−Open-Label Extension Study in Rheumatoid Arthritis Patients Who Have Completed Phase IIb Study or Phase III Study of ASP015K−

ISN/Protocol 015K-CL-RAJ2

ClinicalTrials.gov Identifier: NCT01638013

Date of Protocol: Version 7.0, dated 29 March 2019

Sponsor: Astellas Pharma Inc. (API)

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Protocol for Extension Study/ Post-marketing Clinical Study of ASP015K

–Open-Label Extension Study in Rheumatoid Arthritis Patients Who Have Completed Phase IIb Study or Phase III Study of ASP015K–

Sponsor:

Astellas Pharma Inc. (API)

After ASP015K receives the marketing approval in Japan, this study will continue as a "post-marketing clinical study". In this case, the term "clinical study" in this protocol should be read as "post-marketing clinical study." In Korea and Taiwan, this study will continue as a "clinical study" after the marketing approval in Japan.

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Created 29 March 2019 (Ver. 7.0)

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I. SIGNATURE

AGREEMENT BETWEEN THE SPONSOR'S RESPONSIBLE PERSON AND THE INVESTIGATOR

This clinical study will be conducted in adherence to GCP, GPSP, and applicable laws and regulatory requirements, as well as this study protocol. As the evidence of the agreement, the investigator (CHIKEN SEKININ ISHI) and responsible person of the sponsor (CHIKEN IRAI SEKININSHA) shall inscribe their signatures on the bipartite agreement.

II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Contact Information for the Sponsor

[redacted]

[redacted]an

TEL: [redacted]

FAX: [redacted]

Persons in charge: [redacted]

[Contact numbers during non-business hours and for emergency]:

[redacted]

[redacted]

Contact Information for the Contract Research Organization (CRO)

- Japan

[redacted]

Location: [redacted]

TEL: [redacted]

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Persons in charge: [redacted]

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Person in charge: [redacted]

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Location: [redacted]

TEL: [redacted]

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Person in charge: [redacted]

[Contact numbers during non-business hours and for emergency]:

[redacted]

III. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
AST	Aspartate aminotransferase (GOT)
ASP015K	Astellas Pharmaceuticals compound 015K
AUC	Area under the concentration – time curve
AUC_{inf}	AUC from the time of dosing up to infinity with extrapolation of the terminal phase
AUC_{last}	AUC from the time of dosing to the last measurable concentration
BUN	Blood urea nitrogen
C_{max}	Maximum concentration
C_{trough}	Trough concentration
CK/CPK	Creatine kinase/creatine phosphokinase
CK-MB	Creatine kinase MB isozyme
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CYP	Cytochrome P450
DAS	Disease activity score
DDI	Drug-drug interaction
DILI	Drug induced liver injury
DIP	Distal interphalangeal joint
DMARD	Disease-modifying antirheumatic drug
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic Acid
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
F	Bioavailability
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GMP	Good Manufacturing Practice
GPSP	Good Post-marketing Study Practice
γ-GTP	γ-glutamyl transpeptidase (GGT)
HAQ-DI	Health Assessment Questionnaire – Disability Index
HBc antibody	Hepatitis B core antibody
HBs antigen/antibody	Hepatitis B surface antigen/antibody

HBV	Hepatitis B virus
HCV	Hepatitis C virus
hERG	Ether-a-go-go related gene
HIV	Human immunodeficiency virus
HSA	Human serum albumin
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethic Committee
IL	Interleukin
IND	Investigational new drug
INR	International normalized ratio
IP	Interphalangeal joint
IRB	Institutional review board
ISN	International study number
IV	Intravenous
JAK	Janus kinase
LA-CRF	Liver abnormality-CRF
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
MCP	Metacarpophalangeal joint
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MMP-3	Matrix metalloproteinase 3
MPA	Mycophenolic acid
MPAG	Mycophenolic acid glucuronide
MTP	Metatarsophalangeal joint
MTX	Methotrexate
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NDA	New drug application
NK	Natural killer
NOAEL	No observed adverse effect level
NSAIDs	Non-steroidal anti-inflammatory Drugs
NYHA	New York Heart Association
PASI	Psoriasis area and severity index
PD	Pharmacodynamic
PGA	Physician's Global Assessment of Arthritis
PIP	Proximal interphalangeal joint
QOL	Quality of life
RA	Rheumatoid arthritis
RBC	Red blood cell
SAE	Serious adverse event
SAF	Safety analysis set
SDAI	Simplified Disease Activity Index
SF-36v2®	Short form health survey – 36 questions, version 2: SF-36 v2®
SFL	Screening Failure Log
SGA	Subject's Global Assessment of Arthritis
SJC	Swollen joint count
SOP	Standard operating procedure
STAT5	Signal transducers and activators of transcription 5
SUSAR	Suspected unexpected serious adverse reactions

TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TJC	Tender joint count
TNF	Tumor necrosis factor
$t_{1/2}$	Apparent terminal elimination half-life
t_{max}	Time to attain C_{max}
TYK2	Tyrosine kinase 2
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WPAI	Work Productivity and Activity Impairment Questionnaire

List of Key Study Terms

Terms	Definition of terms
Adverse event	An adverse event is as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment.
Baseline	The last measured values/findings prior to dosing
Study discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a study by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) discontinuation initiated by the investigator or other responsible personnel (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis.
Enroll	To register or enter into a clinical study; transitively and intransitively. Informed consent precedes enrollment.
Follow-up period	The follow-up period begins at the completion of all assessments/measurements at end of treatment/early termination and ends upon completion of all assessments/measurements at end of study (at time of follow-up).
Serious adverse event	Any adverse event that is judged “serious” by the investigator/sub-investigator or the sponsor and results in any of the following outcomes: death, a life-threatening condition, persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect, hospitalization or prolongation of hospitalization, and other medically significant occurrences.
Screening failure	A subject from whom informed consent was obtained but who did not fulfill protocol inclusion and/or exclusion criteria and did not receive the study drug
Study period	Period of time from obtaining informed consent from subjects to the end of the final evaluation/observation specified in the protocol
Subject	An individual who participates in a clinical study, as a recipient of either the test drug(s) or comparative drug(s)
Subject ID	A unique identifier code assigned to each subject signing the informed consent.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values

IV. SYNOPSIS

Title of Study	Extension Study of ASP015K –Open-Label Extension Study in Rheumatoid Arthritis Patients Who Have Completed Phase IIb Study or Phase III Study of ASP015K– (Protocol Number: 015K-CL-RAJ2)
Planned Study Period	From February 2012 up to a maximum of 6 months after the NDA approval at one of the regions (After the NDA approval in Japan, the post-marketing clinical study will be ended once the study drug is available in the clinical sites as a commercially available product. The planned study period will be up to a maximum of 6 months after the NDA approval in Japan). Sponsor will immediately inform sites when the NDA approval date at one of the regions is confirmed.
Study Objectives	This is an extension study conducted in rheumatoid arthritis (RA) patients who have completed the Phase IIb Study of ASP015K [015K-CL-RAJ1 (hereinafter referred to as study RAJ1)], Phase III Study of ASP015K [015K-CL-RAJ3 (RAJ3)], or Phase III Study of ASP015K [015K-CL-RAJ4 (RAJ4)] to investigate the safety and efficacy of long-term administration of ASP015K. Another objective of this study is to devise rescue measures for providing the active drug to patients who participated in the Phase IIb Study or Phase III Study of ASP015K, as described in "Guidelines on methodology for clinical assessment of antirheumatic drugs" (PFSB/ELD Notification No. 0217001, dated 17 February, 2006).
Planned Total Number of Study Centers and Location	Approximately 170 centers Japan, Korea, and Taiwan
Design and Methodology	This study is an extension study conducted as an open-label, multicenter study in RA patients who have completed studies RAJ1, RAJ3, or RAJ4. The protocols (ver. 2.0 and ver. 3.0) will become applicable when they are approved by the Institutional Review Board (IRB) of each study center and when the study drugs after the change of specifications become available for use. In the protocol ver. 6.0, the clinical study will transfer to a post-marketing clinical study after the NDA approval in Japan. In Korea and Taiwan, this study will continue as a clinical study after the NDA approval in Japan. [Subjects who transferred from studies RAJ3 or RAJ4] Patients who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will receive oral ASP015K 100 mg once daily (QD) after breakfast as the starting dose. [Subjects who transferred from study RAJ1] Patients who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will be registered and will receive oral ASP015K 50 mg QD after breakfast as the starting dose. Subjects who have been receiving ASP015K at a dose of 50 mg/day before the revision of the protocol to ver. 2.0/ver. 3.0 shall be included in the clinical study under the protocol (ver. 2.0/ver. 3.0), and the need for a change in the dose shall be discussed when the study drugs after the change of specifications become available for use. Treatment extension with a dose of 50 mg/day should be allowed for subjects for whom the investigator or sub-investigator considers a dose increase to be inappropriate in terms of safety and treatment extension with a dose of 50 mg/day to provide greater therapeutic benefit for the treatment of RA. For subjects who have been receiving ASP015K at a dose

	of 50 mg/day in Japan, the dose will be increased to 100 mg/day after the NDA approval in Japan. Any subjects for whom the dose cannot be increased should be withdrawn from the study. For subjects who have no safety problems but show a lack of efficacy, the dosage may later be increased from 100 mg/day to 150 mg/day. Only in Korea and Taiwan, the dosage may be reduced from 100 mg/day or 150 mg/day to 50 mg/day at the discretion of the investigator or sub-investigator. This study will be conducted as a post-marketing clinical study up to a maximum of 6 months after the NDA approval in Japan. (After the NDA approval in Japan, the post-marketing clinical study will be ended once the study drug is available in the clinical sites as a commercially available product. The planned study period will be up to a maximum of 6 months after the NDA approval in Japan). In Korea and Taiwan, this study will continue as a clinical study after the NDA approval in Japan. The duration of treatment with the study drug will differ depending on the subject. To prevent purposeless continuation of dosing without effect, the investigator or sub-investigator will assess each subject for efficacy and safety at each visit, confirm the appropriateness of continued administration for each individual, and decide whether or not to continue dosing.
Number of Subjects Planned	Approximately 800 subjects will receive the study drug.
Selection Criteria	[Subjects who transferred from study RAJ1] <Inclusion Criteria> Subject is eligible for the study if all of the following apply: 1. Subject has received a full explanation of the study drug and this study in advance, and written informed consent to participate in the study has been obtained from the subject himself/herself. 2. Subject has completed treatment with the study drug in study RAJ1 as specified in the protocol and has also completed the tests and assessment performed at the study visit in Week 16. 3. The subject himself/herself wishes to continue taking the study drug, and the investigator or sub-investigator deems continued administration to be necessary or appropriate. 4. Subject must be willing and able to comply with the study requirements. <Exclusion Criteria> Subject will be excluded from participation if any of the following apply: 1. Subject has developed an adverse reaction related to the study drug in study RAJ1 and the risks of continuing treatment with this drug are expected to outweigh the benefits. 2. There were abnormal findings in the x-ray taken at Week 0, and an acute or chronic infection, tuberculosis infection, or malignant tumor is suspected. 3. Subject has received live or live attenuated virus vaccination within 30 days prior to the first dose of study drug. 4. Subject is a hepatitis B virus or hepatitis C virus carrier or has a history of a positive test for HIV infection. 5. Subject has concurrent autoimmune disease (except Sjogren's syndrome) other than RA or a history of it. 6. Subject has a clinically significant infection or disease (requiring hospitalization or parenteral therapy). 7. Subject has a history of any malignant tumor, except for successfully

	treated basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix, or subject has a concurrent malignant tumor. 8. Subject has taken one of the following drugs between the end of the assessments at Week 12 of study RAJ1 and the start of treatment with the study drug in this extension study. • Biologic DMARD: Etanercept, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab • Non-biologic DMARD: Methotrexate (MTX), salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib (However, topical drugs other than those for the treatment of RA may be used concomitantly.) • Other drugs used in the treatment of RA: Cyclosporine, cyclophosphamide, azathioprine, minomycin, etc. 9. Subject has received plasma exchange therapy between the end of the assessments at Week 12 of study RAJ1 and the start of treatment with the study drug in this extension study. 10. Subject has received any of the following CYP3A substrates with narrow therapeutic range within 14 days prior to starting treatment with the study drug: Dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, and temsirolimus 11. Subject has any of the following laboratory values at the study visit in Week 12 of study RAJ1: • Hemoglobin < 10 g/dL • White blood cell (WBC) count < 3000/μL • Absolute neutrophil count (ANC) < 2000/μL • Absolute lymphocyte count < 800/μL • Platelet count < 100000/μL • ALT ≥ 2 × ULN • AST ≥ 2 × ULN • Total bilirubin (TBL) ≥ 1.5 × ULN • Estimated glomerular filtration rate (GFR) ≤ 40 mL/min, as measured by the MDRD method • CPK > 1.5 × ULN • β-D-glucan ≥ 11 pg/mL 12. Subject has symptomatic CPK elevation (CPK > 1.5 × ULN with myalgia, muscular weakness, or severe unusual muscle twitching) at the study visit in Week 12 of study RAJ1. 13. Subject is found to have symptoms of myopathy such as myalgia, muscular weakness, and severe unusual muscle twitching regardless of CPK level that persist for at least 2 weeks or that worsen rapidly within 2 weeks, at study visit in Week 12 of study RAJ1. 14. Subject has concurrent cardiac failure with NYHA classification of Class III or higher, or a history of it. 15. Subject has concurrent long QT syndrome or history of it. Subject exhibits QT interval prolonged at the study visit in Week 0. 16. Subject has any ongoing severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, or infectious disease, or any ongoing illness which would make the subject unsuitable for the study as determined by the investigator/sub-investigator. 17. Subject has any condition possibly affecting oral absorption (e.g., gastrectomy or clinically significant diabetic gastroenteropathy). 18. Subject has received surgical treatment and the investigator/sub-investigator judges there to be residual effects of surgical stress. Or, the subject plans to have surgical treatment that will require hospitalization

	during the study period or surgery on the joints. 19. The subject is a woman who is pregnant or might be pregnant, is nursing, wishes to conceive within 60 days after end of treatment drug, or for whom the possibility of pregnancy cannot be ruled out as a result of the pregnancy test given at Week 0. 20. The subject is a man who cannot practice proper contraception with a condom from the time informed consent is given until 90 days after end of treatment, or the subject is a woman who could become pregnant and cannot practice proper contraception with a condom from the time informed consent is given until 60 days after end of treatment. 21. The subject has been judged unsuitable to participate in the study for other reasons by the investigator/sub-investigator. [Subjects who transferred from studies RAJ3 or RAJ4] <Inclusion Criteria> Subject is eligible for the study if all of the following apply: 1. Subject has received a full explanation of the study drug and this study in advance, and written informed consent to participate in the study has been obtained from the subject himself/herself. 2. Subject who has completed treatment with the study drug in studies RAJ3 or RAJ4 as specified in the protocol and has also completed the tests and assessments scheduled for the Week 52 visit. 3. The subject himself/herself wishes to continue taking the study drug, and the investigator or sub-investigator deems continued administration to be necessary or appropriate. 4. Subject must be willing and able to comply with the study requirements. <Exclusion Criteria> Subject will be excluded from participation if any of the following apply: 1. The subject is a woman who is pregnant or might be pregnant, is nursing, wishes to conceive within 60 days after end of treatment drug, or for whom the possibility of pregnancy cannot be ruled out as a result of the pregnancy test given at Week 0. 2. Subject is a man who cannot practice 2 or more methods of proper contraception from the time informed consent is given to 90 days after the end of treatment, or subject is a woman who could become pregnant and cannot practice 2 or more methods of proper contraception from the time informed consent is given to 60 days after the end of treatment. 3. Subject is a man who cannot be prohibited from sperm donation from the time informed consent is given to 90 days after the end of treatment, or subject is a woman who cannot be prohibited from egg donation from the time informed consent is given to 60 days after the end of treatment. 4. Subject who has tested positive for any of the following at screening for studies RAJ3 or RAJ4: HBs antigen, HBc antibody, HBs antibody, and HBV-DNA assay (However, if a subject is negative for HBs antigen and HBV-DNA assay, and positive for either or both HBc and HBs antibodies, the subject may be included provided that the subject is monitored by performing HBV-DNA assay at every scheduled visit after initiation of study drug administration.) 5. Subject has received a prohibited concomitant medication or prohibited concomitant therapy during the time from the end of the assessments at Week 52 of studies RAJ3 or RAJ4 to the first dose of the study drug in this extension study. 6. Subject has QTc < 300 msec on ECG measurements performed at the study site at Week 52 of studies RAJ3 or RAJ4 and has QTc < 300 msec at retest.

	7. The subject has been judged unsuitable to participate in the study for other reasons by the investigator/sub-investigator.
Discontinuation Criteria	The investigator/sub-investigator should discontinue the study if any of the following criteria are met: 1. Subject withdraws consent. 2. The study drug is not sufficiently effective, and a change in treatment method is deemed to be in the subject's best interest by the investigator or sub-investigator. 3. Symptomatic CPK elevation, defined as CPK > 1.5 × ULN with severe unusual myalgia, muscular weakness, or muscle twitching. 4. Any event of myopathy defined as severe unusual myalgia, muscular weakness, and muscle twitching regardless of CPK level that persists for at least 2 weeks or that worsens rapidly within 2 weeks. 5. Subject infected with HBV who has tested positive for either of or both of HBc and HBs antibodies and is found to be positive for HBV-DNA assay during the study period. Abrupt discontinuance of immunosuppressive therapy may precipitate severe or fulminant hepatitis. Therefore, when HBV reactivates, nucleic acid analog therapy should be immediately initiated, and a hepatologist should be consulted regarding the continuation of ASP015K and concomitant DMARD (unique to Japan: as indicated by "Proposal for Management of Rheumatic Disease Patients with Hepatitis B Virus Infection Receiving Immunosuppressive Therapy" by the Japan College of Rheumatology.) 6. Subject has a malignant tumor. 7. Subject has an adverse event (AE) such as a serious infection, and the investigator or sub-investigator considers that it is not in the subject's best interest to continue the study. 8. Subject receives or requires a prohibited concomitant medication (including other study drugs) or prohibited concomitant therapy that may affect the evaluation of efficacy; subject receives or requires live vaccine or live attenuated vaccine. 9. Subject receives or requires drug interruption for a longer period than that stipulated for interruption. 10. Subject is deemed lost to follow-up by the investigator/sub-investigator (subject can no longer come to the study center; subject can no longer be contacted, etc.). 11. It comes to light after the administration of the first dose of study drug that the inclusion criteria were not met at the time of case enrollment or that criteria for exclusion were met. It comes to light that there was some other major deviation from the protocol. 12. Investigator or sub-investigator decides it is in the subject's best interest to discontinue. 13. The sponsor has requested that administration of the study drug be discontinued because of a safety problem in a particular subject, or the sponsor has decided to discontinue the study altogether. 14. Subject has QTc < 300 msec on ECG measurements and has QTc < 300 msec at retest. The Appendix 6 entitled "Liver Safety Monitoring and Assessment" describes liver function tests raised providing grounds for considering discontinuation. Refer to this if liver function tests raised is observed.
Suspension, Interruption, and Resumption of the Study Drug	If either of the below criteria for suspension or interruption of the study drug are met during the treatment period with the study drug, the investigator or sub-investigator is to suspend or interrupt administration of the study drug

	without delay. Administration of the study drug may be resumed after the initiation of suspension or interruption if a retest shows that none of the following criteria are met, provided that the investigator or sub-investigator deems resumption to be in the subject's best interest, taking the risk/benefit ratio into consideration: 1. Subject has any of the following laboratory values: • Hemoglobin < 8.0 g/dL • ANC < 500/μL • Absolute lymphocyte count < 500/μL • Platelet count < 50000/μL • Serum creatinine > 150% of baseline at 2 consecutive Scheduled Visits • CPK > 10 × ULN 2. β-D-glucan > ULN [in case of Japan: ≥ 11 pg/mL] 3. Subject requires a concomitant medication that is prohibited because of a possible drug interaction. 4. Suspected pregnancy. 5. The investigator or sub-investigator considers suspension or interruption of the study drug to be in the subject's best interest. 6. The sponsor has requested suspension or interruption of the study drug because of a safety problem in a particular subject. <u>Suspension of the study drug</u> Administration of the study drug may be suspended within the scope of the below stipulations if the investigator or sub-investigator deems a temporary discontinuation (suspension) of dosing to be necessary. Suspension of the study drug beyond the scope of the following stipulation is handled as interruption: • Suspension is defined as a temporary discontinuation of study drug administration for 7 days or less. • If administration of the study drug is suspended repeatedly, the discontinuation of the clinical study for the particular subject should be considered in consultation with the sponsor. <u>Interruption of the study drug</u> Administration of the study drug may be interrupted within the scope of the below stipulations if the investigator or sub-investigator deems a temporary discontinuation (interruption) of dosing for a period exceeding 7 days to be necessary. If a subject requires interruption beyond the scope described below, the subject has to be withdrawn from the study. • Interruption is defined as a temporary discontinuation of study drug administration for a period exceeding 7 days. • Interruption may not exceed a maximum of 4 consecutive weeks. • Up to 2 interruptions per year may be allowed. Moreover, they must be separated by an interval of 16 weeks or more.
Test Drug **Mode of Administration:** **Dose:** **Duration of Treatment:**	Test drug: ASP015K 50 mg, 100 mg, and 150 mg tablets Dose: [Subjects who transferred from study RAJ1] The starting dose will be 50 mg/day. [Subjects who transferred from studies RAJ3 or RAJ4] The starting dose will be 100 mg/day. For those subjects who have completed study RAJ1 and are continuing treatment with ASP015K at a dose of 50 mg/day, the need for a change in the dose shall be assessed at the initiation of the clinical study under the protocol ver. 2.0/ver. 3.0. If the dose is not increased to 100 mg, and

