent investigator's brochure, and any other necessary documents that have been provided by the study sponsor, and adequately investigate the ethical and scientific appropriateness of conducting the study.

The principal investigator will, based on the results of this investigation, reach an agreement with the study sponsor regarding the contents of the study protocol, and will sign (or print his or her name and affix his or her personal seal to) and date a memorandum of agreement to show that the principal investigator agrees to comply with the study protocol.

14.2 Deviations From or Changes to the Study Protocol

The (sub)investigator must not deviate from or amend the study protocol without obtaining the advance written consent of the study sponsor and principal investigator or without first obtaining written approval following review performed by the institutional review board. However, if it is medically necessary, in

order to avoid an emergency danger to a subject, the (sub)investigator may deviate from or amend the study protocol without the advance written consent of the study sponsor or the advance approval of the institutional review board.

In such cases, the principal investigator must submit the deviation or amendment, as well as the reasons therefor, and also a draft of any proposed revisions to the study protocol, to the study sponsor, the head of the study site, and the institutional review board at soon as possible and have them approved, and must obtain written approval from the head of the study site and written consent from the study sponsor.

The (sub)investigator must record all actions that constitute deviations from the study protocol. The principal investigator must prepare a written record detailing the reasons for all actions that did not conform to the study protocol that were taken either to avoid an emergency danger to a subject or because of some other medically unavoidable reason, and must promptly submit this written record to the study sponsor and the head of the study site, and retain a copy.

The principal investigator must promptly submit a written report to the study sponsor, the head of the study site, and the institutional review board of all changes to the study that could substantially impact the conduction of the study or that could increase the risks to the subjects.

15. Revision of the Study Protocol

If the study sponsor determines during the course of the study that the study protocol needs to be changed, then the study sponsor will revise the study protocol. The study sponsor will discuss the proposed changes with the principal investigator and obtain the principal investigator's agreement, and will then notify the head of the study site promptly and in writing, and will obtain the approval of the institutional review board through the head of the study site.

If the head of the study site indicates that the study protocol should be revised, based on the opinion of the institutional review board, the study sponsor will determine whether or not the change in question is appropriate, and will if necessary revise the study protocol. The study sponsor will discuss the proposed revisions with the principal investigator and obtain the principal investigator's agreement, and will then notify the head of the study site promptly and in writing, and will obtain the approval of the institutional review board through the head of the study site.

If it is determined based on discussions held with the principal investigator that the study protocol needs to be revised, then the study sponsor will determine whether or not the changes are appropriate, and will if necessary revise the study protocol. The study sponsor will obtain the principal investigator's agreement to the proposed revisions and will then notify the head of the study site promptly and in writing, and will obtain the approval of the institutional review board through the head of the study site.

16. Study Discontinuation or Interruption

(1) Criteria for temporarily or permanently discontinuing the study

In the following cases, the study sponsor will investigate whether or not the study should be continued at all or some of the study sites.

1) If information about the quality, efficacy, or safety of the study drugs, or any other information that is important to the proper conduction of the study, is obtained.
2) If the independent data monitoring board recommends that the study be discontinued and the study sponsor accepts this recommendation
3) If it becomes necessary to change the study protocol, and study sites cannot adapt to the changes.
4) If the head of a study site, based on the opinion of the institutional review board, request that the study protocol, etc. be revised, and the study sponsor cannot agree to this request.
5) If the head of a study site instructs that the study be permanently discontinued based on the decision of the institutional review board.
6) If the study site commits major or ongoing violations of the GCP, study protocol, or study contract.

(2) Temporary or permanent discontinuation of the entire study by the study sponsor

If the study sponsor decides to temporarily or permanently discontinue the entire study, the study sponsor will promptly inform the heads of the study sites and the regulatory authorities of this fact, and of the reasons why, in writing. The heads of the study sites will upon being notified by the study sponsor that the study is being temporarily or permanently discontinued in turn notify the principal investigators and institutional review boards of this fact, and of the reasons why, in detail in writing.

The principal investigators will upon being notified by the study sponsor through the heads of the study sites that the study is being temporarily or permanently discontinued promptly notify the subjects of this fact and ensure that the subjects receive proper treatment.

The actions that should be taken with respect to subjects if the study is being permanently discontinued are described in "12.2 Study Discontinuation Procedures."