	treatment is to be continued at a dose of 50 mg/day, the reason for this decision must be entered in the medical record. When the investigator or sub-investigator judges that there to be no safety problem in the subject, the dose may be increased from 50 mg to 100 mg. For subjects who have been receiving ASP015K at a dose of 50 mg/day in Japan, the dose will be increased to 100 mg/day after the NDA approval in Japan. Any subjects for whom the dose cannot be increased should be withdrawn from the study. The dose may be increased from 100 mg to 150 mg at the point in time when the following 2 conditions are fully met: 1) Subject has taken ASP015K 100 mg for at least 4 weeks, and the DAS28-ESR score on the day of the study visit is 3.2 or higher (moderate disease activity or high disease activity). 2) When the investigator or sub-investigator judges there to be no problem with safety for the subject in the assessment performed on the study visit day on which the DAS28-ESR of 3.2 score or higher was exhibited Only in Korea and Taiwan, the dose may be reduced from 100 mg/day or 150 mg/day to 50 mg/day at the discretion of the investigator or sub-investigator. The investigator or sub-investigator will decide whether or not to reduce the dosage on the basis of the following criterion. • If an AE with an NCI-CTCAE grade classification of Grade 2 or higher has developed. A dose increase after a dose reduction and a dose reduction after a dose increase are allowed according to the above criteria. Mode of administration: To be orally administered QD after breakfast. The first dose should be given at each study center on the day of the Week 0 visit after all of the necessary assessments and tests have been completed. The duration of treatment: This study will be conducted as a post-marketing clinical study up to a maximum of 6 months after the NDA approval in Japan. (After the NDA approval in Japan, the post-marketing clinical study will be ended once the study drug is available in the clinical sites as a commercially available product. The planned study period will be up to a maximum of 6 months after the NDA approval in Japan). In Korea and Taiwan, this study will continue as a clinical study after the NDA approval in Japan. The duration of treatment will differ depending on the subject. To prevent purposeless continuation of dosing without effect, the investigator or sub-investigator will assess each subject for efficacy and safety at each visit, confirm the appropriateness of continued administration for each individual, and decide whether or not to continue dosing.
Comparative drug **Mode of Administration:** **Dose:** **Duration of Treatment:**	Not applicable.
Concomitant Treatment	(1) The following concomitant medications and complimentary alternative treatments are prohibited as described.

	➢ Administration or the use of the following medications and therapies will be prohibited from the end of the assessments at Week 12 of study RAJ1 to the initiation of administration of the study drug in this extension study, or from the end of the assessments at Week 52 of studies RAJ3 or RAJ4 to the initiation of administration of the study drug in this extension study, as well as throughout the treatment period of this extension study: 1) Biologic DMARDs: etanercept, anakinra, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab, certolizumab pegol, denosumab, sarilumab. 2) Non-biologic DMARDs: ● Subjects who transferred from study RAJ1: MTX, salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib. ● Subjects who transferred from study RAJ3: non-biologic DMARDs other than those used concomitantly in study RAJ3. ● Subjects who transferred from study RAJ4: salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib. (However, topical drugs other than those for the treatment of RA may be used concomitantly.) 3) Other drugs used in the treatment of RA: cyclosporine, cyclophosphamide, azathioprine, minocycline, etc. 4) Plasma exchange therapy ➢ Administration of the following medications and therapies will be prohibited from the end of the assessments at Week 12 of study RAJ1 to the initiation of administration of the study drug in this extension study, or from the end of the assessments at Week 52 of study RAJ3 or RAJ4 to the initiation of administration of the study drug in this extension study, as well as throughout the treatment period and follow-up period of this extension study: 5) Live or live attenuated virus vaccines ➢ Administration of the following medications is prohibited within 14 days prior to the start of treatment with the study drug, as well as throughout the treatment period and follow-up period: 6) CYP3A substrates with a narrow therapeutic range: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide, etc. ➢ Concomitant use of the following drugs and therapies will be prohibited throughout the treatment period: 7) Oral corticosteroids at doses that exceed the amount used from the initiation of studies RAJ1, RAJ3, or RAJ4 to the initiation of administration of the study drug in this extension study at a daily dose of prednisolone or equivalent. 8) Intra-articular, intravenous, intramuscular, or endorectal corticosteroids (However, suppositories for anal diseases may be used concomitantly.) 9) Oral morphine at doses exceeding 30 mg/day (or the equivalent amount of opioid analgesics). 10) Intra-articular administration of articular cartilage protective agents into joints subject to the assessment. 11) Drainage of fluid accumulated in the joint subject to the assessment, local anesthesia into joints subject to the assessment, and nerve block.

	12) The surgical treatment of joints subject to the assessment. ➢ Concomitant use of the following medications and therapies is prohibited throughout the treatment period and follow-up period: 13) Other study drugs, study drugs from post-marketing clinical studies, or medical devices being studied in clinical studies (2) Restricted concomitant medications <Subjects who transferred from studies RAJ1, RAJ3, or RAJ4> During the treatment period, the following medications may be used concomitantly at the discretion of the investigator or sub-investigator if they meet the following conditions for concomitant use (Both new administration and change in dosage/administration are permitted). 1) Non-steroidal anti-inflammatory drugs (NSAIDs) (excluding topical drugs with a local action). 2) Oral morphine (≤ 30 mg/day, or the equivalent amount of opioid analgesics) 3) Acetaminophen – Conditions for concomitant use – • No changes in the dosage/administration of the drug are allowed within the period of 12 weeks. However, this shall exclude cases where the medication has caused an AE. Moreover, if, after discontinuation of the concomitant medication, it becomes apparent that the suspected medication was not the offending drug that caused the AE, administration may be resumed with the dose prior to discontinuation as the maximum dose. <Subjects who transferred from study RAJ3> Subjects who have been receiving any of the below drugs throughout the treatment period of study RAJ3 shall continue the use of the drug concerned from the end of the assessment at Week 52 of study RAJ3 to the initiation of administration of the study drug in this extension study, as well as throughout the treatment period of this study. It is permitted to discontinue the drug or to increase or decrease the dose within the range not exceeding or falling below the baseline dose in study RAJ3. Administration of the drug may be interrupted, or the dose may be reduced because of an AE. This interruption must not exceed a maximum of 28 days. Administration may be resumed with the baseline dose in study RAJ3 as the maximum dose. ● If MTX is administered with study drug concurrently, the concomitant use of folic acid should be considered whenever possible. The dose of folic acid during the study period will, in principle, be within 10 mg per week, but it may be adjusted. If MTX is administered and ALT/AST becomes ≥ 3 × ULN, MTX must be interrupted, or the dose must be reduced, and daily administration of folic acid should be considered. • Methotrexate (MTX) • Hydroxychloroquine • Salazosulfapyridine • Gold • *D*-penicillamine • Lobenzarit • Actarit • Bucillamine • Iguratimod

	(3) Necessary concomitant medication <Concomitant use of MTX is specified only for subjects who transferred from study RAJ4> • MTX must be used from the end of the assessments at Week 52 of study RAJ4 to the initiation of administration of the study drug in this extension study, as well as throughout the treatment period of this extension study. • It is permitted to discontinue MTX or increase or decrease the dose within the range not exceeding or falling below the baseline dose in study RAJ4. • Administration of MTX may be interrupted, or the dose may be reduced because of an AE. This interruption must not exceed a maximum of 28 days. Administration may be resumed with the baseline dose in study RAJ4 as the maximum dose. • Folic acid should be concomitantly administered whenever possible. The dosage of folic acid during the study period is not more than 10 mg/week in principle; dose adjustment is permitted. • If ALT/AST is ≥ 3 × ULN, MTX should be interrupted or reduced, and daily administration of folic acid should be considered. (4) Rescue medications During the treatment period, the below medications can be used only when needed to treat AEs, complications, or worsening of the primary disease. However, these medications may not be taken within 24 hours prior to the joint assessment at each study visit. 1) NSAIDs: Single use as needed, for a period of 3 days or less 2) Analgesics other than NSAIDs (acetaminophen, opioid analgesics, all-in-one cold and flu medications, etc.): For 7 consecutive days or less 3) Intra-articular administration of corticosteroids, intra-articular administration of articular cartilage protective agents, drainage of fluid accumulated in joint, local anesthesia of joint, and nerve block: Performed once every 24 weeks (on up to 2 joints), starting at or after the Week 12 study visit However, joints on which intra-articular drug administration or rescue procedure has been performed will be assessed as showing disease activity (pain [tenderness]/swelling) after administration of the medication/therapy.
Endpoints (Safety)	• AEs • Vital signs (body temperature, pulse and blood pressure in sitting position) • Body weight • 12-lead Electrocardiogram (ECG) • Chest radiography • Laboratory Assessments
Endpoints (Pharmacodynamics)	Changes from baseline in lymphocyte subsets (CD3, CD4, CD8, CD16, CD19, CD56, CD56/16)
Endpoints (Efficacy)	The following items at each study visit • ACR 20 response rate • ACR 50 response rate • ACR 70 response rate • Change from baseline in Tender Joint Count (TJC) (68 joints) • Change from baseline in Swollen Joint Count (SJC) (66 joints) • Change from baseline in DAS28-CRP and DAS28-ESR scores • Percentage of subjects achieving DAS28-CRP score for remission • Percentage of subjects achieving ACR/EULAR score for remission ACR/EULAR remission is defined as meeting all 4 of the following

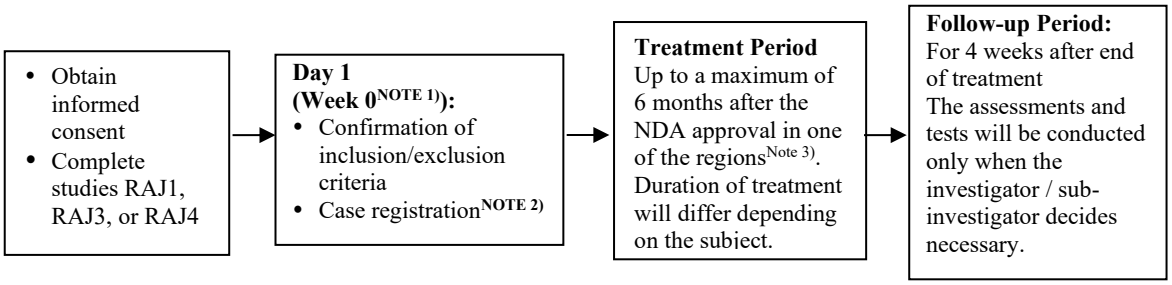
	criteria: ○ TJC ≤ 1 ○ SJC ≤ 1 ○ CRP ≤ 1 mg/dL ○ Subject's Global Assessment of Arthritis (SGA) ≤ 1 cm (0-100 mm on a VAS scale) • Percentage of subjects with a SDAI score of ≤ 3.3 (SDAI remission) • Change from baseline in Physician's Global Assessment of Arthritis (PGA) (VAS) • Change from baseline in SGA (VAS) • Change from baseline in the subject's assessment of pain (VAS) • FACIT-Fatigue score • Change from baseline in WPAI • Change from baseline in HAQ-DI • Change from baseline in SF-36v2® score • Percentage of subjects in EULAR response criterion of "Good Response" • Percentage of subjects in EULAR response criterion of "Moderate Response" • Percentage of subjects in EULAR response criterion of "Good Response" or "Moderate Response" • Incidence of subject withdrawal due to lack of efficacy
Statistical Methods	• In the assessment of efficacy and safety, the following will be calculated for continuous variables: number of subjects, mean, standard deviation, minimum, median, and maximum; categorical variables will be expressed as frequency and percentage. • AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs occurring after administration of the first dose of the study drug will be tallied for the entire study period and for each 3-month sub-period. • Laboratory test values (actually measured values and change from baseline), vital signs (actually measured values and change from baseline), and results of ECG assessment will be tallied at each time point. • Incidence of subject withdrawal due to lack of efficacy will be tallied for the entire study period and each 3-month sub-period. Other efficacy variables will be tallied at each time point.

V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart

In Japan, this study will transfer to a post-marketing clinical study after the NDA approval in Japan.

In Korea and Taiwan, this will continue as a clinical study after the NDA approval in Japan.



NOTE 1: The study visit at Week 0 of this study

- Will coincide with the day of the visit at Week 16/end of the study (follow-up) of study RAJ1,
- Will coincide with the day of the visit at Week 52 of studies RAJ3 or RAJ4, or fall within 28 days from the day of the visit at Week 52 of studies RAJ3 or RAJ4.

NOTE 2:

- Subjects who transferred from study RAJ1 will be registered at Week 0 of the present extension study.
- Subjects who plan to transfer from studies RAJ3 or RAJ4 will be registered at Week 52 of studies RAJ3 or RAJ4 to proceed to study RAJ2.

NOTE 3:

- After the NDA approval in Japan, the post-marketing clinical study will be ended once the study drug is available in the clinical sites as a commercially available product. The planned study period will be up to a maximum of 6 months after the NDA approval in Japan [If the assessments and tests scheduled for the end of study (follow-up) are conducted, this visit should be conducted before 6 months after the NDA approval in Japan].

Start and End of Study

Start of Study: Point in time where informed consent is obtained from the first subject

End of Study: Point in time where final assessment specified in protocol has been performed in the last subject [If the assessments and tests scheduled for the end of study (follow-up) are not conducted, the end of treatment/early termination will be the last visit to the site.]

Treatment period: Period from the initiation of administration of the study drug to completion of the tests and assessments stipulated at the end of treatment

Table 1. Schedule of Assessments

Schedule		**Treatment Period[c]**																					**Follow-up Period**	**Unscheduled Visit**
Visit Timing	**Week 0[b]**	**Week 2[v]**	**Week 4[v]**	**Week 8[v]**	**Week 12**	**Week 16[v]**	**Week 20[v]**	**Week 24**	**Week 28[v]**	**Week 32[v]**	**Week 36**	**Week 40[v]**	**Week 44[v]**	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**	**Week 108**	**Week 120**	**Week 132[w]**	**End of treatment/ early termination[d]**	**End of study (Follow-up)[e]**	
Visit Day[u]	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**421**	**505**	**589**	**673**	**757**	**841**	**925**	**–[s]**	**28 days after end of treatment**	
Allowable range from specified date	**–**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**–[s]**	**±7**	
Assessment																								
Informed consent[a]	X																							
Inclusion/exclusion criteria	X																							
Demographics/medical history	X																							
Weight	X*	X	X	X	X			X			X			X	X	X	X	X	X	X	X	X	X	X[t]
Physical examination[f]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Vital signs	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Laboratory test (blood/urine)[g]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Fasting lipid profile test[h]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Blood sampling for pharmacodynamics (lymphocyte subsets)[m]	X*													X				X				X	X	X[t]
CRP and ESR[i]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
Pregnancy test[j]	X*				X			X			X			X	X	X	X	X	X	X	X	X	X	X[t]
12-Lead ECG[k]	X*													X				X				X		X[t]
Chest radiography[l]	X*													X				X				X[x]		X[t]
Disease activity assessment[n]																								
TJC/SJC	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
PGA and SGA (VAS)	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]
SF-36v2® (from study RAJ1)[o]	X		X	X	X	X	X	X	X	X	X	X	X	X		X		X		X		X		X[t]
SF-36v2® (from studies RAJ3/RAJ4)[o]	X*							X						X		X		X		X		X		X[t]
HAQ-DI	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]

Schedule		**Treatment Period[c]**																					**Follow-up Period**	**Unscheduled Visit**
Visit Timing	**Week 0[b]**	**Week 2[v]**	**Week 4[v]**	**Week 8[v]**	**Week 12**	**Week 16[v]**	**Week 20[v]**	**Week 24**	**Week 28[v]**	**Week 32[v]**	**Week 36**	**Week 40[v]**	**Week 44[v]**	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**	**Week 108**	**Week 120**	**Week 132[w]**	**End of treatment/ early termination[d]**	**End of study (Follow-up)[e]**	
Visit Day[u]	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**421**	**505**	**589**	**673**	**757**	**841**	**925**	**–[s]**	**28 days after end of treatment**	
Allowable range from specified date	**–**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**–[s]**	**±7**	
Assessment																								
WPAI[p] (from studies RAJ3/RAJ4)	X*							X						X		X		X		X		X		X[t]
Assessment of AEs and SAEs[q]	X																				X	X	X	X
Confirm study drug prescription/remaining drug[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Record concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Be sure to obtain informed consent before beginning any of the procedures involved in the study. Regarding subjects from study RAJ1, informed consent should be obtained at the Week 12 visit of study RAJ1 in principle. Informed consent from subjects who transferred from studies RAJ3 or RAJ4 should be obtained before completion of all assessments at Week 52 of studies RAJ3 or RAJ4.

b. [Subjects who transferred from study RAJ1] The assessments and tests at Week 0 should be performed on the day of the visit at Week 16/end of study (follow-up) of study RAJ1. For items marked with the * symbol, the results of the assessments and tests performed at Week 16/end of study (at time of follow-up) in study RAJ1 may be used.
[Subjects who transferred from studies RAJ3 or RAJ4] The assessments and tests at Week 0 should be performed on the day of the Week 52 visit of studies RAJ3 or RAJ4 or within 28 days after the Week 52 visit. If the assessments and tests at Week 0 are performed on the day of the Week 52 visit, results of the assessments and tests at Week 52 of studies RAJ3 or RAJ4 may be used regarding the items marked with the * symbol. If they are not performed on the same day as the Week 52 visit, results of the assessments and tests of studies RAJ3 or RAJ4 during the follow-up period may be used. Only regarding chest radiography, it is allowed to use data obtained within 28 days prior to the Week 0 visit if available.

c. The subject should be contacted twice every 4 weeks between the previous visit to the next scheduled visit to confirm the status of compliance with study drug dosing and the safety of the subject (subjects who transferred from study RAJ1 are to be contacted once a month from the time of the Week 48 visit onward). Because this study will end at the point in time when ASP015K is approved, the duration of treatment with the study drug will differ depending on the subject. Accordingly, the timing for the required visits to the study center will also differ from subject to subject. When administration of the study drug has ended, the assessments and tests scheduled to be performed at the end of treatment and end of study (at time of follow-up) will be performed.

d. The assessments and tests to be performed at the end of treatment should be performed promptly after administration of the study drug has ended. If administration of the study drug has been terminated early, the assessments and tests specified to be performed at the end of treatment/early termination

should be performed within 2 days of the last dose of the study drug if possible. Moreover, even subjects who have had early termination during the scheduled treatment period should visit the study center at the end of study (at time of follow-up). The assessments and tests scheduled for the end of study (follow-up) should be conducted only if the investigator/ sub-investigator decides necessary. If the assessments and tests scheduled for end of study (follow-up) are not conducted, the end of treatment/early termination will be the last visit to the site.

e. The assessments and tests scheduled for end of study (at time of follow-up) should be performed 28 days after the end of administration of the study drug. These assessments and tests will be performed only if the investigator/ sub-investigator decides necessary.

f. Confirmation of physical findings by questioning the subject during the physical examination should be performed at all study visits. A symptom directed physical examination for RA should also be performed at all study visits. See NOTE n with regard to the confirmation of RA symptoms.

g. **Hematology**: Hemoglobin, hematocrit, RBC, WBC, WBC with differential, platelet count; **Biochemistry**: Na, K, Ca, Cl, Mg, HCO_3, BUN, phosphorus, glucose, creatinine, ALP, AST (GOT), ALT (GPT), γ-GTP, TBL, total protein, albumin, uric acid, CPK, LDH, serum amylase, β-D-glucan, eGFR (see Section 5.4.4.1 for procedure at time of CPK elevation); **Urinalysis**: pH, specific gravity, protein, glucose, keton bodies, bilirubin, occult blood, and sediment

h. Subject must fast for at least 8 hours prior to blood sampling for lipid profile (total cholesterol, LDL, HDL and triglycerides [TGs]).