(3) The temporary or permanent discontinuation of the study at a study site by the principal investigator or institutional review board

If the study is temporarily or permanently discontinued at the discretion of the principal investigator, the principal investigator will promptly notify the head of the study site of this fact in writing, and of the reasons why. The head of the study site will promptly notify the study sponsor and the institutional review board of this fact in writing.

If the institutional review board decides to temporarily or permanently discontinue the study, the board will promptly notify the head of the study site of this fact, and of the reasons therefor, in writing. The head of the study site will promptly notify the principal investigator and study sponsor of this fact in writing.

(4) Permanent discontinuation of the study because of the cancellation of the contract with the study site

If the study sponsor permanently discontinues the study because a study site has committed grave or ongoing violations of the GCP, study protocol, or study contract during the study, the study sponsor will promptly report this to the regulatory authorities.

17. Information in the Case Report Form

17.1 Case Report Form, etc. Formats

[redacted]

17.2 Information to be Recorded Directly in the Case Report Form and Considered Source Data

The case report form will serve as the source document for the following parameters. However, if the data in question are clearly noted in, for example, the subject's medical records, then the medical records will be considered the source document.

[redacted]

(1)

(2) [redacted]

(3)

(4)

Furthermore, for information other than that described above, the documents will be determined separately, before the start of the study, by the study sponsor and the principal investigator.

17.3 Precautions for Case Report Form Preparation

The (sub)investigator or a study support staff member will prepare the case report form in accordance with the following rules. Furthermore, the case report form will be prepared in accordance with the "Case Report Form Amendment or Revision Manuals,"* which will be provided separately by the study sponsor.

*: "Case Report Form Amendment or Revision Manuals": EDC Manual, eCRF Entry Manual

(1) Before the case report forms are filled out, the study sponsor will provide the (sub)investigators and study support staff members with user IDs and passwords, and thereby control who is using the system. The provided user IDs and passwords will be controlled by the (sub)investigator or study support staff member and not shared with anyone. In addition, the data will be entered by (sub)investigators or study support staff members who have been granted access to use the system.

(2) Study report forms will be prepared for subjects who have been enrolled in the screening period.

(3) The principal investigator will be able to fill out all of the fields in the case report form. The subinvestigator will be able to fill out all of the fields in the case report form other than the electronic signature. Study support staff members will be able to transcribe from source documents information that is not accompanied by a medical evaluation, such as information that has been entered on medical records and treatment diary.

(4) If the information in a case report form is going to be amended or revised, the reason for the amendment or revision will be recorded as electronic information.

(5) The principal investigator will confirm that the case report form has been prepared accurately and completely and that the audit trail and electronic signature information can be referenced, and will then affix his or her electronic signature to the case report form using the EDC system.

(6) The principal investigator will retain a copy of the case report form that is stored on recording media (e.g., CD-R) (the copy will be a copy of the electronic case report form that has been checked by the principal investigator and that has been saved in PDF format). Furthermore, after the case report form has been signed electronically and before the recording media (e.g., CD-R) has been provided by the study sponsor, in lieu of a copy, an environment will be maintained that allows the electronic case report form to be accessed (access rights to the EDC system).

(7) If there is some sort of discrepancy between the data that have been entered on the case report form and the source documents, the principal investigator will prepare a record explaining the reasons why and submit it to the study sponsor, and retain a copy thereof.

17.4 Timing of Case Report Form Submission

The (sub)investigator will as a rule prepare the case report form and submit it to the study sponsor within 3 days, including an acquisition day of results.

17.5 Handling of the Treatment Diary

Subjects will fill out the parameters stipulated in "8.6.3 Rescue Drug/Treatment Diary" every hight until Week 48 after study treatment initiation to record their level of treatment adherence.

The (sub)investigator or a study support staff member will check the information that has been recorded in the treatment diary that the subject has brought with him or her at the time of the visit. If any information has not been filled out, the subject will be asked to fill this information in as much as possible. If any corrections have already been made by the subject, the (sub)investigator or a study support staff member will check what corrections the subject has made, and will then enter the reasons for the corrections in the treatment diary along with the date the treatment diary was checked, and will then sign (or print his or her name and affix his or her personal seal to) and date the treatment diary.

The (sub)investigator will recover the treatment diary from the subject at the study visit and keep it at the study site.