i. CRP and ESR tests will be performed at each study visit. CRP test will be performed by the Central Laboratory; ESR test should be performed by each study center.

j. A urine pregnancy test should be performed at the study visits every 12 weeks from Week 0 onward, as well as at the end of treatment/early termination and end of study (at time of follow-up). If a urine pregnancy test is positive at any time, a negative serum pregnancy test is required for the subject to continue participation in the study. The pregnancy tests need not be performed if the possibility of pregnancy can clearly be ruled out, such as if the woman is postmenopausal and has not had a menstrual period for 1 year or more, or has had a hysterectomy, bilateral oophorectomy, etc.

k. The 12-lead ECG exams must be performed at the study visits every 48 weeks from Week 0 onward, as well as at the end of treatment/early termination. If a cardiovascular AE is observed, a 12-lead ECG may be performed at any time as necessary, even in an unscheduled visit. Clinical interpretation of the results of the 12-lead ECG at Week 0 must be completed prior to the first dose of the study drug.

l. [Subjects who transferred from study RAJ1] Chest radiography is taken at the Week 0 visit.
[Subjects who transferred from studies RAJ3 or RAJ4] Chest radiography is taken at the Week 0 visit, or data obtained within 28 days prior to the Week 0 visit may be used.
If a respiratory AE is observed, a chest radiography may be taken at any time as necessary, even in an unscheduled visit.

m. Blood samples for pharmacodynamics (lymphocyte subset assay) are collected before the first dose of the study drug on the day of the Week 0 visit.

n. Assessment of disease activity: **Physician** – TJC (68 joints), SJC (66 joints), PGA (VAS); **Subject** – SGA (VAS), subject's assessment of pain (VAS), HAQ-DI, WPAI, and SF-36V2®.

o. SF-36v2® is administered every 4 weeks until Week 48 and every 24 weeks after Week 48 to subjects from study RAJ1 and every 24 weeks throughout the study period to subjects from studies RAJ3 or RAJ4.

p. WPAI is administered only to subjects who transferred from studies RAJ3 or RAJ4.

q. AEs must be collected from the time of the administration of the first dose of study drug to the end of all assessments at the end of study (at time of follow-up).

r. After all of the assessments and tests scheduled for Week 0 have been completed, the subjects will receive the first dose of the study drug at each study center.

s. [Subjects who transferred from study RAJ1] If the study is terminated before the Week 48 visit, the specified date for the study visit at the end of treatment will be the date of the previous visit + 28 days (allowable range, ± 7 days). If the study is terminated in or after the Week 48 visit, the specified date for the study visit at the end of treatment will be the date of the previous visit + 84 days (allowable range, ± 14 days).
[Subjects who transferred from studies RAJ3 or RAJ4] The specified date for the study visit at the end of treatment will be the date of previous study visit + 84 days (allowable range, ± 14 days).

t. For unscheduled visits, these assessments and tests should be performed only if clinically indicated as determined by the investigator.

u. In principle, the subject should visit the study center on the specified date. If it is not possible for subjects to visit the study center on the specified date, the date of the visit should be adjusted to the date closest to the reference date as possible.

v. Only subjects who transferred from study RAJ1 should make study visits at Weeks 2, 4, 8, 16, 20, 28, 32, 40, and 44.

w. At visits after Week 132, the tests and assessments shall be performed in the same manner as scheduled for Weeks 96 to 132.

x. Chest radiography at the end of treatment/early termination is not necessary if one has been taken within 24 weeks from the day of the end of treatment/early termination.

1 INTRODUCTION

1.1 Background

RA is a chronic systemic inflammatory autoimmune disease that targets the synovial tissues [O'Dell, 2004]. The synovial inflammation is associated with irreversible cartilage destruction and erosion of bone, which may cause pain as well as decrease activity of daily living (ADL) due to functional impairment, and therefore reduce quality of life (QOL). The goal of RA treatment is to control the disease activity and achieve remission by preventing or controlling joint destruction, preventing loss of function, and relieving pain, thereby improving patient QOL.

Conventional RA treatments have been based on pain control with nonsteroidal anti-inflammatory drugs and inflammation control with corticosteroids, with which DMARDs have been combined [Nakajima, 2009]. Since the start of use of MTX and introduction of biologic agents, RA treatments have dramatically changed. Recently, therapeutic targets have shifted to prevention of joint destruction. The guidelines for the treatment of RA, published by the ACR in 2002 [American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines, 2002] and issued in Japan in 2004 [Clinical Practice Manual for the Treatment of RA (revised edition), 2004], recommend that pharmacotherapy is based on MTX, which primarily exerts inhibitory effects on activated T cells, because MTX offers the best balance of efficacy, safety and cost. In contrast, treatment of RA outside Japan now focuses on early, aggressive use of effective agents to halt disease progression and prevent joint destruction. The guidelines published by the ACR in 2008 [Saag et al, 2008] recommend the initiation of MTX or leflunomide monotherapy for patients with all disease durations and degrees of disease activity. In particular, MTX has established an impregnable position as the drug of first choice. In Japan, it can be stated that MTX is commonly recognized as such a drug of first choice. Treatment with MTX as an anchor drug in combination with later developed biologic agents such as TNF inhibitors enables approximately 30% of RA patients to achieve remission, almost conquering progression of joint destruction [Tanaka, 2009].

However, all of the existing treatments for RA do not cure the disease. It has been reported that approximately 30% of RA patients are resistant to therapy with TNF inhibitors, representative biologic agents, with only 30% to 50% of patients achieving remission [Yamaoka, 2008]. MTX inhibits cell proliferation nonspecifically, so adverse effects on other proliferating tissues such as the gut and bone marrow are common. These treatments are not without appreciable safety issues. Thus, there currently exists a need for effective new treatments with more targeted mechanism of action and an improved safety profile over existing therapies. Moreover, the need of intravenous or subcutaneous administration and the great financial burden of biologic agents make it difficult for many of the patients to continue treatment. In such a situation, much attention is now being given to low molecular weight compounds with relatively low costs and comparable efficacy to biologic agents.

JAK 3, an important protein in exerting biological activity of cytokines, is one of the tyrosine kinases and is activated intracellularly following cytokine binding to receptors. Because JAK3 deficiency may cause severe combined immunodeficiency (SCID) due to failure of lymphocyte differentiation, a compound to inhibit JAK3 is expected to be a novel immunosuppressant and has been developed. It is suggested that in the course of RA, inflammatory cytokines as well as autoreactive T cell proliferation and T cell products such as interleukin-2 (IL-2), interferon-gamma (IFN-γ), and IL-17 may contribute to the development of the disease, considering that inhibition of proliferation of T-, B-, and NK-cells and reduction of their functions are essential for treating RA.

ASP015K is an orally bioavailable JAK inhibitor discovered by the sponsor with selectivity for JAK3, a protein tyrosine kinase associated intracellularly with the common gamma chain (gamma c) which is a component of receptors of cytokines such as IL-2 produced through immunoreaction. ASP015K inhibits phosphorylation of signal transducer and activator of transcription (STAT) 5 by JAK3 activated following IL-2 receptor binding, thereby blocking differentiation and proliferation of T cells mediated by regulation of cytokine responsive gene expression by STAT5 in the nucleus [O'Shea, 2004]. Because JAK3 shows a restricted tissue expression (primarily hematopoietic cells), JAK3 inhibition is a desirable therapeutic target for immunosuppression in human organ transplantation and immunomodulation in autoimmune disorders [Papageorgiou & Wikman, 2004], without significantly affecting other organ systems [Kremer et al, 2009]. Thus, compounds that inhibit JAK3 activity may have a therapeutic effect on autoimmune diseases such as RA.

Xeljanz® (tofacitinib) 5 mg is a JAK inhibitor approved by the US FDA in 2012 for the treatment of adult patients with moderate to severe RA who had an inadequate response to or are intolerant of MTX. In Japan, this drug was approved in March 2013 for treating RA patients who had an inadequate response to conventional therapies.

Astellas Pharma is pursuing the development program of ASP015K for the indication of RA. In Japan, the Phase IIb dose-finding study (015K-CL-RAJ1, or RAJ1) has been completed, and its long-term extension study (015K-CL-RAJ2, or RAJ2) is ongoing. Overseas, 2 Phase II dose-finding studies (1 with MTX and the other without MTX) have been completed, and their follow-up extension study is underway, similar to the situation in Japan. The results of RAJ1 showed that ASP015K caused a significantly higher improvement in RA than placebo in terms of the ACR response rate, DAS28 score, and other efficacy variables, suggesting its usefulness for treating RA.

1.2 Non-clinical and Clinical Data

1.2.1 Nonclinical Pharmacology and Safety Pharmacology

ASP015K is a novel oral immunosuppressant that exerts it pharmacological action by relatively selectively inhibiting JAK3, a key enzyme in the IL-2 signaling pathway. *In vitro* kinase studies showed that ASP015K also inhibited JAK1, JAK2, and TYK2, although less potently than it inhibited JAK3. The effects of ASP015K were investigated in a rat adjuvant-

induced arthritis model. Data showed that prophylactic administration of ASP015K in which treatment was initiated before the occurrence of pedal edema prevented the event and reduced radiographic joint destruction scores. Therapeutic administration of ASP015K in which treatment was initiated after the occurrence of pedal edema also prevented the event and reduced joint destruction scores.

In safety pharmacology studies, ASP015K showed no effect on human hERG current or action potential duration in isolated guinea pig papillary muscles at clinically relevant concentrations. ASP015K had no effect on the central nervous system (modified Irwin's method) of rats at up to 100 mg/kg orally. In monkeys, loose/watery stools and a tendency towards reduced blood potassium concentrations were observed at 60 mg/kg orally, but there were no effects on the central nervous system, cardiovascular system (ECG, blood pressure or heart rate), or respiratory system of monkeys at up to 60 mg/kg.

1.2.2 Pharmacokinetics and Pharmacodynamics

1.2.2.1 Nonclinical Pharmacokinetics

Absolute bioavailability ranged from 39.8% to 46.4% in rats and 18.9% to 19.2% in monkeys. Following a single oral dose of 3 mg/kg ^{14}C-ASP015K in Sprague-Dawley rats, radioactivity distributed rapidly into tissues with no long-term tissue retention observed. In a study with pigmented rats, the dosed radioactivity was rapidly excreted within the first 24 hours after administration in almost all tissues with the exception of the eyeball ($t_{1/2}$ of 1105.8 hours). No apparent differences were noted in radioactivity concentration-time profiles between nonpigmented and pigmented skin, and the radioactivity was not detected in these skins for a long time. These data suggest that ASP015K-related compounds may have bound to melanin, but binding was likely weak and reversible. In Sprague-Dawley rats orally administered ^{14}C-ASP015K 3 mg/kg once daily for 21 days, radioactivity was slowly eliminated from the lung, spleen, skin, bone marrow, testis, and thoracic aorta. With the exception of the thoracic aorta, the radioactivity levels 168 hours after the last dose were reduced to 19% or less of the levels measured 0.25 hours after the last dose. The mean radioactivity of the thoracic aorta at 168 hours of the last dose was as low as less than 3 times the lower limit of quantification.

The *in vitro* plasma protein binding rates of ASP015K and its metabolite AS2628528 (H2) were determined in the concentration range of 0.2–20 μg/mL. The plasma protein binding rates in mice, rats, rabbits, dogs, monkeys, and humans were in the ranges of 59%–95% for ASP015K and 84%–99% for H2. Among human plasma proteins, human serum albumin (HSA) most preferentially bound to ASP015K and H2.

In pregnant and lactating rats administered a single oral dose of ^{14}C-ASP015K 3 mg/kg, the radioactivity was distributed widely across different tissues of the dams, although the tissue radioactivity almost completely disappeared within 24 hours. Although the levels of placental radioactivity transfer were low, comparatively higher levels of radioactivity were rapidly transferred to the milk, leading to elevated radioactivity in pups via lactation.

When ^{14}C-ASP015K was orally administered alone to rats at a dose of 3 mg/kg, 3 radioactivity peaks were detected in plasma on the radiochromatogram, with the main peak

being that of the unchanged drug. *In vitro* metabolic profile of ^{14}C-ASP015K was performed in liver microsomes and cryopreserved hepatocytes from mice, rats, rabbits, dogs, cynomolgus monkeys, and humans. No human-specific metabolites were identified in either assay. In *in vitro* metabolic studies, ASP015K was metabolized to H2 by human sulfotransferase 2A1 (hSULT2A1) and to AS2604202 (H4) by human nicotinamide N-methyltransferase (hNNMT).

In rats administered ^{14}C-ASP015K, urinary and biliary excretion of the dosed radioactivity within 72 hours was 25.2% and 46.7%, respectively, suggesting high oral absorption of ASP015K. In monkeys administered ^{14}C-ASP015K, urinary and biliary excretion of the dosed radioactivity within 72 hours was 22.3% and 26.4%, respectively.

1.2.2.2 Clinical Pharmacokinetics and Pharmacodynamics

A total of 17 clinical studies of ASP015K have been completed till date. These studies included 14 pharmacokinetic studies in healthy adult volunteers, 1 pharmacokinetic study in RA patients, 1 efficacy and safety study in patients with psoriasis, and 1 efficacy and safety study in RA patients. More specifically, they were as follows: a single-dose and repeated-dose study in Japanese and Caucasian subjects conducted in Japan (015K-CL-HV03), an overseas single ascending dose and food effect study (015K-CL-HV01), an overseas repeated-dose study (015K-CL-HV02), a mass balance study using radiolabeled ASP015K (015K-CL-PK03), a regional absorption study (015K-CL-PK15), 4 relative bioavailability and food effect studies (015K-CL-PK09, 015K-CL-PK18, 015K-CL-PK19, 015K-CL-PK51), 5 drug–drug interaction (DDI) studies in healthy adult volunteers (015K-CL-PK01, 015K-CL-PK02, 015K-CL-PK05, 015K-CL-PK16, and 015K-CL-PK26), 1 DDI study in RA patients (015K-CL-PK13), 1 efficacy and safety study in psoriasis patients (015K-CL-PS01), and 1 efficacy and safety study in RA patients (015K-CL-RAJ1).

These completed studies involved 472 healthy adults and 296 RA patients; they received ASP015K doses ranging from 3 to 300 mg/day in single-dose studies and from 10 to 200 mg twice daily (BID) in repeated-dose studies. In addition, 124 patients with psoriasis were enrolled and were administered 10 to 100 mg BID or 50 mg once daily (QD).

After a single dose of 3 to 300 mg/day administered under fasting conditions in Study 015K-CL-HV01, ASP015K was rapidly absorbed with a median t_{max} ranging from 1.0 to 1.75 hours across the dose groups. The AUC_{inf}, AUC_{last} and C_{max} of ASP015K increased dose proportionally. Elimination occurred in a multiphasic manner with a mean $t_{1/2}$ value of 2.8 to 18.5 hours. Compared to administration under fasting conditions, the mean C_{max} of ASP015K administered under fed conditions increased by 5%. Similarly, the mean AUC_{inf} increased by 27% with t_{max} being prolonged for approximately 2.5 hours. Urinary excretion of ASP015K accounted for between 9% and 15% of the oral dose. ASP015K inhibited JAK3-mediated phosphorylation of STAT5 dose-dependently. Peak inhibition of JAK3-mediated phosphorylation of STAT5 was observed around 1 to 2 hours (median) following administration of ASP015K under fasting conditions. At a dose of 60 mg, the peak inhibition reached 84% of the maximum. The mean changes from baseline lymphocyte counts and

peripheral lymphocyte subsets suggested there were no time or dose-dependent changes after a single oral dose of ASP015K.

Study 015K-CL-HV02, in which ASP015K was given at doses of 30 mg BID, 100 mg BID, or 200 mg BID for 14 days under non-fasting conditions, demonstrated no clear difference in pharmacokinetics of ASP015K after repeated dosing between the morning and evening doses, although the trough level after the morning dose tended to be lower. Steady state in plasma ASP015K concentrations was achieved by day 3. The mean accumulation factor on day 14 was between 1.12 and 1.65 for C_{max}, 1.38 and 1.65 for AUC_{12}, and 2.02 and 2.71 for $C_{trough,PM}$. At steady state, the peak-trough ratios (peak/trough levels) of ASP015K concentrations were between 8.8 and 18. Overall, C_{max} and AUC_{12} values generally increased dose proportionally over the range of 30 to 100 mg BID. There was no sex difference in ASP015K exposure with the 100 mg BID dose.

As a result of metabolite analysis of samples collected in 015K-CL-HV01 and 015K-CL-HV02, 3 metabolites (H1, H2, H4) were identified from plasma samples and 6 metabolites (H1 to H6) were identified from urine samples.

Results from the mass balance study (015K-CL-PK03) indicated that unchanged ASP015K accounted for 36% of the total radioactivity in plasma (metabolites accounted for the remaining 64%). Approximately 36.8% of the total radioactivity was excreted in urine and 56.6% in feces. Unchanged ASP015K accounted for 36% of the total radioactivity in urine.

In Study 015K-CL-HV03, Japanese had greater ASP015K exposure than Caucasian. After adjustment for dose and body weight, C_{max} was 42.9% to 53.9% higher and AUC_{inf} was 22.5% to 44.9% higher in Japanese relative to Caucasian. JAK3 inhibition was dose-dependent in Japanese and Caucasian. Consistent with the generally higher plasma concentrations of ASP015K in Japanese, the peak inhibition of JAK3 following a single dose of ASP015K was also higher in Japanese. Overall, the mean change from baseline for T cell subsets was similar with ASP015K single or repeated dosing, with little variation among ethnicity.

Results from a regional absorption study (015K-CL-PK15) indicated that absorption primarily (≥ 50%) occurred in the proximal small bowel, and the rate and extent of absorption decreased as the delivery site became more distal within the gastrointestinal tract.

In Study 015K-CL-PK19, subjects were administered ASP015K (5 tablets of 30 mg) after a meal (approximately 500 to 600 kcal, with fat accounting for 25% to 35% of the total calories). Compared with fasting conditions, t_{max} was extended by 0.5 hours, and C_{max} and AUC increased by 34% and 27%, respectively.

In the 6 DDI studies, the pharmacokinetic profile of ASP015K was investigated in the presence of: mycophenolate mofetil (MMF) (015K-CL-PK01), tacrolimus (015K-CL-PK02 and 015K-CL-PK16), midazolam (015K-CL-PK05), MTX (015K-CL-PK13), and rosuvastatin (015K-CL-PK26). MMF, tacrolimus, midazolam, and rosuvastatin were administered in healthy adult volunteers, whereas MTX was used in RA patients.

Administration of ASP015K 100 mg BID had no effect on the pharmacokinetic profile of MTX in patients with RA or the MMF metabolites MPA and MPAG in healthy volunteers. ASP015K 60 mg and 100 mg BID did increase tacrolimus levels in whole blood following oral administration of tacrolimus 5 mg, but not when tacrolimus was administered as a 1 mg intravenous dose. Concomitant use of ASP015K elevated the plasma midazolam concentrations after a single oral dose of midazolam 3 mg. It also raised the plasma rosuvastatin levels following a single oral dose of rosuvastatin 10 mg. However, steady-state pharmacokinetics of ASP015K were not significantly impacted by MTX 15 to 25 mg, MMF 1 g, midazolam 3 mg, oral tacrolimus 5 mg, or intravenous tacrolimus 1 mg doses.

In Study 015K-CL-PS01 that enrolled patients with psoriasis, the administration of ASP015K 10 to 100 mg BID elevated ASP015K exposure (C_{max}, AUC_{last}, and AUC_{6h}) in a dose-dependent manner. The median t_{max} values were in the range of approximately 1.0 to 1.8 hours. STAT5 phosphorylation and JAK3 activity were inhibited in a dose-dependent manner. Although no consistent trends were noted for the absolute lymphocyte count, a slight dose-dependent decreasing trend was noted for the proportions and absolute counts of NK and B cells.

In Study 015K-CL-RAJ1 of Japanese patients with RA, matrix metalloproteinase 3 levels decreased in a dose-dependent manner following the administration of ASP015K 25 to 150 mg QD. Although no consistent trends were noted for the absolute lymphocyte count, NK cell counts decreased and B cell counts increased in a dose-dependent manner.

1.2.3 Toxicology

Nonclinical repeated-dose toxicity studies of ASP015K were conducted using rats (up to 26 weeks) and monkeys (up to 52 weeks). Toxicities observed in these studies were mainly related to gastrointestinal, hematopoietic, muscular, and immune systems. All these findings were reversible and resolved upon the withdrawal of ASP015K. Muscle toxicity was observed in monkeys: mild multifocal muscle necrosis in 1 female at 60 mg/kg per day in the 4-week preliminary study; elevation of CPK and LDH without histopathological change of the muscle in 2 males at 60 mg/kg per day in the 4-week preliminary study; elevation of CPK and LDH without histopathological changes in 1 male that was sacrificed in extremis in 13-week study, and a transient increase of CPK without histopathological changes observed in another male in the same 13-week study.

Genotoxicity studies were conducted *in vitro* and *in vivo*. ASP015K was negative in the reverse mutation test in bacteria but was positive in an *in vitro* chromosomal aberration test in Chinese hamster lung cells. ASP015K was negative in 2 *in vivo* genotoxicity studies, the unscheduled DNA synthesis test in rats and the micronucleus test in mice. These results suggested that ASP015K had little potential to induce chromosomal aberrations in *in vivo*.

In toxicity studies on the fertility and early embryonic development in rats, the viability of embryos decreased after implantation and the number of live embryos decreased in the 100 mg/kg per day group compared with the control group. ASP015K neither induced general toxicity nor impacted male or female fertility up to the dose of 100 mg/kg/day. In an

embryo–fetal development study in rats, increased incidences of skeletal abnormalities and variations and visceral variations were noted at 30 mg/kg/day and higher, while increased incidences of visceral and external abnormalities were observed at 300 mg/kg/day. NOAEL for embryo–fetal development in rats was 10 mg/kg/day. In an embryo–fetal developmental toxicity study in rabbits, no teratogenicity was observed; however, increased postimplantation loss and decreased numbers of live fetuses were noted at 10 mg/kg/day.

Four- and 13-week toxicity studies of ASP015K administered in combination with tacrolimus, MMF, or MTX demonstrated no significant synergistic toxicities in rats.

1.2.4 Efficacy

In a double-blind, placebo-controlled study conducted in Japan (015K-CL-RAJ1), the dose response for the efficacy and safety of once-daily oral ASP015K (25, 50, 100, 150 mg) administered for 12 weeks was investigated in 281 patients with moderate to severe RA. Its primary efficacy variable was the ACR20 response rate at Week 12. The ACR20 response rates were 10.7% for placebo, 23.6% for 25 mg, 31.6% for 50 mg, 54.5% for 100 mg, and 65.5% for 150 mg groups. Significant improvements over placebo were noted for 50 mg ($P=0.021$), 100 mg ($P<0.001$), and 150 mg groups ($P<0.001$). In addition, logistic regression analysis demonstrated a statistically significant dose–response relationship ($P<0.001$). Secondary efficacy variables, the ACR50 response rate, ACR70 response rate, and DAS28-CRP, exhibited significant improvements for ASP015K over placebo. A long-term extension study (015K-CL-RAJ2) for patients who completed this study is underway to investigate the efficacy and safety of ASP015K administered over an extended period of time.

Overseas, 3 clinical studies of patients with moderate to severe RA have been completed (015K-CL-RA21, 015K-CL-RA22, 015K-CL-RA25). 015K-CL-RA21 and 015K-CL-RA22 were dose-finding studies of ASP015K administered with and without MTX, respectively. 015K-CL-RA25 was a long-term follow-up extension study that enrolled the patients who completed either of the 2 studies.

In a US double-blind, placebo-controlled study in patients with moderate to severe psoriasis vulgaris (015K-CL-PS01), 124 subjects were orally administered ASP015K (10, 25, 60, 100 mg BID or 50 mg QD) over 6 weeks. Compared with placebo, all ASP015K groups showed greater improvements in terms of change from baseline in the PASI score (primary efficacy variable), depicting a statistically significant difference in the overall therapeutic response. For secondary efficacy variables, the treatment success based on Physician’s Static Global Assessment (PSGA) and 75% reduction in the PASI score (PASI 75 response) demonstrated the efficacy of ASP015K.

1.3 Summary of Key Safety Information for Study Drugs

The safety and tolerability of ASP015K were evaluated in 14 studies in healthy adult volunteers (13 overseas and 1 Japanese), 2 studies in RA patients (1 each overseas and Japanese), and 1 study in patients with psoriasis (overseas). In these studies, a single dose of 3 to 300 mg and repeated doses of 10 to 200 mg BID were administered in 423 healthy adults

and 14 RA patients. In addition, 225 RA patients received repeated doses of 25 to 150 mg QD, and 95 psoriasis patients received repeated doses of 10 to 200 mg BID or 50 mg QD.

Treatment-emergent adverse events (TEAEs) that occurred relatively frequently in these studies included gastrointestinal disorders (e.g., diarrhoea, nausea, flatulence, vomiting) and nervous system disorders (e.g., headache).

There were 7 subjects in the following 3 overseas studies who experienced a TEAE that resulted in discontinuation. In the overseas repeated-dose study of ASP015K in healthy volunteers (015K-CL-HV02), 2 subjects discontinued ASP015K due to neutrophil count decreased (1 male in the 200 mg BID group and 1 female in the 100 mg BID group) that was considered probably related to study drug. The neutrophil count decreased resolved the day after discontinuation in both cases. A third subject, a male in the 100 mg BID group, discontinued ASP015K due to moderate vomiting that was considered probably related to the study drug.

In the single-dose, mass balance study of ASP015K 10 mg (015K-CL-PK03), 3 subjects were withdrawn from the study, 2 due to upper respiratory tract infection and 1 due to nasopharyngitis, which all occurred during a washout period. These TEAEs were mild in severity and were considered to be unrelated to ASP015K.

In the study in psoriasis patients (015K-CL-PS01), 1 patient in the 60 mg BID group was withdrawn from the study due to neutrophil count decreased, which was mild in severity and was considered to be possibly related to ASP015K by a physician.

The more common TEAEs across the 11 completed clinical studies were gastrointestinal disorders (e.g., diarrhoea, nausea, flatulence, vomiting) and headache.

In the overseas single-dose study (015K-CL-HV01), there was no evidence of clinically significant safety findings in subjects who received single oral doses of ASP015K (3, 10, 30, 60, 120, 200 and 300 mg) under fasted conditions or a single 120 mg oral dose in the fed state. The more common TEAEs in this study that occurred in multiple subjects were headache (7 subjects; moderate in 1 and mild in 6), mild tension headache (3 subjects); flatulence (3 subjects; moderate in 1 and mild in 2), and mild, asymptomatic bradycardia (2 subjects).

In the overseas repeat-dose study (015K-CL-HV02), the more common TEAEs in the 36 subjects receiving ASP015K were neutropenia (14 subjects; severe in 1 subject, moderate in 3 subjects, and mild in 10 subjects); headache (7 subjects; moderate in 2 subjects and mild in 5 subjects); mild abdominal pain (6 subjects); mild, diarrhoea (4 subjects) and nausea (4 subjects; moderate in 1 subject and mild in 3 subjects). Dose-dependent gastrointestinal disorders (e.g., nausea, diarrhoea, dyspepsia, and abdominal pain) and neutropenia were observed, especially in approximately two-thirds of subjects (6 of 9 subjects) in the highest dose group (ASP015K 200 mg BID). In this repeat-dose study, 2 subjects experienced severe TEAEs and 8 experienced moderate TEAEs. Severe TEAEs included elevated lipase and CPK elevation that occurred in 1 male subject (200 mg BID group) and neutropenia in 1 female subject (100 mg BID group).

In the single-dose and repeated-dose study in Japanese and Caucasian volunteers (015K-CL-HV03), the only TEAE observed in at least 1 subject after a single dose of ASP015K was mild white blood cell count increased in 2 of 6 Japanese subjects receiving ASP015K 60 mg and 1 of 6 Japanese subjects receiving ASP015K 200 mg. TEAEs observed in at least 1 subject who received repeated doses of ASP015K were mild neutrophil count decreased in 3 of 6 Japanese male subjects receiving ASP015K 100 mg BID; mild white blood cell count increased in 2 of 6 Japanese male subjects receiving ASP015K 30 mg BID and 1 of 6 Japanese male subjects receiving ASP015K 10 mg BID; and mild alanine aminotransferase increased in 1 of 6 Japanese male subjects receiving ASP015K 10 mg BID and in 1 of 6 Japanese male subjects receiving ASP015K 100 mg BID.

There were no vital sign or ECG findings observed in subjects following administration of ASP015K in the previous clinical pharmacology studies that were considered clinically relevant, except mild, asymptomatic bradycardia (possible related; recovered) in 2 subjects in the overseas single-dose study (015K-CL-HV01), and intermittent, mild arrhythmia (not related; recovered) lasting for approximately 5 hours in 1 subject after a single dose of ASP015K 100 mg in the DDI study of ASP015K with midazolam (015K-CL-PK05).

DDI studies involving MTX, MMF, midazolam, tacrolimus, and rosuvastatin (015K-CL-PK01, 015K-CL-PK02, 015K-CL-PK05, 015K-CL-PK13, 015K-CL-PK16, 015K-CL-PK26) demonstrated that ASP015K administered in combination with these agents was well tolerated, and reported TEAE incidence rates comparable with those documented for ASP015K as single-agent therapy.

In the Japanese clinical trial in RA patients (015K-CL-RAJ1), the incidence rates of AEs in the ASP015K 25 mg, 50 mg, 100 mg, and 150 mg groups were 70.9%, 64.9%, 52.7%, and 67.2%, respectively. These rates were comparable with that of the placebo group (64.3%). The incidence rates of AEs whose relationship to the study drug could not be ruled out for the ASP015K 25 mg, 50 mg, 100 mg, and 150 mg groups were 38.2%, 43.9%, 29.1%, and 55.2%, respectively. These rates were higher than that reported for the placebo group (28.6%). By severity (NCI-CTCAE), most were either Grade 1 or Grade 2. In the placebo and ASP015K 25 mg, 50 mg, 100 mg, and 150 mg groups, the numbers of subjects with serious adverse events (SAEs) were 1 (1.8%), 1 (1.8%), 2 (3.5%), 3 (5.5%), and 0, respectively. Death was reported from 1 subject of the 50 mg group (cerebral haemorrhage). AEs resulted in treatment discontinuation in 10 (17.9%), 7 (12.7%), 5 (8.8%), 6 (10.9%), and 4 (6.9%) subjects of the placebo, 25 mg, 50 mg, 100 mg, and 150 mg groups, respectively. The most common reason was rheumatoid arthritis aggravated (21/32). Rheumatoid arthritis, nasopharyngitis, blood creatine phosphokinase (CPK) increased, diarrhoea, cystitis, constipation, stomatitis, dyspepsia, lipids increased, and blood triglycerides increased were reported at ≥ 5% incidence rates from 1 or more groups. By the MedDRA System Organ Class (SOC), Infections and infestations, Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Investigations showed high incidence rates. Blood creatine phosphokinase increased were observed in 0, 2 (3.6%), 1 (1.8%), 1 (1.8%), and 7 (12.1%) subjects of the placebo, 25 mg, 50 mg, 100 mg, and 150 mg groups, respectively. Most cases were transient, and all subjects except 1 who prematurely discontinued the study recovered or

were recovering. With regard to clinical laboratory testing, compared with the placebo group, the ASP015K groups showed decreased levels of neutrophils, platelets, and estimated glomerular filtration rate (eGFR) and elevated levels of CPK, hemoglobin, lymphocytes, creatinine, total cholesterol, LDL, HDL, and triglycerides. No noteworthy changes were detected in vital signs or ECG recordings.

In the overseas study in psoriasis patients (015K-CL-PS01), none of the AEs observed were apparently dose-dependent, although the overall incidence of AEs in patients receiving ASP015K was higher than in those receiving placebo. No SAEs were reported. However, 1 subject treated with 60 mg BID prematurely discontinued the study owing to mild neutrophil count decreased, and this case was judged possibly related to the study drug. The more common AEs were pharyngitis, diarrhoea, and flatulence, which did not occur more frequently in a specific treatment group including the placebo group. Mild neutrophil count decreased was observed in patients receiving ASP015K, with none having neutrophil count of less than $1000/mm^3$. The mean CPK level increased with dose. A total of 4 AEs of creatine phosphokinase increased were reported, each in the placebo, 10 mg BID, 25 mg BID, and 100 mg BID groups, none of which were associated with symptoms suggestive of myopathy. During this study, no anaemia occurred. While mild to moderate increases in HDL, TGs, and total cholesterol were observed, there was no change from baseline in LDL.

For more information regarding the efficacy and safety of ASP015K, refer the current version of the Investigator's Brochure.

The following shows the summary of safety results of two completed phase 3 studies (015K-CL-RAJ3 and 015K-CL-RAJ4).

For the 015K-CL-RAJ3 study, which Japanese, Korean and Taiwanese were included, from week 0 through week 12, TEAEs were reported in 54 (53.5%), 59 (56.7%) and 55 (53.9%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. Drug-related TEAEs were reported in 29 (28.7%), 33 (31.7%) and 38 (37.3%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. The majority of TEAEs were grade 1 or 2 in severity.

In the etanercept group, TEAEs were reported in 119 (59.5%) patients and drug-related TEAEs were reported in 75 (37.5%) patients.

For overall period, no major differences were observed in the overview of TEAEs compared with from week 0 through week 12. TEAEs were reported in 92 (88.5%) and 89 (87.3%) patients in the ASP015K 100 mg and 150 mg groups, respectively. The majority of TEAEs were grade 1 or 2 in severity. TEAEs occurring in ≥ 5% of patients in the placebo or ASP015K groups included nasopharyngitis (5.9%, 9.6% and 18.6% in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively), rheumatoid arthritis (10.9%, 2.9% and 2.0%) and hepatic function abnormal (3.0%, 0% and 6.9%).

Drug-related TEAEs occurring in ≥ 5% of patients in the placebo or ASP015K groups included nasopharyngitis (3.0%, 4.8% and 7.8% in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively).

TEAEs occurring in ≥ 5% of patients in the etanercept group included injection site reaction (12.5%), nasopharyngitis (8.0%) and hepatic function abnormal (5.0%). Drug-related TEAEs occurring in ≥ 5% of patients in the etanercept group included injection site reaction (12.5%).

For overall period, TEAEs occurring in ≥ 5% of patients in the ASP015K 100 mg or ASP015K 150 mg groups included nasopharyngitis (28.8% and 28.4% in the ASP015K 100 mg and ASP015K 150 mg groups, respectively), blood creatine phosphokinase increased (9.6% and 10.8%), influenza (6.7% and 5.9%), upper respiratory tract infection (5.8% and 6.9%), cough (5.8% and 6.9%), nausea (7.7% and 3.9%), rheumatoid arthritis (5.8% and 4.9%), upper respiratory tract inflammation (4.8% and 5.9%), hepatic function abnormal (1.9% and 7.8%), pharyngitis (6.7% and 2.9%), bronchitis (6.7% and 1.0%) and eczema (1.9% and 5.9%).

Drug-related TEAEs occurring in ≥ 5% of patients in the ASP015K 100 mg or ASP015K 150 mg groups included nasopharyngitis (14.4% and 13.7% in the ASP015K 100 mg and ASP015K 150 mg groups, respectively), blood creatine phosphokinase increased (7.7% and 7.8%), nausea (5.8% and 2.9%) and bronchitis (5.8% and 1.0%).

Death after the end of study was reported in 1 patient due to thyroid cancer in the etanercept group and was considered to be possibly related to etanercept.

From week 0 through week 12, SAEs were reported in 4 (4.0%), 3 (2.9%) and 2 (2.0%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. From week 0 through week 12, no serious TEAEs occurred in ≥ 2 patients in the placebo or ASP015K groups.

For overall period, SAEs were reported in 7 (6.7%) and 8 (7.8%) patients in the ASP015K 100 mg and 150 mg groups, respectively. Drug-related SAEs were reported in 3 (2.9%) and 3 (2.9%) patients in the ASP015K 100 mg and 150 mg groups, respectively. For overall period, no serious TEAEs occurred in ≥ 2 patients in the ASP015K 100 mg or ASP015K 150 mg groups except for spinal compression fracture (2 patients in the ASP015K 150 mg group).

AEs leading to permanent discontinuation of study drug were reported in 4 (4.0%), 6 (5.8%) and 3 (2.9%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. Drug-related AEs leading to permanent discontinuation of study drug were reported in 1 (1.0%), 4 (3.8%) and 2 (2.0%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. From week 0 through week 12, TEAEs leading to permanent discontinuation of study drug occurring in ≥ 2 patients in the placebo or ASP015K groups included rheumatoid arthritis (3 and 2 patients in the placebo and ASP015K 100 mg groups, respectively).

For overall period, AEs leading to permanent discontinuation of study drug were reported in 13 (12.5%) and 6 (5.9%) patients in the ASP015K 100 mg and 150 mg groups, respectively. Drug-related AEs leading to permanent discontinuation of study drug were reported in 7

(6.7%) and 4 (3.9%) patients in the ASP015K 100 mg and 150 mg groups, respectively. TEAEs leading to permanent discontinuation of study drug occurring in ≥ 2 patients in the ASP015K 100 mg and ASP015K 150 mg groups included rheumatoid arthritis (3 patients in the ASP015K 100 mg group).

With regard to the analysis per 100 patient-years for serious infections and herpes zoster related disease (herpes zoster and varicella), the incidence rates of serious infections and herpes zoster related disease (herpes zoster and varicella) were higher in the ASP015K groups compared with the placebo group; however, no dose dependency was observed between the ASP015K 100 mg and 150 mg groups.

There was no major difference among the treatment groups for malignancy.

Increases in creatine kinase were observed in the ASP015K groups compared with the placebo group. Increases in hemoglobin, creatinine, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides, and decreases in lymphocytes, platelets, total cholesterol/HDL ratio and LDL/HDL ratio were also observed.

No notable trend was observed in vital signs or ECG findings.

For the 015K-CL-RAJ4 study, which only Japanese are included, from week 0 through week 12, TEAEs were reported in 84 (49.4%), 89 (51.1%) and 104 (59.8%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. Drug-related TEAEs were reported in 47 (27.6%), 57 (32.8%) and 80 (46.0%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. The majority of TEAEs were grade 1 or 2 in severity.

No major differences were observed in the overview of TEAEs from week 12 through week 28 compared with from week 0 through week 12.

No major differences were observed in the overview of TEAEs from week 28 through week 52 compared with from week 0 through week 12.

For overall period, no major differences were observed in the overview of TEAEs compared with from week 0 through week 12. TEAEs were reported in 154 (88.5%) and 153 (87.9%) patients in the ASP015K 100 mg and 150 mg groups, respectively. Drug-related Treatment-emergent Adverse Events were reported in 118 (67.8%) and 123(70.7%) patients in the ASP015K 100mg and 150mg groups, respectively. The majority of TEAEs were grade 1 or 2 in severity.

TEAEs occurring in ≥ 5% of patients in any treatment group included nasopharyngitis (8.2%, 10.9% and 9.2% in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively). Drug-related TEAEs occurring in ≥ 5% of patients in any treatment group included nasopharyngitis (4.1%, 6.3% and 6.9% in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively).

The incidences of common AEs and drug-related AEs from week 12 through week 28 were generally similar to those from week 0 through week 12.

The incidences of common AEs and drug-related AEs from week 28 through week 52 were generally similar to those from week 0 through week 12.

For overall period, TEAEs occurring in ≥ 5% of patients in any treatment group included nasopharyngitis (29.9% and 33.3% in the ASP015K 100 mg and ASP015K 150 mg groups, respectively), blood creatine phosphokinase increased (5.7% and 11.5%), hepatic function abnormal (6.9% and 6.9%), pharyngitis (6.3% and 6.9%), upper respiratory tract infection (5.7% and 6.9%), bronchitis (4.6% and 6.3%), herpes zoster (6.9% and 3.4%), hypertension (4.0% and 6.3%), diarrhoea (4.0% and 5.7%), dental caries (5.7% and 2.9%), headache (1.7% and 6.9%), stomatitis (2.9% and 5.2%), lymphocyte count decreased (5.2% and 2.9%), cough (2.9% and 5.2%) and gastritis (1.7% and 5.2%).

Drug-related TEAEs occurring in ≥ 5% of patients in any treatment group included nasopharyngitis (17.8% and 17.8% in the ASP015K 100 mg and ASP015K 150 mg groups, respectively), blood creatine phosphokinase increased (5.2% and 7.5%), hepatic function abnormal (5.7% and 4.6%), upper respiratory tract infection (4.0% and 6.3%), herpes zoster (6.9% and 2.9%), pharyngitis (5.2% and 4.0%), lymphocyte count decreased (5.2% and 2.9%) and hypertension (2.3% and 5.7%).

Death was reported in 1 patient due to completed suicide in the placebo/100 mg (week 28) group after switching to ASP015K 100 mg and was considered to be not related to the study drug.

From week 0 through week 12, SAEs were reported in 4 (2.4%), 5 (2.9%) and 3 (1.7%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. Drug-related SAEs were reported in 2 (1.2%), 3 (1.7%) and 3 (1.7%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. No serious TEAEs occurred in ≥ 2 patients in any treatment groups.