17.6 Handling of the IVRS

Every night until the day befor Week 16 after study treatment initiation, subjects will enter into the IVRS the information stipulated in "8.6.4 IVRS."

The (sub)investigator or a study support staff member will check the subject's reporting status, and if a report has not been submitted, the subject will be asked to report the NRS score for the average pain on walking in the evaluated joint. If the subject discontinues from the study before Week 16, the (sub)investigator or a study support staff member will register said discontinuation.

The principal investigator will retain a copy of the IVRS that has been stored on recording media (e.g., CD-R) provided by the study sponsor.

18. Direct Access to Source Documents

The principal investigator and the head of the study site will agree to cooperate with the monitoring and auditing of the study sponsor and the inspections of the institutional review board and regulatory authorities, and to provide these parties with direct access to all materials pertaining to the study.

19. Study Quality Control and Quality Assurance

The study sponsor must perform "study quality control" and "study quality assurance" based on Mitsubishi Tanabe Pharma's GCP Standard Operating Procedures, in order to maintain the quality and reliability of this study. In addition, the study sites and the principal investigators must cooperate with the study quality control and quality assurance activities of the study sponsor.

In the study quality control activities, the monitors will directly access the source data, as appropriate, to confirm that the study is being conducted in compliance with the written procedures pertaining to the study of the study site, the most recent version of the study protocol, and the GCP. The monitors will also confirm that the information that has been recorded in the case report form that has been reported by the (sub)investigator is accurate and complete, and can be verified by comparing it against study-related records, such as source documents.

In addition, in order to ensure that the study is being conducted in compliance with the study protocol and the GCP, the audit staff will perform audits in accordance with the GCP Standard Operating Procedures to confirm that quality control is being done properly.

20. Ethics

20.1 Ethical Implementation of the Study

This study must be conducted in accordance with the Pharmaceutical Affairs Law, the GCP, and the study protocol, and in accordance with the ethical principles of the Helsinki Declaration.

20.2 Institutional Review Board

The study review board will review the conduction and continuation of the study from ethical, scientific, and medical/pharmacological perspectives based on the information contained in the investigator's brochure, study protocol, and informed consent form/explanation sheet.

20.3 Preservation of Subject Confidentiality

All parties involved in the study will identify the subjects in the subject records and case report forms using the subject ID codes and will protect the confidentiality of the subjects when source documents pertaining to the conduct of the study are being accessed, published in medical journals, submitted to the regulatory authorities, etc.

21. Record Storage

(1) Records stored at the study site

A storage manager appointed by the head of the study site will store the documents or records pertaining to the study that should be stored at the study site until 1) or 2) below, whichever comes later. However, if the study sponsor states that these documents or records should be stored for a longer period, the study site will hold discussions with the study sponsor about the term and method of storage.

If the study sponsor decided not to append the clinical study test result data that have been collected in the course of the study to the approval application form, the study sponsor will inform the study site directors of this fact, and of the reason(s) why, in writing.

In addition, if marketing approval is obtained for this study drug, or if the study sponsor decides to discontinue development of this study drug before approval is obtained, then the study sponsor will inform the study site directors of this fact in writing.

1) Date of marketing approval for the study drug (in the case of an additional indication, the date of the supplemental J-NDA) (if a notification has been received that development is being discontinued or the study results are not being appended to the approval application, then the date on which 3 years have passed since the date this information was received).
2) Once 3 years have passed since the discontinuation or completion of the study

(2) Records stored at the study sponsor

The study sponsor will store the documents or records pertaining to the study that should be stored at the study sponsor until 1) or 2) below, whichever comes later.

1) The date marking 5 years since the date of marketing approval for the study drug (or the date of approval of the supplemental approval application in the case of an additional indication) (or, if development is discontinued, the date marking 3 years from the date on which the decision was made to discontinue development) or the date marking the end of reexamination.
2) 3 years after the discontinuation or completion of the study

22. Monetary Payments

Payments of monetary compensation to subjects and study sites will be made in accordance with the contracts or memoranda of agreement between the study sites and the study sponsor.