For overall period, SAEs were reported in 19 (10.9%) and 13 (7.5%) patients in the ASP015K 100 mg and ASP015K 150 mg groups, respectively. Drug-related SAEs were reported in 10 (5.7%) and 8 (4.6%) patients in the ASP015K 100 mg and ASP015K 150 mg groups, respectively. Serious TEAEs occurring in ≥ 2 patients in any treatment group included pneumonia (3 and 2 patients in the ASP015K 100 mg and ASP015K 150 mg groups, respectively), spinal compression fracture (2 and 1 patients in the ASP015K 100 mg and ASP015K 150 mg groups, respectively) and cellulitis (2 patients in the ASP015K 150 mg group).

From week 0 through week 12, AEs leading to permanent discontinuation of study drug were reported in 7 (4.1%), 5 (2.9%) and 5 (2.9%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. Drug-related AEs leading to permanent discontinuation of study drug were reported in 6 (3.5%), 3 (1.7%) and 5 (2.9%) patients in the placebo, ASP015K 100 mg and ASP015K 150 mg groups, respectively. No TEAEs

leading to permanent discontinuation of study drug occurring in ≥ 2 patients in any treatment group.

For overall period, AEs leading to permanent discontinuation of study drug were reported in 13 (7.5%) and 12 (6.9%) patients in the ASP015K 100 mg and ASP015K 150 mg groups, respectively. Drug-related AEs leading to permanent discontinuation of study drug were reported in 7 (4.0%) and 11 (6.3%) patients in the ASP015K 100 mg and ASP015K 150 mg groups, respectively. TEAEs leading to permanent discontinuation of study drug occurring in ≥ 2 patients in any treatment group included rheumatoid arthritis (2 and 1 patients in the ASP015K 100 mg and ASP015K 150 mg groups, respectively).

With regard to the analysis per 100 patient-years for serious infections and herpes zoster related disease (herpes zoster and varicella), the incidence rates were higher in theASP015K groups compared with the placebo group; however, no dose dependency was observed.

There was no major difference among the treatment groups for malignancy.

Increases in creatine kinase were observed in the ASP015K groups compared with the placebo group. Decreases in absolute neutrophil count, lymphocytes, platelets, total cholesterol/high-density lipoprotein (HDL) ratio and low-density lipoprotein (LDL)/HDL ratio and increases in hemoglobin, creatinine, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were also observed.

No notable trend was observed in vital signs or ECG findings.

1.4 Risk-Benefit Assessment

Findings from nonclinical studies of ASP015K suggest that the primary areas of toxicity are the gastrointestinal system, hematopoietic system, and muscle tissue. The commonly observed AEs during clinical studies conducted to date included reversible neutrophil count decreased, gastrointestinal disorders (e.g., diarrhoea, nausea, flatulence, vomiting), blood creatine phosphokinase increased without evidence of myopathy, and headache. In the clinical trial of ASP015K in Japanese patients with RA (015K-CL-RAJ1), 1 or more groups reported rheumatoid arthritis, nasopharyngitis, blood creatine phosphokinase increased, diarrhoea, cystitis, constipation, stomatitis, dyspepsia, lipids increased, and blood triglycerides increased at incidence rates of ≥ 5%. By the MedDRA System Organ Class (SOC), Infections and infestations, Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Investigations showed high incidence rates. Thus, these events may occur in the present study.

In the 015K-CL-QT01 study to evaluate the effect of ASP015K on cardiac function (QT interval), single doses of ASP015K 150 mg and 450 mg shortened the QTcF interval (QT interval corrected using Fridericia's Correction). The maximum decrease in the mean change from placebo- and baseline-adjusted QTcF occurred at 2 and 4 hours post dose with values of -12.0 and -14.7 msec for the 150 mg and 450 mg treatments, respectively. Therefore, shortened QT interval may be observed in the present study. The risk of drug-induced QT shortening is uncertain.

Because ASP015K is an immunosuppressive agent, it may increase the risk of infections and reactivation of latent, chronic infections. In particular, excessive immunosuppression can lead to serious infections. Of note is the fact that Xeljanz® (tofacitinib) 5 mg, a member of the class of JAK inhibitors to which ASP015K belongs, has been associated with new onset or aggravation of serious infections such as tuberculosis, pneumonitis, sepsis, viral infections, and opportunistic infectious diseases including fungal infections. In addition, several cases of malignant tumors have been reported, although their causal relation to the agent has not been established. Based on the data pooled from 5 domestic and overseas comparative studies of Xeljanz® (tofacitinib) 5 mg, the incidence density of malignancies (excluding non-melanoma skin cancers) among RA patients treated with 5 mg BID for a maximum of 1 year was 0.55/100 person-years (incidence rate 0.5% < 5/1216) [Xeljanz® Pharmaceutical Interview Form (in Japanese)]. These findings suggest that investigators pay particular attention to the possible development of infections and malignancies and take appropriate measures. Three cases of malignancies (stomach cancer, uterine sarcoma, chronic myelogenous leukemia) have been reported as of the cut-off date of 5 December 2013, from completed and ongoing national and international studies of ASP015K. Only the case of uterine sarcoma was judged as related to ASP015K.

In the Japanese clinical trial in patients with moderate to severe RA (015K-CL-RAJ1), 50 mg and higher doses of ASP015K significantly improved the ACR20 response rate versus placebo. Xeljanz® (tofacitinib) 5 mg, which acts via the same mechanism as ASP015K, was approved by the US FDA in 2012 for the treatment of adult patients with moderate to severe RA who had an inadequate response to or are intolerant of MTX. In March 2013, Xeljanz® (tofacitinib) 5 mg tablets was authorized for marketing in Japan for treating RA patients who had an inadequate response to conventional therapies. Therefore, a potential benefit of JAK inhibitor ASP015K is to improve RA.

Furthermore, the long-term control of RA disease activity with prolonged administration of ASP015K is expected to improve patient QOL.

For further information in detail, refer to the latest investigator’s brochure.

2 STUDY OBJECTIVE(S), DESIGN, AND VARIABLES

2.1 Study Objectives

This is an extension study conducted in RA patients who have completed the Phase IIb Study of ASP015K [015K-CL-RAJ1 (hereinafter referred to as study RAJ1)], Phase III Study of ASP015K [015K-CL-RAJ3 (RAJ3)], or Phase III Study of ASP015K [015K-CL-RAJ4 (RAJ4)] to investigate the safety and efficacy of long-term administration of ASP015K.

Another objective of this study is to devise rescue measures for providing the active drug to patients who participated in the Phase IIb Study or Phase III Study of ASP015K, as described in the “Guidelines on methodology for clinical assessment of antirheumatic drugs” (PFSB/ELD Notification No. 0217001, dated 17 February, 2006).

2.2 Study Design and Dose Rationale

2.2.1 Study Design

This study is an extension study conducted as an open-label, multicenter study in RA patients who have completed studies RAJ1, RAJ3, or RAJ4.

Patients who meet all the inclusion criteria and do not fall under any of the exclusion criteria will receive oral ASP015K 100 mg QD after breakfast as the starting dose. For subjects who have been receiving ASP015K at a dose of 50 mg/day in Japan, the dose will be increased to 100 mg/day after the NDA approval in Japan. Any subjects for whom the dose cannot be increased should be withdrawn from the study. Subjects who have no safety problems but show lack of efficacy may later increase the dose to 150 mg/day. Only in Korea and Taiwan, the dosage may be reduced from 100 mg/day or 150 mg/day to 50 mg/day at the discretion of the investigator or sub-investigator. The starting dose for subjects who transferred from study RAJ1 is 50 mg/day. For subjects who transferred from study RAJ1 and are continuing to receive 50 mg/day, treatment extension using a dose of 50 mg/day should be allowed when the investigator or sub-investigator considers a dose increase to be inappropriate in terms of safety and treatment extension with a dose of 50 mg/day to provide greater therapeutic benefit for the treatment of RA.

This study will be conducted as a post-marketing clinical study up to a maximum of 6 months after the NDA approval in Japan. (After the NDA approval in Japan, the post-marketing clinical study will be ended once the study drug is available in the clinical sites as a commercially available product. The planned study period will be a maximum of 6 months after the NDA approval in Japan). In Korea and Taiwan, this study will continue as a clinical study after the NDA approval in Japan. The duration of treatment will differ depending on the subject. To prevent purposeless continuation of dosing without effect, the investigator or sub-investigator will assess each subject for efficacy and safety at each visit, confirm the appropriateness of continued administration for each individual, and decide whether or not to continue dosing.

2.2.2 Dose Rationale

[Rationale for setting dose]

The starting dose for this extension study will be 100 mg/day, to be increased to 150 mg/day at the time of dose escalation.

The dose levels for study RAJ1 have been set at ASP015K 0 mg/day (placebo), 25 mg/day, 50 mg/day, 100 mg/day, and 150 mg/day. As a result, the ACR20 response rate at Week 12 (or early termination) in ASP015K groups receiving 50 mg/day or more showed a statistically significant increase over the placebo group; the increase in the ACR20 response rate was dose dependent up to 150 mg. Compared with the placebo group, a significant and dose-dependent decrease was also found in the reduction of DAS28-CRP score at Week 12 (or early termination) in the 50 mg, 100 mg, and 150 mg groups. A comparison of the

interview forms of Enbrel®, Simponi®, Xeljanz®, and Humira® showed that ASP015K at a dose of 100 mg or higher was found to have the same efficacy as the other drugs at their approved doses. Based on these results, the dose levels for the Phase III studies (RAJ3 and RAJ4) have been set at ASP015K 100 mg/day and 150 mg/day.

Due to safety considerations, the starting dose for this extension study has been set at 100 mg/day, which was the lower of the two doses set for the Phase III studies. For subjects who have no safety problems but show a lack of efficacy, the dosage may later be increased from 100 mg/day to 150 mg/day. However, in subjects who transferred from study RAJ1, the extension study is performed using a dosage design with 50 mg/day as the starting dose and 100 mg/day as the increased dose. Subjects who completed study RAJ1 and are continuing the treatment with ASP015K at a dose of 50 mg/day shall be included in the clinical study under the protocol ver. 2.0/ver. 3.0; later, when the study drugs after the change in specifications become available for use, the dose shall be increased to 100 mg/day, with the exception of the subjects for whom the investigator or sub-investigator considers a dose increase to be inappropriate in terms of safety and treatment extension with a dose of 50 mg/day to provide greater therapeutic benefit for the treatment of RA. If treatment is to be continued at a dose of 50 mg/day, the reason for this decision must be recorded in the medical record.

For subjects who have been receiving ASP015K at a dose of 50 mg/day in Japan, the dose will be increased to 100 mg/day in accordance with the dosage and administration section of the package insert. Any subjects for whom the dose cannot be increased should be withdrawn from the study.

Only in Korea and Taiwan, the dosage may be reduced from 100 mg/day or 150 mg/day to 50 mg/day at the discretion of the investigator or sub-investigator.

[Rationale for mode of administration]

Findings from nonclinical studies suggest that AUC is the pharmacokinetic parameter, which is most correlated with the pharmacological effects of ASP015K. In Study 015K-CL-PS01 with a different target disease, i.e., in psoriasis patients, no major differences in efficacy and safety were observed between the dose levels of 50 mg QD and 25 mg BID. With reference to this, and out of consideration for the convenience of the patients and for adherence, the mode of administration adopted for this study is once-daily administration. Moreover, the period after breakfast was selected as the timing for taking the study drug, out of consideration for adherence. The once-daily administration after breakfast was also adopted in study RAJ1 and resulted in good adherence and efficacy in terms of the ACR20 response rate, etc.

[Rationale for treatment period]

The treatment period for this study has been set as the period of time until ASP015K is approved for the purpose of devising rescue measures for providing the active drug to patients who have reached the end of the 12-week period of treatment with the study drug in the preceding study RAJ1 or the end of the 52-week period in studies RAJ3 or RAJ4, without

any safety problems, as described in "Guidelines on methodology for clinical assessment of antirheumatic drugs" (PFSB/ELD Notification No. 0217001, dated 17 February 2006). This study will be conducted as a post-marketing clinical study up to a maximum of 6 months after the NDA approval in Japan. (After the NDA approval in Japan, the post-marketing clinical study will be ended once the study drug is available in the clinical sites as a commercially available product. The planned study period will be up to a maximum of 6 months after the NDA approval in Japan). In Korea and Taiwan, this study will continue as a clinical study after the NDA approval in Japan.

However, because no safety data on treatment periods longer than 12 weeks are available at the present time for administration at 150 mg/day, an independent DSMB will be established to study the advisability of continuing or discontinuing the study, or changing the protocol while confirming the safety data on individual subjects obtained through this study as well as the safety data on the study as a whole, periodically or as urgent contingency requires. Moreover, in order to prevent treatment from continuing purposely without effect, the investigator or the sub-investigator will investigate efficacy and safety at each study visit, confirm the appropriateness of continuing treatment for each individual subject, and decide whether or not to continue treatment.

2.3 Variables

2.3.1 Safety Variables

- AEs
- Vital signs (body temperature, pulse and blood pressure in sitting position)
- Body weight
- 12-lead ECG
- Chest radiography
- Laboratory assessments

2.3.2 Efficacy Variables

- The following items at each study visit:

- ACR20 response rate
- ACR50 response rate
- ACR70 response rate
- Change from baseline in Tender Joint Count (TJC) (68 joints)
- Change from baseline in Swollen Joint Count (SJC) (66 joints)
- Change from baseline in DAS28-CRP and DAS28-ESR scores
- Percentage of subjects achieving DAS28-CRP score for remission
- Percentage of subjects achieving ACR/EULAR score for remission
  ACR/EULAR remission is defined as meeting all 4 of the following criteria:
  - TJC ≤ 1
  - SJC ≤ 1
  - CRP ≤ 1 mg/dL
  - Subject's Global Assessment of Arthritis (SGA) ≤ 1 cm (0-100 mm on a VAS scale)
- Percentage of subjects with a SDAI score of ≤ 3.3 (SDAI remission)

- Change from baseline in Physician's Global Assessment of Arthritis (PGA) (VAS)
- Change from baseline in SGA (VAS)
- Change from baseline in the subject's assessment of pain (VAS)
- FACIT-Fatigue score (only in subjects who transferred from study RAJ1)
- Change from baseline in WPAI (only in subjects who transferred from studies RAJ3 or RAJ4)
- Change from baseline in HAQ-DI
- Change from baseline in SF-36v2® score
- Percentage of subjects in EULAR response criterion of "Good Response"
- Percentage of subjects in EULAR response criterion of "Moderate Response"
- Percentage of subjects in EULAR response criterion of "Good Response" or "Moderate Response"
- Incidence of subject withdrawal due to lack of efficacy

[Rationale for efficacy variables]

The efficacy variables were established with reference to "Guidelines on methodology for clinical assessment of antirheumatic drugs" (PFSB/ELD Notification No. 0217001, dated 17 February, 2006), overseas clinical studies of ASP-015K, and other recently reported clinical studies conducted in RA patients.

2.3.3 Pharmacodynamics Variables

Changes from baseline in lymphocyte subsets (CD3, CD4, CD8, CD16, CD19, CD56, CD56/16)

3 STUDY POPULATION

3.1 Selection of Study Population

The target population for this extension study is RA patients who have completed studies RAJ1, RAJ3, or RAJ4, who wish to continue treatment with the study drug, and for whom the investigator or sub-investigator deems continued treatment to be necessary or appropriate.

3.2 Inclusion Criteria

Subject is eligible for the study if all of the following apply:

[Subjects who transferred from study RAJ1]

1. Subject has received a full explanation of the study drug and this study in advance, and written informed consent to participate in the study has been obtained from the subject himself/herself.
2. Subject has completed treatment with the study drug in study RAJ1 as specified in the protocol and has also completed the tests and assessment performed at the study visit in Week 16.

3. The subject himself/herself wishes to continue taking the study drug, and the investigator or sub-investigator deems continued administration to be necessary or appropriate.
4. Subject must be willing and able to comply with the study requirements.

[Rationale for inclusion criteria]

1: Established with consideration for ethics of conducting the study.

2: Established to select RA patients for inclusion in the study population for this extension study.

3: Established with consideration for ethics of conducting the study.

4: Established to select subjects in whom clinical assessments of this study can be appropriately conducted.

[Subjects who transferred from studies RAJ3 or RAJ4]

1. Subject has received a full explanation of the study drug and this study in advance, and written informed consent to participate in the study has been obtained from the subject himself/herself.
2. Subject who has completed treatment with the study drug in studies RAJ3 or RAJ4 as specified in the protocol and has also completed the tests and assessments scheduled for the Week 52 visit.
3. The subject himself/herself wishes to continue taking the study drug, and the investigator or sub-investigator deems continued administration to be necessary or appropriate.
4. Subject must be willing and able to comply with the study requirements.

[Rationale for inclusion criteria]

1: Established with consideration for ethics of conducting the study.

2: Established to select RA patients for inclusion in the study population for this extension study.

3: Established with consideration for ethics of conducting the study.

4: Established to select subjects in whom clinical assessments of this study can be appropriately conducted.

3.3 Exclusion Criteria

Subject will be excluded from participation if any of the following apply:

[Subjects who transferred from study RAJ1]

1. Subject has developed an adverse reaction related to the study drug in study RAJ1 and the risks of continuing treatment with this drug are expected to outweigh the benefits.

2. There were abnormal findings in the X-ray taken at Week 0, and an acute or chronic infection, tuberculosis infection, or malignant tumor is suspected.
3. Subject has received live or live attenuated virus vaccination within 30 days prior to the first dose of study drug.
4. Subject is a hepatitis B virus or hepatitis C virus carrier or has a history of a positive test for HIV infection.
5. Subject has a concurrent autoimmune disease (except Sjogren's syndrome) other than RA or a history of it.
6. Subject has a clinically significant infection or disease (requiring hospitalization or parenteral therapy).
7. Subject has a history of any malignant tumor, except for successfully treated basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix, or subject has a concurrent malignant tumor.
8. Subject has taken one of the following drugs between the end of the assessments at Week 12 of study RAJ1 and the start of treatment with the study drug in this extension study.
    - Biologic DMARDs: Etanercept, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab
    - Non-biologic DMARDs: MTX, salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib (However, topical drugs other than those for the treatment of RA may be used concomitantly.)
    - Other drugs used in the treatment of RA: Cyclosporine, cyclophosphamide, azathioprine, minomycin, etc.
9. Subject has received plasma exchange therapy between the end of the assessments at Week 12 of study RAJ1 and the start of treatment with the study drug in this extension study.
10. Subject has received any of the following CYP3A substrates with narrow therapeutic range within 14 days prior to starting treatment with the study drug: Dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, and temsirolimus
11. Subject has any of the following laboratory values at the study visit in Week 12 of study RAJ1:
    - Hemoglobin < 10 g/dL
    - White blood cell (WBC) count < 3000/μL
    - Absolute neutrophil count (ANC) < 2000/μL
    - Absolute lymphocyte count < 800/μL
    - Platelet count < 100000/μL
    - ALT ≥ 2 × ULN
    - AST ≥ 2 × ULN
    - Total bilirubin (TBL) ≥ 1.5 × ULN
    - Estimated GFR ≤ 40 mL/min, as measured by the MDRD method
    - CPK > 1.5 × ULN
    - β-D-glucan ≥ 11 pg/mL

12. Subject has symptomatic CPK elevation (CPK > 1.5 × ULN with myalgia, muscular weakness, or severe unusual muscle twitching*) at the study visit in Week 12 of study RAJ1.
    * Muscle twitching: A condition in which there is a cramp in a muscle, such as cramps in the calves
13. Subject is found to have symptoms of myopathy such as myalgia, muscular weakness, and severe unusual muscle twitching* regardless of CPK level that persist for at least 2 weeks or that worsen rapidly within 2 weeks, at study visit in Week 12 of study RAJ1.
    * Muscle twitching: A condition in which there is a cramp in a muscle, such as cramps in the calves
14. Subject has concurrent cardiac failure with NYHA classification of Class III or higher, or a history of it.
15. Subject has concurrent long QT syndrome or a history of it. Subject exhibits QT interval prolonged at the study visit in Week 0.
16. Subject has any ongoing severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, or infectious disease, or any ongoing illness which would make the subject unsuitable for the study as determined by the investigator/sub-investigator.
17. Subject has any condition possibly affecting oral absorption (e.g., gastrectomy or clinically significant diabetic gastroenteropathy).
18. Subject has received surgical treatment and the investigator/sub-investigator judges there to be residual effects of surgical stress. Or, the subject plans to have surgical treatment that will require hospitalization during the study period or surgery on the joints.
19. The subject is a woman who is pregnant or might be pregnant, is nursing, wishes to conceive for a period running from the time informed consent is given within 60 days after end of treatment, or for whom the possibility of pregnancy cannot be ruled out as a result of the pregnancy test given at Week 0.
20. The subject is a man who cannot practice proper contraception with a condom from the time informed consent is given until 90 days after end of treatment, or the subject is a woman who could become pregnant and cannot practice proper contraception with a condom from the time informed consent is given until 60 days after end of treatment.
21. The subject has been judged unsuitable to participate in the study for other reasons by the investigator/sub-investigator.

[Rationale for exclusion criteria]

1-7: Established out of consideration for the safety of the subjects.

8-9: Established to eliminate factors affecting the evaluation.

10-16: Established out of consideration for the safety of the subjects.

17: Established to eliminate factors affecting the evaluation.

18: Established out of consideration for the safety of the subjects and to eliminate factors affecting the evaluation.

19-20: Established on the basis of general considerations for clinical studies.

21: In addition to 1 through 20 above, the exclusion criteria were established in light of scientific and ethical aspects of the study, envisioning situations in which the investigator/sub-investigator would deem a potential subject to be unsuited to participating in this study.

[Subjects who transferred from studies RAJ3 or RAJ4]

1. The subject is a woman who is pregnant or might be pregnant, is nursing, wishes to conceive within 60 days after end of treatment drug, or for whom the possibility of pregnancy cannot be ruled out as a result of the pregnancy test given at Week 0.
2. Subject is a man who cannot practice 2 or more methods of proper contraception from the time informed consent is given to 90 days after the end of treatment, or subject is a woman who could become pregnant and cannot practice 2 or more methods of proper contraception from the time informed consent is given to 60 days after the end of treatment (if the possibility of pregnancy can be completely ruled out by other tests, the subject is eligible for enrollment).
3. Subject is a man who cannot be prohibited from sperm donation from the time informed consent is given to 90 days after the end of treatment, or subject is a woman who cannot be prohibited from egg donation from the time informed consent is given to 60 days after the end of treatment.
4. Subject who has tested positive for any of the following at screening for studies RAJ3 or RAJ4: HBs antigen, HBc antibody, HBs antibody, and HBV-DNA assay (However, if a subject is negative for HBs antigen and HBV-DNA assay, and positive for either or both HBc and HBs antibodies, the subject may be included provided that the subject is monitored by performing HBV-DNA assay at every scheduled visit after initiation of study drug administration.)
5. Subject has received a prohibited concomitant medication or prohibited concomitant therapy during the time from the end of the assessments at Week 52 of studies RAJ3 or RAJ4 to the first dose of the study drug in this extension study.
6. Subject has QTc < 300 msec on ECG measurements performed at the study site at Week 52 of studies RAJ3 or RAJ4 and has QTc < 300 msec at retest.
7. The subject has been judged unsuitable to participate in the study for other reasons by the investigator/sub-investigator.

[Rationale for exclusion criteria]

1-3: Established on the basis of general considerations for clinical studies.

4, 6: Established out of consideration for the safety of the subjects.

5: Established to eliminate factors affecting the evaluation and out of consideration for the safety of the subjects.

7: In addition to 1 through 6 above, the exclusion criteria were established in light of scientific and ethical aspects of the study, envisioning situations in which the investigator/sub-investigator would deem a potential subject to be unsuited to participating in this study.

3.4 Discontinuation Criteria for Individual Subjects

A discontinuation means that a subject who has enrolled in the study prematurely terminates study treatment prior to the completion of all protocol-required elements.

The subject is free to withdraw from the study treatment and/or study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if this is considered necessary because of the subject's clinical condition.

Discontinuation Criteria for Individual Subjects:

The investigator/sub-investigator should discontinue the study if any of the following criteria are met:

1. Subject withdraws consent.
2. The study drug is not sufficiently effective, and a change in treatment method is deemed to be in the subject's best interest by the investigator or sub-investigator.
3. Symptomatic CPK elevation, defined as CPK > 1.5 × ULN with severe unusual myalgia, muscular weakness, or muscle twitching*.
   * Muscle twitching: A condition in which there is a cramp in a muscle, such as cramps in the calves
4. Any event of myopathy defined as severe unusual myalgia, muscular weakness, and muscle twitching* regardless of CPK level that persists for at least 2 weeks or that worsens rapidly within 2 weeks.
   * Muscle twitching: A condition in which there is a cramp in a muscle, such as cramps in the calves
5. Subject infected with HBV who has tested positive for either of or both of HBc and HBs antibodies and is found to be positive for HBV-DNA assay during the study period. Abrupt discontinuance of immunosuppressive therapy may precipitate severe or fulminant hepatitis. Therefore, when HBV reactivates, nucleic acid analog therapy should be immediately initiated, and a hepatologist should be consulted regarding the continuation of ASP015K and concomitant DMARD (unique to Japan: as indicated by "Proposal for Management of Rheumatic Disease Patients with Hepatitis B Virus Infection Receiving Immunosuppressive Therapy" by the Japan College of Rheumatology).

6. Subject has a malignant tumor.
7. Subject has an adverse event (AE) such as a serious infection, and the investigator or sub-investigator considers that it is not in the subject's best interest to continue the study.
8. Subject receives or requires a prohibited concomitant medication (including other study drugs) or prohibited concomitant therapy that may affect the evaluation of efficacy; subject receives or requires live vaccine or live attenuated vaccine.
9. Subject receives or requires drug interruption for a longer period than that stipulated for interruption.
10. Subject is deemed lost to follow-up by the investigator/sub-investigator (subject can no longer come to the study center; subject can no longer be contacted, etc.).
11. It comes to light after the administration of the first dose of study drug that the inclusion criteria were not met at the time of case enrollment or that criteria for exclusion were met. It comes to light that there was some other major deviation from the protocol.
12. Investigator or sub-investigator decides it is in the subject's best interest to discontinue.
13. The sponsor has requested that administration of the study drug be discontinued because of a safety problem in a particular subject, or the sponsor has decided to discontinue the study altogether.
14. Subject has QTc < 300 msec on ECG measurements and has QTc < 300 msec at retest.

Subjects who discontinue early from the study should be given the necessary tests and assessments specified to be performed at end of treatment/early termination within 2 days after taking the final dose of the study drug if possible (see "Table 1, Schedule of Assessments"). Moreover, these subjects should receive the tests and assessments scheduled for end of study (at time of follow-up). These assessments and tests will be conducted only if the investigator/ sub-investigator decides necessary.

If the discontinuation has been for reasons of AEs, appropriate treatment should be provided as necessary.

Subjects with early termination will be treated as discontinuations, and the investigator/sub-investigator must clearly identify the date of discontinuation and the reason for discontinuation, as well as retain all clinical study data on the discontinuations and submit it to the sponsor in the CRF, report of follow-up investigation, etc.

The Appendix 6 entitled "Liver Safety Monitoring and Assessment" describes liver function tests raised that provide grounds for discontinuation. Refer to this if liver function tests raised is observed.

3.4.1 Suspension, Interruption, and Resumption of the Study Drug

If either of the criteria in Section 3.4.1.1, Criteria for Suspension or Interruption of the Study Drug, is met during the treatment period with the study drug, the investigator or sub-investigator is to suspend or interrupt administration of the study drug without delay. Administration of the study drug may be resumed after the initiation of suspension or

interruption if a retest shows that none of the following criteria are met, provided that the investigator or sub-investigator deems resumption to be in the subject's best interest, taking the risk/benefit ratio into consideration.

Suspension of the study drug

Administration of the study drug may be suspended within the scope of the below stipulations if the investigator or sub-investigator deems a temporary discontinuation (suspension) of dosing to be necessary. Suspension of the study drug beyond the scope of the following stipulation is handled as interruption:

- Suspension is defined as a temporary discontinuation of study drug administration for 7 days or less.
- If administration of the study drug is suspended repeatedly, the discontinuation of the clinical study for the particular subject should be considered in consultation with the sponsor.

Interruption of the study drug

Administration of the study drug may be interrupted within the scope of the below stipulations if the investigator or sub-investigator deems a temporary discontinuation (interruption) of dosing for a period exceeding 7 days to be necessary. If a subject requires interruption beyond the scope described below, the subject has to be withdrawn from the study.

- Interruption is defined as a temporary discontinuation of study drug administration for a period exceeding 7 days.
- Interruption may not exceed a maximum of 4 consecutive weeks.
- Up to 2 interruptions per year may be allowed. Moreover, they must be separated by an interval of 16 weeks or more.

3.4.1.1 Criteria for Suspension or Interruption of the Study Drug

If either of the below criteria is met during the treatment period with the study drug, the investigator or sub-investigator is to suspend or interrupt the administration of the study drug without delay. The administration of the study drug may be resumed after the initiation of suspension or interruption if a retest shows that none of the following criteria are met:

1. Subject has any of the following laboratory values. Administration of the study drug is to be discontinued until a retest shows that none of the following criteria are met:
    - Hemoglobin < 8.0 g/dL
    - ANC < 500/μL
    - Absolute lymphocyte count < 500/μL
    - Platelet count < 50000/μL
    - Serum creatinine > 150% of baseline at 2 consecutive Scheduled Visits
    - CPK > 10 × ULN
2. β-D-glucan > ULN [in case of Japan: ≥ 11 pg/mL]

3. Subject requires a concomitant medication that is prohibited because of a possible drug interaction.
4. Suspected pregnancy.
5. The investigator or sub-investigator considers suspension or interruption of the study drug to be in the subject's best interest.
6. The sponsor has requested suspension or interruption of the study drug because of a safety problem in a particular subject.

4 STUDY DRUGS

4.1 Description of Study Drugs

The test drugs for this study are ASP015K tablets of 50 mg, 100 mg, and 150 mg doses.

4.1.1 Test Drug(s)

Code name	ASP015K
Generic Name	Peficitinib hydrobromide
Chemical name	4-{[(1*R*,2*S*,3*S*,5*S*,7*S*)-5-hydroxy-2-adamantyl]amino}-1*H*-pyrrolo[2,3-*b*]pyridine-5-carboxamide monohydrobromide
Molecular formula (molecular weight)	$C_{18}H_{22}N_4O_2 \cdot HBr$ (407.30)
Content and dosage form	ASP015K tablet 50 mg: A round, yellow, film-coated tablet containing the ASP015K drug substance at 50 mg (as free form) ASP015K tablet 100 mg: An elliptical, pale-red, film-coated tablet containing the ASP015K drug substance at 100 mg (as free form) ASP015K tablet 150 mg: An elliptical, yellow, film-coated tablet containing the ASP015K drug substance at 150 mg (as free form)
Manufacturer	Astellas Pharma Inc. (API)
Lot No.	Noted in SOP for handling of study drugs
Storage method	Store at room temperature
Expiration date	Noted in SOP for handling of study drugs

4.1.2 Comparative Drug(s)

Not applicable.

4.2 Packaging and Labeling

All medication used in this study will be manufactured, packaged, and labeled under the responsibility of the Quality Assurance Manager in accordance with sponsor's SOP, GMP guidelines, GCP, and applicable local laws/regulations. (Refer to the study drug handling manual for details)

4.2.1 Packaging Form

1. For 50 mg/day administration

ASP015K tablets will be supplied in sheets holding 14 days' worth of medication (14 of the ASP015K tablets 50 mg). These sheets will be packaged 4 sheets to a small box.

[Test drug count]

	ASP015K tablets 50 mg
Per day	1 tablet
Per sheet (14 days' worth)	14 tablets
Per box (8 weeks' worth)	56 tablets

2. For 100 mg/day administration

ASP015K tablets will be supplied in sheets holding 14 days' worth of medication (14 of the ASP015K tablets 100 mg). These sheets will be packaged 4 sheets to a small box.

[Test drug count]

	ASP015K tablets 100 mg
Per day	1 tablet
Per sheet (14 days' worth)	14 tablets
Per box (8 weeks' worth)	56 tablets

3. For 150 mg/day administration

ASP015K tablets will be supplied in sheets holding 14 days' worth of medication (14 of the ASP015K tablets 150 mg). These sheets will be packaged 4 sheets to a small box.

[Test drug count]

	ASP015K tablets 150 mg
Per day	1 tablet
Per sheet (14 days' worth)	14 tablets
Per box (8 weeks' worth)	56 tablets

4.2.2 Labeling

In case of Japan (Package design of study drug for Korea and Taiwan is described in the study drug handling manual):

The following labels will be affixed to the small boxes. After transferring to the post-marketing clinical study, the label "for clinical study use" will be replaced as "for post-marketing clinical study use" and the study drug will be used throughout the post-marketing clinical study.

1. For 50 mg/day administration

For clinical study

Lot No.○○○○○○
56 tablets (14 tablets × 4 sheets)

Extension Study of ASP015K
For 50 mg dose level

Caution: Please retain any remaining medication and this box without discarding them until they are collected by the sponsor.
Storage method: Store at room temperature
Expiration date: Specified in SOP for handling of study drugs

Astellas Pharma Inc. (API)
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo

2. For 100 mg/day administration

For clinical study

Lot No.○○○○○○
56 tablets (14 tablets × 4 sheets)

Extension Study of ASP015K
For 100 mg dose level

Caution: Please retain any remaining medication and this box without discarding them until they are collected by the sponsor.
Storage method: Store at room temperature.
Expiration date: Specified in SOP for handling of study drugs

Astellas Pharma Inc. (API)
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo

3. For 150 mg/day administration

For clinical study

Lot No.○○○○○○
56 tablets (14 tablets × 4 sheets)

Extension Study of ASP015K
For 150 mg dose level

Caution: Please retain any remaining medication and this box without discarding them until they are collected by the sponsor.
Storage method: Store at room temperature.
Expiration date: Specified in SOP for handling of study drugs

Astellas Pharma Inc. (API)
2-5-1 Nihonbashi-Honcho, Chuo-ku, Tokyo

Lot No. is given in SOP on handling of study drugs.

4.3 Study Drug Handling

Japan:

The head of the study center or the study drug storage manager should take accountability for the study drugs as following issues:

- The study drug storage manager should store and take accountability for the study drugs in conformity with the procedures for handling the study drugs created by the sponsor.
- The study drug storage manager should prepare and retain records of the study drug's receipt, the inventory at the study center, the use by each subject, and the return to the sponsor or alternative disposal of unused study drugs. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the subject identification codes.
- The study drug storage manager should prepare and retain records that document adequately that the subjects were provided the doses specified in the protocol, and reconcile all the study drugs supplied from the sponsor.

Korea and Taiwan:

The procedures will be specified separately in the study drug handling manual in accordance with the local requirements.

4.4 Blinding

Not applicable.

4.5 Assignment and Allocation

Not applicable.

5 TREATMENTS AND EVALUATION

5.1 Dosing and Administration of Study Drugs and Other Medications

5.1.1 Dose/Dose Regimen and Administration Period

(1) Starting dose (100 mg/day as ASP015K)

The subjects will take 1 tablet of ASP015K 100 mg orally QD after breakfast. The first dose will be administered at each study center at the Week 0 visit after all the scheduled assessments and tests have been completed.

* The starting dose for subjects who transferred from study RAJ1 is 50 mg/day. After implementation of the study protocol (ver. 2.0/ver. 3.0), only subjects who transferred from studies RAJ3 or RAJ4 will be enrolled newly.

(2) Increased dose (150 mg/day as ASP015K)

The subjects will take 1 tablet of ASP015K 150 mg orally QD after breakfast.

For the subjects who have completed study RAJ1 and are continuing treatment with ASP015K at a dose of 50 mg/day, the need for a change in the dose shall be assessed at the initiation of the clinical study under the protocol ver. 2.0/ver. 3.0. If the dose is not increased to 100 mg and treatment is to be continued at a dose of 50 mg/day, the reason for this decision must be entered in the medical record.

For subjects who have been receiving ASP015K at a dose of 50 mg/day in Japan, the dose will be increased to 100 mg/day after approval in Japan. Any subjects for whom the dose cannot be increased should be withdrawn from the study. This study will be conducted as a post-marketing clinical study up to a maximum of 6 months after the NDA approval in Japan. (After the NDA approval in Japan, the post-marketing clinical study will be ended once the study drug is available in the clinical sites as a commercially available product. The planned study period will be up to a maximum of 6 months after the NDA approval in Japan). In Korea and Taiwan, this study will continue as a clinical study after the NDA approval in Japan. The duration of treatment will differ depending on the subject. Moreover, in order to prevent treatment from continuing purposelessly without effect, the investigator or the sub-investigator will investigate efficacy and safety at each study visit, confirm the appropriateness of continuing treatment for each individual subjects, and decide whether or not to continue treatment.

5.1.2 Increase or Reduction in Dose of the Study Drugs

The dose increase/reduction of study drugs is allowed only when the following criteria are met. For subjects who have been receiving ASP015K at a dose of 50 mg/day in Japan, the dose will be increased to 100 mg/day after approval in Japan. Any subjects for whom the dose cannot be increased should be withdrawn from the study.

[The increase in dose from 50 mg/day to 100 mg/day]

Japan: For subjects who have been receiving ASP015K at a dose of 50 mg/day in Japan, the dose will be increased to 100 mg/day after approval. Any subjects for whom the dose cannot be increased should be withdrawn from the study.

Korea and Taiwan: When the investigator or sub-investigator judges that there is no safety problem in the subject, the dose may be increased from 50 mg to 100 mg.

[The increase in dose from 100 mg/day to 150 mg/day]

The dose may be increased from 100 mg to 150 mg at the time point when the following 2 conditions are met:

1) The subject has taken ASP015K 100 mg for at least 4 weeks, and the DAS28-ESR score is 3.2 or higher (moderate disease activity or high disease activity) on the study visit days.
2) When the investigator or sub-investigator judges there to be no problem with safety for the subject in the assessment performed on the study visit day on which the DAS28-ESR score of 3.2 or higher was exhibited.

[The reduction in dose from 100/day mg or 150 mg/day to 50 mg/day]

Japan: After the NDA approval in Japan, dose reduction for the study drugs is not allowed.

Korea and Taiwan: After the dose increase, the dose may be reduced from 100 mg/day or 150 mg/day to 50 mg/day at the discretion of the investigator or sub-investigator.

The investigator or sub-investigator will decide whether or not to reduce the dosage on the basis of the following criterion.

- If an AE with NCI-CTCAE grade classification of Grade 2 or higher has developed.

A dose increase after a dose reduction and a dose reduction after a dose increase are allowed according to the above criteria.

If the dose of study drug has been increased or reduced, the investigator or sub-investigator should record this information in the CRF.

5.1.3 Previous and Concomitant Medication (Drugs and Therapies)

The survey period and survey method for previous and concomitant medication (drugs and therapies) will be as follows. Previous medications do not need to be recorded in the CRF for this study.

(1) Concomitant medications

The survey period will be from the start of administration of the study drug to the end of study (day of follow-up). The pharmaceutical name, daily dose, route of administration, treatment period, and reason for administration of DMARD, limited concomitant medications, rescue medications, and prohibited concomitant medications shall be collected.

The pharmaceutical name, route of administration, treatment period, and reason for administration shall be collected with regard to medications other than DMARD, limited concomitant medications, rescue medications, prohibited concomitant medications, and medications listed below:

- Diluent solution (water for injection, saline solution), antiseptic solution, wash, topical anesthesia used in tests and treatments (Xylocaine jelly, etc.), contrast medium for examination (barium, non-iodine based contrast media, etc.), anticoagulants for indwelling iv line, effervescent agents and purgatives used in examinations, and topical drugs with local action other than those for the treatment of RA.

  *Medications used for the treatment of AEs shall be recorded in the CRF.

(2) Concomitant therapies

The name, duration, and reason for therapies used to treat RA or AEs from the start of administration of the study drug to the end of study (day of follow-up) shall be collected. Procedures related to surgery (such as change in gauze) and therapies (rehabilitation therapy, etc.) are excluded.

5.1.3.1 Previous Medication (Drugs and Therapies)

The following stipulations will apply to previous treatment used before the start of administration of the study drug.

(1) Administration or use of the following drugs and therapies will be prohibited from the end of the assessments at Week 12 of study RAJ1 to the initiation of administration of the study drug in this extension study or from the end of the assessments at Week 52 of studies RAJ3 or RAJ4 to the initiation of administration of the study drug in this extension study.

1) Biologic DMARDs: etanercept, anakinra, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab, certolizumab pegol, denosumab, sarilumab.

2) Non-biologic DMARDs:

- Subjects who transferred from study RAJ1: MTX, salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib.
- Subjects who transferred from study RAJ3: non-biologic DMARDs other than those concomitantly used in study RAJ3.
- Subjects who transferred from study RAJ4: salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib.

(However, topical drugs other than those for the treatment of RA may be used concomitantly.)

3) Other drugs used in the treatment of RA: cyclosporine, cyclophosphamide, azathioprine, minocycline, etc.

4) Live or live attenuated virus vaccines

5) Plasma exchange therapy

(2) The following CYP3A substrates with narrow therapeutic range within 14 days prior to first dose of study drug:

Dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide, etc.