23. Compensation for Health Injuries, and Insurance

23.1 Compensation for Health Injuries

If a subject suffers a health injury as a result of the conduction of this study, the study sponsor will compensate the subject appropriately, based on predetermined criteria, except in cases where a causal relationship to the study has been ruled out (said compensation will include the subject's medical treatment fee copayments, a medical allowance, and compensation money). In such cases, the subject will be under no burden to prove that there is a causal relationship.

23.2 Insurance

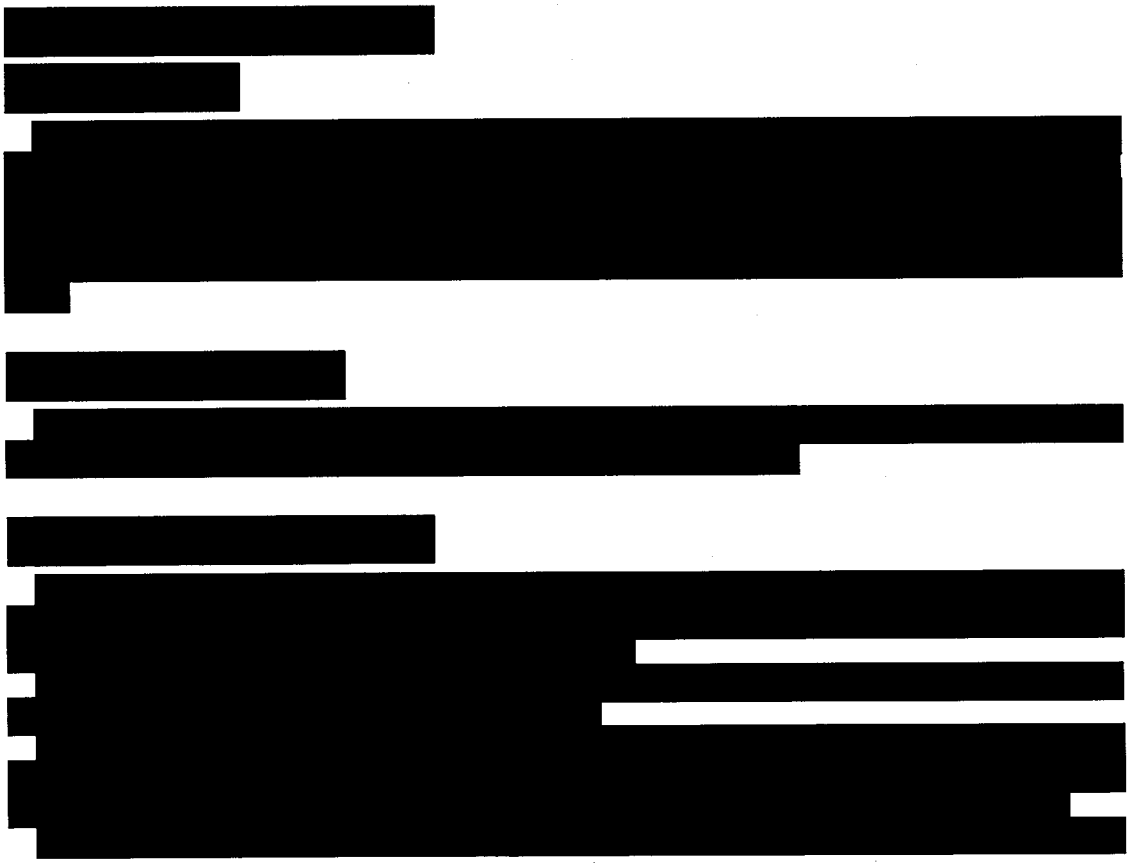
The study sponsor will take out insurance and will take any other necessary actions to ensure that the sponsor is indemnified against health injuries experienced by subjects in connection with the study.