[Rationale for prohibitions on previous medications (drugs and therapies)]

The aforementioned prohibitions on previous medications (drugs, therapies) were established taking into account the possibility that use of the previous medication immediately prior to administration of the study drug could affect the evaluation of the study drug, as well safety of the subjects.

5.1.3.2 Concomitant Medication (Drugs and Therapies)

(1) The following concomitant medications and complimentary alternative treatments are prohibited as described.

Concomitant use of the following drugs and therapies is prohibited during the treatment period:

1) Biologic DMARDs: etanercept, anakinra, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab, certolizumab pegol, denosumab, sarilumab.

2) Non-biologic DMARDs:

- Subjects who transferred from study RAJ1: MTX, salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib.
- Subjects who transferred from study RAJ3: non-biologic DMARDs other than those used concomitantly in study RAJ3.
- Subjects who transferred from study RAJ4: salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib.

(However, topical drugs other than those for the treatment of RA may be used.)

3) Other drugs used in the treatment of RA: cyclosporine, cyclophosphamide, azathioprine, minocycline, etc.

4) Oral corticosteroids at doses that exceed the amount used from the initiation of studies RAJ1, RAJ3, or RAJ4 to the initiation of administration of the study drug in this extension study at a daily dose of prednisolone equivalent

5) Intra-articular, intravenous, intramuscular, or endorectal corticosteroids (However, suppositories for anal diseases may be used concomitantly.)

6) Oral morphine at doses exceeding 30 mg/day (or the equivalent amount of opioid analgesics).

7) Intra-articular administration of articular cartilage protective agents into joints subject to the assessment.

8) Drainage of fluid accumulated in the joint subject to the assessment, local anesthesia into joints subject to the assessment, and nerve block.

9) Plasma exchange therapy.

10) The surgical treatment of joints subject to the assessment.

The following drugs and therapies are also prohibited during the treatment period and follow-up period:

11) CYP3A substrates with narrow therapeutic range: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide, etc.

12) Live or live attenuated virus vaccines

13) Other study drugs, study drugs from post-marketing clinical studies, or medical devices being studied in clinical studies

[Rationale for prohibitions on concomitant drugs and therapies]

The prohibitions were established because there is a possibility that concomitant use of the aforementioned drugs and therapies might affect the evaluation of efficacy and safety of the study drug.

(2) Limited concomitant medications

<Subjects who transferred from studies RAJ1, RAJ3, or RAJ4>

During the treatment period, the following medications may be used concomitantly at the discretion of the investigator or sub-investigator if they meet the following conditions for concomitant use (Both new administration and change in dosage/administration are permitted).

1) Non-steroidal anti-inflammatory drugs (NSAIDs) (excluding topical drugs with a local action)

2) Oral morphine (≤ 30 mg/day, or the equivalent amount of opioid analgesics)

3) Acetaminophen

- Conditions for concomitant use -

- No changes in the dosage/administration of the drug are allowed within the period of 12 weeks. However, this shall exclude cases where the medication has caused an AE. Moreover, if, after discontinuation of the concomitant medication, it becomes apparent that the suspected medication was not the offending drug that caused the AE, administration may be resumed with the dose prior to discontinuation as the maximum dose.

[Rationale for establishing limitations on the aforementioned drugs]

Limitations were imposed upon use of these drugs because they act to improve QOL for RA patients within a short period of time and frequent changes in dosage/administration could greatly influence the efficacy evaluation for this study drug, and a prohibition has been placed upon changing the dosage/administration for the same limited medication within a period of 12 weeks.

<Subjects who transferred from study RAJ3>

Subjects who have been receiving any of the below drugs throughout the treatment period of study RAJ3 shall continue the use of the drug concerned from the end of the assessment at Week 52 of study RAJ3 to the initiation of administration of the study drug in this extension study, as well as throughout the treatment period of this study.

It is permitted to discontinue the drug or to increase or decrease the dose within the range not exceeding or falling below the baseline dose in study RAJ3.

Administration of the drug may be interrupted, or the dose may be reduced because of an AE. This interruption must not exceed a maximum of 28 days. Administration may be resumed with the baseline dose in study RAJ3 as the maximum dose.

- If MTX is administered with study drug concurrently, the concomitant use of folic acid should be considered whenever possible. The dose of folic acid during the study period will, in principle, be within 10 mg per week, but it may be adjusted. If MTX is administered and ALT/AST becomes ≥ 3 × ULN, MTX must be interrupted, or the dose must be reduced, and daily administration of folic acid should be considered.

- Methotrexate (MTX)
- Hydroxychloroquine
- Salazosulfapyridine
- Gold
- *D*-penicillamine
- Lobenzarit
- Actarit
- Bucillamine
- Iguratimod

(3) Necessary concomitant medication

<Concomitant use of MTX is specified only for subjects who transferred from study RAJ4>

- MTX must be used from the end of the assessments at Week 52 of study RAJ4 to the initiation of administration of the study drug in this extension study, as well as throughout the treatment period of this extension study.
- It is permitted to discontinue MTX or increase or decrease the dose within the range not exceeding or falling below the baseline dose in study RAJ4.
- Administration of MTX may be interrupted, or the dose may be reduced because of an AE. This interruption must not exceed a maximum of 28 days. Administration may be resumed with the baseline dose in study RAJ4 as the maximum dose.
- Folic acid should be concomitantly administered whenever possible. The dosage of folic acid during the study period is not more than 10 mg/week in principle; dose adjustment is permitted.
- If ALT/AST is ≥ 3 × ULN, MTX should be interrupted or reduced, and daily administration of folic acid should be considered.

(4) Rescue medications

During the treatment period, the below medications can be used only when needed to treat AEs, complications, or worsening of the primary disease. However, these medications may not be taken within 24 hours prior to the joint assessment at each study visit.

1) NSAIDs: Single use as needed, for a period of 3 days or less

2) Analgesics other than NSAIDs (acetaminophen, opioid analgesics, all-in-one cold and flu medications, etc.): For 7 consecutive days or less

3) Intra-articular administration of corticosteroids, intra-articular administration of articular cartilage protective agents, drainage of fluid accumulated in joint, local anesthesia of joint, and nerve block: Performed once every 24 weeks (on up to 2 joints), starting at or after the Week 12 study visit.
However, joints on which intra-articular drug administration or rescue procedure has been performed will be assessed as showing disease activity (pain [tenderness]/swelling) after administration of the medication/therapy.

5.1.4 Treatment Compliance

The investigator, sub-investigator, or study drug storage manager will provide the subjects with an explanation of how to take the study drug, paying particular attention to the following points when they hand the study drug to each subject.

1. Do not take multiple doses all at once if doses of the study drug have been missed.
2. Bring any remaining study drug with you to the next scheduled examination.
3. If you do not have sufficient study drug until the next visit, for example, because it has been misplaced, inform the investigator, sub-investigator, or collaborator without delay.

The investigator/sub-investigator will confirm each subject's compliance status during the period of treatment with the study drug on the basis of the information given by the subject and the number of tablets of the study drug collected from the subject and record the

compliance status in the CRF. If there is judged to be a problem with the rate of compliance, patient compliance guidance should be provided to the subject again to improve the rate of compliance after investigating the reasons for the problem.

In addition, the subject should be contacted twice every 4 weeks between the previous visit to the next scheduled visit to confirm the status of compliance with study drug administration and the safety of the subject (subjects who transferred from study RAJ1 are to be contacted from the Week 48 visit onward).

5.1.5 Emergency Procedures and Management of Overdose

If any symptoms have developed as a result of an overdose of ASP015K, the investigator/sub-investigator will provide emergency treatment appropriate for each symptom to ensure the safety of the subject.

Experience with the administration of ASP015K to humans remains limited, and overdose of ASP015K has not been reported. However, based on the data on AEs reported from previous studies, the first signs of overdose of ASP015K may be nausea, diarrhea, other GI symptoms, CPK increased, lymphocyte count decreased, or neutropenia.

5.1.6 Compliance Rules to be Observed by Subjects throughout the Study

The investigator, sub-investigator, or collaborator will explain the following to the subjects during the study period.

- The subject should come to the study center on the day of each study visit without taking that day's dose of the study drug prior to the visit. The subject must also fast for at least 8 hours prior to the blood sampling at the time of the study visit. If need arises for the subject to visit the study center on an unscheduled day after taking that day's dose, for reasons such as AE, the subject should visit the study center regardless of whether and when the study drug and meal have been taken.
- If a new treatment (starting to take a new drug or use a new therapy, etc.) has been prescribed by another department or another medical institution during the study period, the subject should contact the investigator/sub-investigator before starting to use the new treatment, and follow the instructions given by the investigator/sub-investigator. If it is not possible to contact the investigator or sub-investigator in advance, the subject should contact one of them, or the collaborator, as soon as possible.
- Any subject who wishes to take a prescription medicine or over-the-counter drug unconfirmed by the investigator/sub-investigator should consult with the investigator/sub-investigator or collaborator in advance.
- Because the effects that the study drug may have upon pregnancy and the unborn child remain unclear, subjects should be certain to practice 2 or more methods of proper contraception that shall be used by male subjects throughout the study period and for 90 days after end of treatment, and by female subjects throughout the study period and for 60 days after end of treatment.

- Female subjects must not nurse during the study period and for 60 days after the end of treatment.
- In principle, the subject will come to the study center for the study visits on the specified dates. If it is not possible to come on the specified date, the date of the visit will be adjusted to the nearest possible date.
- The subject should visit the study center without delay when instructed by the investigator or sub-investigator to do so because, for example, the laboratory testing has revealed CPK or liver function values to be in the range that requires CPK monitoring or liver function monitoring.

5.2 Demographics and Baseline Characteristics

5.2.1 Demographics

The date of obtaining informed consent, date of birth, sex, and study region will be recorded in the eCRF (date of birth and study region will be entered only for subjects who transferred from studies RAJ3 or RAJ4). Sex and weight will be confirmed at Week 0 and recorded in the CRF.

5.2.2 Medical History

Diseases that remain uncured at the time of the first dose of study drug will be regarded as concurrent diseases. All concurrent diseases will be investigated, and the name of the diagnosis and the time of onset will be recorded in the medical record or other source document, as well as in the CRF (for subjects who were transferred from studies RAJ3 or RAJ4, the onset date of concurrent diseases does not need to be recorded in the CRF). Moreover, AEs that have continued to be present since studies RAJ1, RAJ3, or RAJ4 will be recorded in the CRF.

Previous diseases need not be recorded in the CRF.

5.2.3 Duration, Severity, Drug History, and Treatment Response of Target Disease

The following items of information will be obtained at Week 0 and recorded in the CRF.

- RA dysfunction classification (1991 revised criteria) (Appendix 4)
- Duration of RA and classification of degree of progression (Appendix 5)

5.3 Efficacy and Pharmacodynamics Assessments

5.3.1 Efficacy Assessments

5.3.1.1 Tender and Swollen Joint Counts

(1) Tender joint count

At the time of each study visit (see Table 1, Schedule of Assessments), the investigator/sub-investigator will examine the subject for tender joints, assessing the 68 joints listed below, and confirm the location of each tender joint.

temporomandibular joint (2), sternoclavicular joints (2), acromioclavicular joint (2), shoulder joints (2)*, elbow joints (2)*, wrist joints (2)*, DIP joints (8), PIP joints of both hands (10)*, MCP joints (10)*, hip joints (2), knee joints (2)*, ankle joints (2), tarsal bones (2), MTP joints (10), interphalangeal joint joints of toes (2), PIP joints of both feet (8)

*: Joints subject to DAS28 assessment

(2) Number of swollen joints

At the time of each study visit (see Table 1, Schedule of Assessments), the investigator/sub-investigator will examine the subject for swollen joints, assessing the 66 joints representing the aforementioned with the exception of the hip joints (2), and confirm the location of the swollen joints.

5.3.1.2 Assessment of Pain and Overall Assessment of Disease Activity

The following assessments will be performed at each study visit.

(1) Subject's assessment of pain: The subject assesses his own pain severity on a VAS of 0-100 mm.

(2) SGA: The subject assesses his own disease activity on a VAS of 0-100 mm.

(3) PGA: The investigator/sub-investigator assesses the subject's disease activity on a VAS of 0-100 mm.

5.3.1.3 Acute Phase Reactants (CRP and ESR)

CRP and ESR will be measured at each study visit. The measurement of CRP will be performed by the central laboratory, and the measurement of ESR will be performed by each study center. These results will be used to calculate DAS28 (see Section 5.3.1.5, DAS28), SDAI (see Section 5.3.1.6, SDAI), and ACR response criteria assessment (see Section 5.3.1.7, ACR Response Criteria Assessment). ESR will be performed at the end of 1 hour, and the dates and results of measurements will be recorded in the eCRF.

5.3.1.4 EULAR Response Criteria

EULAR Response Criteria categorize response to treatment as "No response," "Moderate response," or "Good response," according to the definitions given in TTable 2 [van Gestel et al, 1996; van Gestel et al, 1998].

Table 2 Definition of EULAR Response Criteria Assessment

DAS28 after treatment	DAS28 improvement (DAS28 before treatment - DAS28 after treatment)		
	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤3.2	Good response	Moderate response	No response
> 3.2 and ≤ 5.1	Moderate response	Moderate response	No response
> 5.1	Moderate response	No response	No response

5.3.1.5 DAS28

The subject's DAS28 will be calculated at each study visit (see Table 1, Schedule of Assessments), using data from the following assessments, together with the formula shown below [Prevoo et al, 1995; van der Heijde et al, 1990; Fransen et al, 2003; Mallya et al, 1982; Wolfe, 1997].

- TJC (28 joints)
- SJC (28 joints)
- CRP or ESR
- SGA

[When CRP is used]
$DAS28 = 0.56\sqrt{(TJC)} + 0.28\sqrt{(SJC)} + 0.36 \ln (CRP + 1) + 0.014 \times SGA + 0.96$

[When ESR is used]
$DAS28 = 0.56\sqrt{(TJC)} + 0.28\sqrt{(SJC)} + 0.70 \ln ESR + 0.014 \times SGA$

DAS28 score is assessed as below.

High disease activity: DAS28 score exceeding 5.1

Moderate disease activity: DAS28 score exceeding 3.2 to 5.1

Low disease activity: DAS28 score of less than or equal to 3.2

If the DAS28 score is less than 2.6, the subject will be considered to be in DAS28 remission [van Gestel et al, 1998; Fransen and van Riel, 2005].

5.3.1.6 SDAI Score

The SDAI score at each study visit will be calculated using data from the following assessments, together with the formula shown below [Smolen et al, 2003; Aletaha and Smolen, 2005; Felson et al, 2011].

- TJC (28 joints)
- SJC (28 joints)
- SGA
- PGA
- CRP (mg/dL)

$SDAI = TJC + SJC + SGA + PGA + CRP$

The SDAI score is assessed as below.

- High disease activity: SDAI score exceeding 26
- Moderate disease activity: SDAI score exceeding 11 and not greater than 26

- Low disease activity: SDAI score exceeding 3.3 and not greater than 11

If the SDAI score is 3.3 or less, the subject will be considered to be in SDAI remission.

5.3.1.7 ACR Response Criteria Assessment

ACR Response Criteria [Felson et al, 1995] measure improvement in TJC, SJC, subject's assessment of pain, SGA, PGA, assessment of physical function using the Disability Index of the HAQ-DI, and acute phase reactant (CRP or ESR).

ACR20 response requires that all criteria (1) through (3) below be met. ACR50 response indicates a 50% improvement for all criteria (1) through (3) below, and ACR70 response similarly indicates a 70% improvement. For [5], assessment in this study is separately performed with regard to CRP and ESR.

(1) TJC: ≥ 20% reduction compared to before administration of study drug

(2) SJC: ≥ 20% reduction compared to before administration of the study drug

(3) ≥ 20% improvement in 3 of the following 5 parameters, compared to before administration of study drug

[1] Subject's assessment of pain
[2] SGA
[3] PGA
[4] Disability Index (HAQ-DI)
[5] CRP or ESR

5.3.1.8 Patient Reported Outcomes/Assessments

Subjects will complete the following questionnaires according to Table 1, Schedule of Assessments. The answers written in the questionnaire will be recorded in the eCRF.

- HAQ-DI [Fries et al, 1982; Ramey et al, 1992]
- SF-36v2® [Ware, 2004]
- WPAI [Takeuchi T, 2011; Reilly MC, 1993] (WPAI is only administered to subjects who transferred from studies RAJ3 or RAJ4)

5.3.2 Pharmacodynamics Assessments

Blood samples will be collected on the assessment days after the baseline as specified in the Schedule of Assessments. The measurements will be performed by the central laboratory. See Table 1, Schedule of Assessments, for the testing schedule. Results of the assessments and tests at Week 52 or follow-up of studies RAJ3 or RAJ4 that are to be used as the baseline data of this extension study will be reported to the sponsor and the study center after unblinding of the studies RAJ3 or RAJ4.

5.3.2.1 Lymphocyte Subsets

Lymphocyte subsets CD3, CD4, CD8, CD16, CD19, CD56, and CD56/16 will be determined, and changes from baseline will be calculated. The day of blood sampling will be recorded in the eCRF.

5.4 Safety Assessment

The following tests and observations will be made for the purpose of safety assessment. With the exception of urine tests for pregnancy testing, measurement of laboratory test values will be performed by the central laboratory. See Table 1, Schedule of Assessments, for the testing schedule.

Information on Liver Safety Monitoring and Assessment is given in Appendix 6. If an abnormality is found in the results of liver function tests, liver safety will be evaluated according to these procedures.

5.4.1 Vital Signs

Vital signs (body temperature, pulse rate, and blood pressure in sitting position) will be collected at each study visit, as shown in Table 1, Schedule of Assessments. The dates and results of measurements of vital signs will be recorded in the source document as well as in the eCRF.

5.4.2 Body Weight

Body weight will be measured according to Table 1, Schedule of Assessments. The dates and results of measurements will be recorded in the eCRF.

5.4.3 Adverse Events

The investigator/sub-investigator will confirm all AEs occurring in the period from the start of study drug administration to the end of the final observation. AEs will be handled according to the stipulations of Section 5.5, Adverse Events and Other Safety Aspects.

If an AE related to hepatic function abnormal is found, refer to the procedure in Appendix 6 entitled “Liver Safety Monitoring and Assessment.”

If herpes zoster is reported, it will be recorded in the eCRF as adverse event information; a Herpes Zoster (shingles) Worksheet will be separately prepared, a copy of which will be submitted to the sponsor. For other AEs too, when the sponsor considers necessary and requests to submit additional information using a specific form, such a form must be filled out and submitted to the sponsor.

5.4.4 Laboratory Assessments

1) Hematology, biochemistry (including fasting lipid profile tests), urinalysis

   As shown in Table 1, Schedule of Assessments, the following hematology, biochemistry, fasting lipid profile tests, and urinalysis will be performed at each study visit. Measurements will be made by the central laboratory. Dates of blood sampling for lipid profile tests will be recorded in the eCRF.

   - Hematology
     Hemoglobin, hematocrit, erythrocytes (RBC), leukocytes (WBC), differential WBC (neutrophils, lymphocytes, monocytes, eosinophils, basophils), platelet count

- Biochemistry
  Na, K, Ca, Cl, Mg, HCO_3, BUN, phosphorus, glucose, creatinine, ALP, AST (GOT), ALT (GPT), γ-GTP, TBL, total protein, albumin, uric acid, CPK, LDH, serum amylase, β-D-glucan, eGFR
- Fasting lipid profile tests
  Total cholesterol, LDL, HDL, TGs
  (Blood specimens for these tests should be drawn after the subject has fasted for at least 8 hours.)
- Urinalysis
  pH, specific gravity, protein, glucose, keton bodies, bilirubin, occult blood, sediment

2) Pregnancy test (for females only)

- Urine pregnancy testing will be performed at the study visits every 12 weeks from Week 0 onward, as well as at end of treatment/early termination and end of study (at time of follow-up). The tests scheduled for the end of study (follow-up) will be performed only if the investigator/ sub-investigator decides necessary.
- Urinalysis will be performed at each study center, using the kits provided by the central laboratory.
- If a urine pregnancy test is positive at any time, a negative serum pregnancy test (with measurements performed by the central laboratory) is required for the subject to continue participation in the study. The study may be continued if the possibility of pregnancy can clearly be ruled out by other tests.
- The pregnancy tests need not be performed if the possibility of pregnancy can clearly be ruled out, such as if the woman is postmenopausal or has not had a menstrual period for 1 year or more, or has had a hysterectomy, bilateral oophorectomy, etc.
- Tests for pregnancy are not included in safety assessment.

3) Hepatitis tests

- A subject who has tested positive for either or both HBc and HBs antibodies at screening for studies RAJ3 or RAJ4 will be monitored by performing HBV-DNA assay at specified visits during the treatment period.
  Results of HBV-DNA assay after the baseline will not be included in safety analysis.