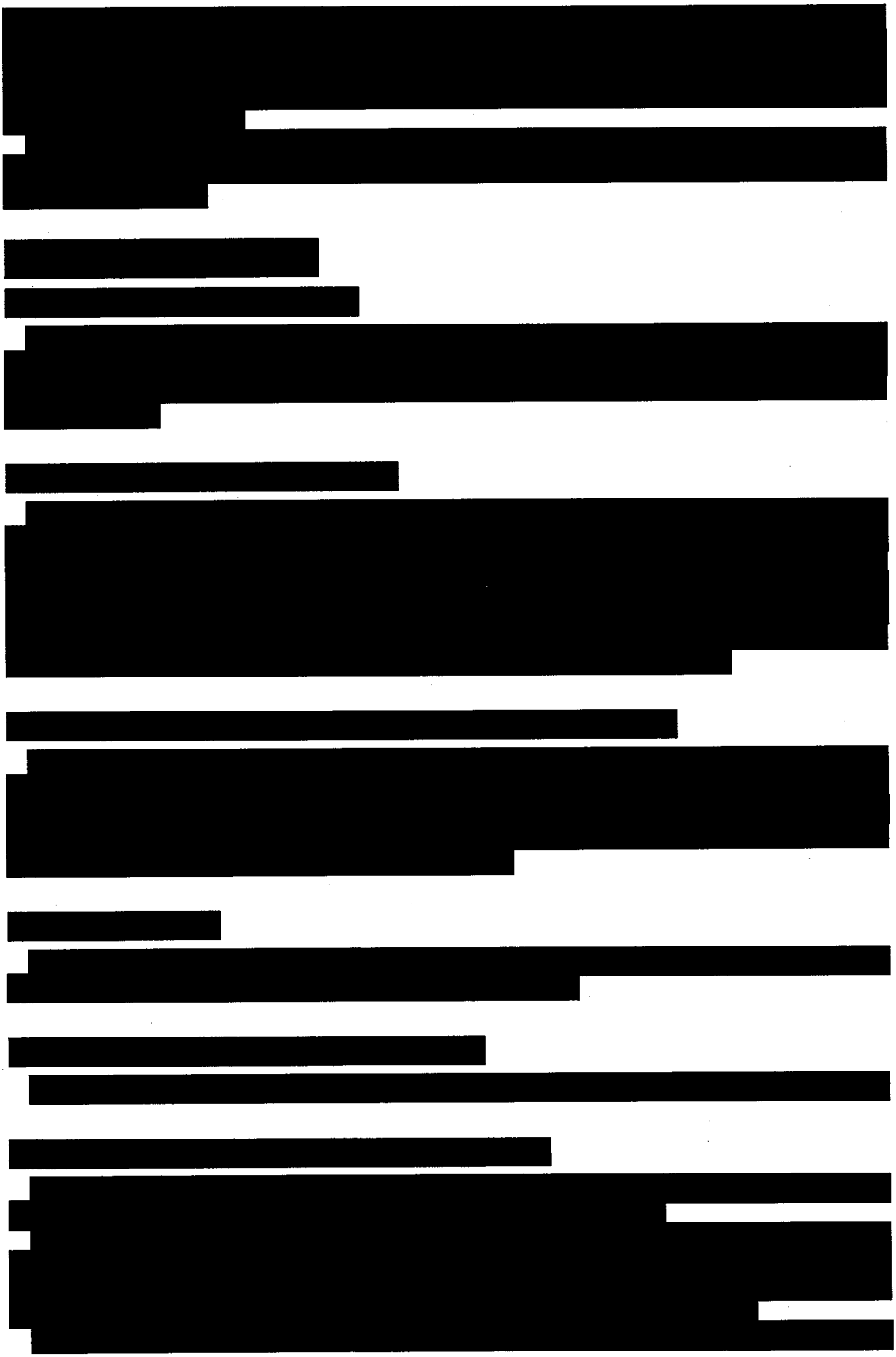
24. Agreement on Publication

The information that is contained in this study protocol is the property of the study sponsor, and although it will be provided to the institutional review boards and relevant parties, such as the (sub)investigators conducting the study, it must not be divulged to any outside party without the written consent of the study sponsor, unless this is necessary for the conduction of the study.

In addition, if the information that is obtained by the conduction of this study is going to be presented to any outside parties, such as at a specialist conference, by any study site staff involved in the study, such as a (sub)investigator, the consent of the study sponsor must be obtained in advance.

Furthermore, the study sponsor may freely report the information obtained in this study to the regulatory authorities or for a purpose such as the appropriate use or marketing of the drug product.





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Contact information

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Contact for nights and holidays

On the holiday of the sponsor such as night (17:30 to next morning 9:00), Saturdays, Sundays, and national holidays, and year-end and new year, the below Emergency Contact Center will receive an emergency contact and relay the message to the monitor.

Emergency Contact Center, Mitsubishi Tanabe Pharma Corporation

[redacted] (toll-free number)

[redacted]