4) CPK monitoring

- At time of CPK elevation, CPK, CK-MB, troponin T levels, and aldolase levels will be measured according to Section 5.4.4.1, CPK Monitoring. As part of the physical examination, urinalysis (blood and microscopy) will be performed.

5.4.4.1 CPK Monitoring

If a CPK elevation is observed after administration of the study drug begins, CPK will be monitored as follows.

- If CPK is > 3 × ULN after the start of study drug administration and the subject is asymptomatic, retest CPK to confirm the CPK value, preferably within approximately 1 week from the previous blood sampling. In addition, retest CPK weekly, starting from the date of the initial CPK elevation to > 3 × ULN, until CPK is ≤ 3 × ULN or until the investigator or sub-investigator considers CPK to have achieved a steady state. If the retest cannot be performed within 1 week from the collection time of the blood sample with the CPK value because of which the monitoring was initiated, suspension or interruption of the study drug should be considered until results of the retest are known.
- If CPK is > 3 × ULN already at baseline and is elevated to > 2 × baseline after the start of study drug administration and the subject is asymptomatic, retest CPK to confirm the value, preferably within approximately 1 week from the previous blood sampling. In addition, retest CPK weekly, starting from the date of the initial CPK elevation to > 2 × baseline value, until CPK is ≤ 2 × baseline or until the investigator or sub-investigator considers CPK to have achieved a steady state. If the retest cannot be performed within 1 week from the collection time of the blood sample with the CPK value because of which the monitoring was initiated, suspension or interruption of the study drug should be considered until the results of the retest are known.
- If CPK > 10 × ULN is confirmed after the start of study drug administration, suspend or interrupt the administration of the study drug immediately and retest CPK (see Section 3.4.1, Suspension, Interruption, and Resumption of the Study Drug).
- If a symptomatic CPK elevation (CPK elevation > 1.5 × ULN, accompanied by unusual severe myalgia, muscular weakness, and muscle twitching) is reported by the investigator or sub-investigator, the study will be discontinued (see Section 3.4, Discontinuation Criteria for Individual Subjects).

At the time of CPK monitoring, the following parameters will also be measured. The answers given in the subject questionnaire will be recorded in the eCRF.

- Laboratory tests
  (Parameters to be measured: CK-MB, troponin-T, aldolase)
- A targeted physical examination* and subject questionnaire to assess muscle strength and tenderness
  *: As part of the targeted physical examination, urinalysis (blood and microscopy) will be performed.

5.4.4.2 Liver Safety Monitoring and Assessment

If laboratory testing for a subject enrolled in a study and receiving the study drug reveals > 3 × ULN elevation in serum aminotransferases (ALT, AST) or TBL elevation to > 2 × ULN, the liver function test must be repeated including at least the 4 parameters ALT, AST, ALP,

and TBL. The retest is to be performed between 48 hours and 72 hours after notification of the test results.

See Appendix 6 “Liver Safety Monitoring and Assessment” for the assessment of additional information and liver function values in the monitoring.

If a subject enrolled in a study and receiving the study drug reveals > 3 × ULN elevation in serum aminotransferases (ALT, AST) concurrently with bilirubin > 2 × ULN, the investigator will decide whether the event is SAE. Even if the abnormal change is not considered by the investigator or sub-investigator to be SAE, it has to be reported to the sponsor or CRO as in the case of SAE.

5.4.5 Physical Examination

A physical examination will be performed at each study visit and during unscheduled visits, if necessary, to confirm physical findings, in accordance with Table 1, Schedule of Assessments.

A symptom directed physical exam for RA will be performed at all study visits.

5.4.6 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be obtained at the study visits every 48 weeks from Week 0 onward according to Table 1, Schedule of Assessments, as well as at end of treatment/early termination. The investigator or sub-investigator will confirm the ECG chart, assess the results as “normal,” “abnormal but not to a clinically significant degree,” and “clinically significant abnormality” and record the results of the assessment in the CRF. If the finding is “abnormal but not to a clinically significant degree” or “clinically significant abnormality,” the finding will be recorded in the CRF.

In addition, the clinical interpretation of the 12-lead ECG performed at Week 0 must be completed before the first dose of the study drug.

5.4.7 Radiography

Chest radiography will be obtained at the study visits every 48 weeks from Week 0 onward according to Table 1, Schedule of Assessments, as well as at end of treatment/early termination. However, chest radiography at end of treatment/early termination need not be performed if data obtained within 24 weeks prior to the end of treatment/early termination are available. The investigator or sub-investigator will read the chest radiographs, assess the result as “normal,” “abnormal but not to a clinically significant degree,” or “clinically significant abnormality” and record the results of the assessment in the CRF. If the finding is “abnormal but not to a clinically significant degree” or “clinically significant abnormality,” the finding will be recorded in the CRF.

5.5 Adverse Events and Other Safety Aspects

5.5.1 Definition of Adverse Events (AEs)

An AE is defined as any untoward medical occurrence in a subject administered a study drug that does not necessarily have a causal relationship to this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

All AEs newly observed in the period from the first dose of study drug to end of study (at time of follow-up) or spontaneously reported AEs will be recorded in the medical record or other source document, as well as in the CRF. If a concurrent disease has clearly worsened to an extent that exceeds the usual course after the first dose of the study drug, it will be mentioned among the AEs as a worsening of a concurrent disease. If an AE recurs after having temporarily disappeared, it will be handled as a new AE.

An abnormality identified during a medical test (e.g., laboratory parameter, vital sign, ECG data, physical examination) should be defined as an AE only if the abnormality meets one of the following criteria:

- Induces clinical signs or symptoms
- Requires active intervention
- Requires suspension, interruption, or discontinuation of study medication
- The abnormality or laboratory test value is clinically significant based on the opinion of the investigator or other responsible personnel

The particulars to be noted with respect to the AE are the name of the event, date of onset, date of disappearance, severity (at peak time), seriousness, treatment of the study drug, other treatment, outcome, causal relationship to the study drug, and rationale for the assessment of causal relationship. Recording the rationale for the assessment of causal relationship for all AEs is not required; this should be handled at the sponsor's request. The severity of each event should be recorded on a scale of Grade 1 to Grade 5 in the CRF, and the causal relationship to the study drug should be recorded as "Probably," "Possible," or "Not related" (see Section 5.5.3, Criteria for Causal Relationship to the Study Drug, and Section 5.5.4, Criteria for Defining the Severity of an Adverse Event). The treatment of the AE (whether it was treated with pharmacotherapy or by other means) and the treatment of the study drug should be recorded in the medical record or other source document, as well as in the CRF. The outcome should be recorded in the medical record or other source document, as well as the CRF, as "resolved," "alleviated," "unresolved," "resolved but with late effect," "death," or "unknown."

5.5.2 Definition of Serious Adverse Events (SAEs)

An AE is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Results in death.

- Is life threatening (an AE is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- Results in persistent or significant disability/incapacity.
- Results in congenital anomaly or birth defect.
- Requires inpatient hospitalization or leads to prolongation of hospitalization (Hospitalization for treatment/observation/examination caused by AE is considered to be serious).
- Other medically important events

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent any of the other outcomes listed in the definition above. These events, including those that may result in disability/incapacity, should also usually be considered serious. Examples of such events are allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In addition, all sponsor's clinical studies have the requirement that all of the medical events described in Appendix 3 "Events Always Considered to be Serious" and Appendix 6 "Liver Safety Monitoring and Assessment" be reported by the investigator as SAEs even if they do not meet the aforementioned conditions.

5.5.3 Criteria for Causal Relationship to the Study Drug

AEs that fall under either "Possible" or "Probable" should be defined as "AEs whose relationship to the study drugs could not be ruled out."

Causal Relationship to Study Drug	Related Assessment Criteria
Not related	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and/or in which other drugs, chemicals or underlying disease provide plausible explanations.
Possible	A clinical event with a reasonable time sequence to administration of the drug, to which one of the following applies: • Could also be explained by concurrent/underlying disease or other drugs • Information on drug withdrawal is lacking or unclear
Probable	A clinical event with a reasonable time sequence to administration of the drug, to which one of the following applies: • Recurs upon re-administration of the drug, or disappears or is alleviated when the drug is withdrawn • Cannot be explained by concurrent/underlying disease or other drugs, or is unlikely to be attributable to them

5.5.4 Criteria for Defining the Severity of an Adverse Event

The AE grades will be based on NCI-CTCAE [Japan Clinical Oncology Group (JCOG), 2011]. Items unspecified by these criteria will be assessed according to the following criteria and recorded.

Grade	Assessment Criteria
Grade 1 (Mild)	Mild; asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated.
Grade 2 (Moderate)	Moderate; minimal; local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3 (Severe)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4 (Life threatening or incapacitating)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Death)	Death related to AE.

5.5.5 Reporting of Serious Adverse Events (SAEs)

In the case of an SAE, the investigator/sub-investigator must report the SAE to the head of the study center and also contact the sponsor by telephone, e-mail, or fax immediately (within 24 hours of awareness) [in case of Japan: in addition to reporting to the head of the study center].

The investigator should complete and submit an SAE report containing all information that is required by the regulatory authorities to the sponsor or CRO [in case of Japan: and to the head of the study center] by e-mail or fax immediately (within 24 hours of awareness). If e-mail transmission or faxing of an SAE report is not possible, or is not possible within 24 hours, the sponsor or delegated CRO should be informed by phone.

For contact details, see SECTION II, CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL.

Send the SAE report to the below FAX number.

Contact Information for the Sponsor

[redacted]

TEL: [redacted], FAX: [redacted]

Contact Information for the CRO

Japan:

[redacted]

TEL: [redacted] FAX: [redacted]

Korea:

[redacted]

TEL: [redacted], FAX: [redacted]

Taiwan:

[redacted]

TEL: [redacted], FAX: [redacted]

5.5.6 Follow-up to Adverse Events

All AEs occurring during or after the subject has discontinued the study are to be followed up until resolved or judged to be no longer clinically significant, or until they become chronic to the extent that they can be fully characterized.

If during AE follow-up, the AE progresses to an "SAE," or if a subject experiences a new SAE, the investigator must immediately report the information to the sponsor/delegated CRO.

Even if the subject does not return to normal or to his or her previous state, the follow-up can be considered finished when the following procedures have been taken.

1. The investigator judges that the follow-up of the subject concerned is no longer necessary based on the progress made during the follow-up,
2. The reason for such a judgment is entered as a comment in the CRF for the follow-up, and
3. The sponsor judges that the reason is acceptable with regard to the safety of the subject concerned.

Refer to Appendix 6 "Liver Safety Monitoring and Assessment" for the details of follow-up of DILI (medical history, concomitant medications, history of alcohol intake and narcotic use).

5.5.7 Procedure in Case of Pregnancy

If a woman becomes pregnant or is proven to be pregnant during the study dosing period of within 28 days from end of treatment or early termination, the investigator should report the information to the sponsor or CRO in the same manner as for an SAE. The expected date of delivery, estimated fertility date, pregnancy result and neonatal data, etc., should be included in this information.

The investigator or other responsible personnel will handle the pregnancy in the same manner as an SAE and will follow the medical status of the mother, as well as the fetus, and report the outcome to the sponsor.

When the outcome of the pregnancy falls under the criteria for SAEs [spontaneous abortion, induced abortion, stillbirth, death of newborn, congenital anomaly (including anomaly in a miscarried fetus)] and when information on newborn falls under the criteria for SAEs

(including death, congenital anomaly, and other, the investigator should respond in accordance with the report procedure for SAEs.

Additional information regarding the outcome of a pregnancy (which is categorized as an SAE) is mentioned below.

- "Spontaneous abortion" includes abortion and missed abortion.
- Death of a newborn within 1 month after birth should be reported as an SAE regardless of its relationship with the study drug
- If a newborn dies more than 1 month after the birth, it should be reported if a relationship between the death and intrauterine exposure to the study drug is judged as "possible" by the investigator or other responsible personnel
- In the case of a delivery of a living newborn, the "normality" of the newborn is evaluated at the birth.
- "Normality" of a miscarried fetus is evaluated by visual examination unless test results that indicate a congenital anomaly are obtained prior to miscarriage.

If a male subject impregnates his partner during the conduct of the clinical study, the subject should report the pregnancy to the investigator or other responsible personnel. The investigator must report the pregnancy to the sponsor or CRO.

5.5.8 Supply of New Information Affecting the Conduct of the Study

In Japan:

1. When information is obtained regarding serious and unexpected adverse drug reactions (or other) that are specified in Article 80-2 Paragraph 6 and Article 273 of the Law for Ensuring the Quality, Efficacy, and Safety of Drugs and Medical Devices (or adverse drug reactions during the post-marketing clinical study), the sponsor should inform all the investigators involved in the clinical study, the head of the study center, and the regulatory authorities of such information.
   Upon receiving such a report, the head of the study center will decide whether the clinical study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the subjects, in compliance with Section 8.2.3.2, Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information.
2. In addition to 1 above, the head of the study center should submit any reports received from the sponsor or investigator to the IRB regarding revision of the investigator's brochure (This is not applicable during a post-marketing clinical study) or the protocol, revision of the written information, particulars related to the quality, efficacy, or safety of the study drug, important information on properly conducting the study, or other revision of materials for discussion by the IRB.

In Korea and Taiwan:

When the sponsor gains new information suggesting adverse impact on the subjects' safety, safe conduct of the clinical study, or the IRB/IEC approval for study continuation, the sponsor will immediately notify all investigators, all study sites, and relevant regulatory authorities.

The sponsor must immediately report SAEs to all participating principal investigators, study sites (and the IRBs/IECs if appropriate) in compliance with local requirements and the relevant regulatory authorities.

When information necessary for conducting the clinical study properly (including "Dear Doctor Letters" but not limited to that) becomes available and leads to a protocol amendment, the sponsor should inform the regulatory authorities, as well as all investigators and medical institutions involved in the clinical study, who will then inform the IRB/IEC of such information, and when needed, should amend the Written Information.

5.5.9 Deviations from the Protocol and Other Actions Taken to Avoid Life-Threatening Risks to Subjects

The investigator or other responsible personnel must not deviate from or amend the protocol, without obtaining prior written agreement with the sponsor and prior written approval based on the review by the IRB/IEC.

In Japan:

However, when the investigator does not follow the protocol for medically inevitable reason and in order to avoid urgent risks for subjects, the investigator should take the following actions:

1. Describe the content of the deviation or amendment and the reason for it in a written notice and immediately send the document stating the deviation or amendment and the reasons to the sponsor and the head of the study center. Keep a copy of the notice.
2. Consult with the sponsor at the earliest possibility for cases in which it is necessary to amend the protocol in order to avoid risk to the subjects. Obtain approval for a draft of the amended protocol from the IRB and the head of the study center as well as written agreement with the sponsor.

In Korea and Taiwan:

When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should report to sponsor, IRB/IEC, and regulatory authority (if applicable) in compliance with local requirements.

5.6 Test Drug Concentration

Not applicable.

5.7 Other Measurements, Assessments, or Methods

5.7.1 Pharmacodynamic Parameters

For the assessment of pharmacodynamics, lymphocyte subset determination is performed in this study (Section 5.3.2, Pharmacodynamics Assessments).

Blood samples for the lymphocyte subset determination are drawn using 2 mL vacutainer tube containing EDTA-2K in Japan, and 3 mL vacutainer tube containing EDTA-2K in Korea and Taiwan. For the procedures of collection, storage, and dispatch of blood samples, refer to the explanation of test procedures supplied with the test kit.

5.8 Total Amount of Blood

The total amount of blood drawn for samples will differ from subject to subject in this study because duration of participation in the study will differ depending upon the subject.

The volume of blood drawn per sample and the total annual sample volume are shown in the table below. In addition, blood samples are collected for ESR determination performed at each study center; the volume will differ from center to center (approximately 1 to 2 mL per sample). See Table 1, Schedule of Assessments, for details regarding the blood-sampling schedule.

Blood samples will be taken at other times as necessary to follow up on laboratory test values obtained.

[Subjects who transferred from RAJ1]

Assessment	Volume of sample	Total annual sample volume (No. of draws)	
		First year	2nd year and later
Hematology	2 mL	28 mL (14 times)	8 mL (4 times)
Biochemistry (including CRP and lipid profile tests)	14 mL	196 mL (14 times)	56 mL (4 times)
Lymphocyte subsets	2 mL	4 mL (2 times)	2 mL (1 time)
Total	18 mL	228 mL	66 mL

[Subjects who transferred from RAJ3 or RAJ4]

Assessment	Volume of sample	Total annual sample volume (No. of draws)	
		First year	2nd year and later
Hematology	Japan: 2 mL Korea: 3 mL Taiwan: 3 mL	Japan: 10 mL (5 times) Korea: 15 mL (5 times) Taiwan: 15 mL (5 times)	Japan: 8 mL (4 times) Korea: 12 mL (4 times) Taiwan: 12 mL (4 times)
Biochemistry (including CRP and lipid profile tests)	Japan: 14 mL Korea: 15.5 mL Taiwan: 13.5 mL	Japan: 70 mL (5 times) Korea: 77.5 mL (5 times) Taiwan: 67.5 mL (5 times)	Japan: 56 mL (4 times) Korea: 62 mL (4 times) Taiwan: 54 mL (4 times)
Lymphocyte subsets	Japan: 2 mL Korea: 3 mL Taiwan: 3 mL	Japan: 4 mL (2 times) Korea: 6 mL (2 times) Taiwan: 6 mL (2 times)	Japan: 2 mL (1 time) Korea: 3 mL (1 time) Taiwan: 3 mL (1 time)
Total	Japan: 18 mL Korea: 21.5 mL Taiwan: 19.5 mL	Japan: 84 mL Korea: 98.5 mL Taiwan: 88.5 mL	Japan: 66 mL Korea: 77 mL Taiwan: 69 mL

* Additional 5 mL of blood per sample needs to be drawn in Japan and Taiwan, and 8.5 mL in Korea at the scheduled visits after initiation of study drug administration if HBV-DNA assay is performed.

* Additional 4 mL of blood per sample needs to be drawn in Japan, and 5 mL in Korea and Taiwan if determination of CK-MB, troponin T, and aldolase is performed.

6 TERMINATION OF THE CLINICAL STUDY

1. When the sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the sponsor may discontinue the clinical study and send a written notice of the discontinuation along with the reasons to the investigator [unique to Japan: and the head of the study center].

2. If the investigator wishes to discontinue the study in the particular study center while the study is still in progress, the investigator should contact the sponsor [unique to Japan: and the head of the study center] immediately to inform them of the discontinuation and the reason for it.

7 STATISTICAL METHODOLOGY

A detailed elaboration of the statistical analysis will be included in a separate statistical analysis plan based on the opinions and advice from a medical expert. After review, it will be finalized prior to data lock. For the analyses of efficacy and pharmacodynamics variables in this extension study, values at the baseline in the previous studies (RAJ1, RAJ3, and RAJ4) will be used as the baseline values. However, changes from baseline values of this extension study will also be examined where appropriate. For the evaluation of safety, Week 0 of this extension study (015K-CL-RAJ2) will be referred to as the baseline; however, changes from baseline values of the previous studies (RAJ1, RAJ3, and RAJ4) will also be examined where appropriate.

7.1 Sample Size

Approximately 800 treated patients

[Rationale for the sample size]

The sample size estimation is based on the number of subjects who have completed the preceding study of ASP015K (Study 015K-CL-RAJ1) and participate in this extension study (201 subjects), the planned number of subjects in Study 015K-CL-RAJ3 excluding those in the reference group (300 subjects), and the planned number of subjects in Study 015K-CL-RAJ4 (510 subjects).

7.2 Analysis Set

The study analyses will be performed on the following analysis sets. Final judgments on inclusion/exclusion of subjects from the analyses will be made following case reviews based on the opinions and advice from a medical expert.

7.2.1 Full Analysis Set (FAS)

The FAS is defined as all subjects who receive at least one dose of study drug and have measurements for any of the efficacy endpoints.

7.2.2 Safety Analysis Set (SAF)

The SAF is defined as all subjects who received at least one dose of the study drug.

7.2.3 Pharmacodynamics Analysis Set (PDAS)

The PDAS is defined as all subjects who receive at least one dose of the study drug and from whom a pharmacodynamics sample is collected at one or more points of time.

7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized for the SAF. Descriptive statistics will include sample size, mean, standard deviation, minimum, median and maximum for continuous variables, and frequency and percentage for categorical variables. Unless otherwise specified, data will be tallied by each preceding study (RAJ1, RAJ3, and RAJ4) and for the entire population of RAJ2. When needed, analyses will take into consideration the treatment groups in the preceding studies as well as the regions (i.e. Japan, Korea, and Taiwan).

7.4 Analysis of Efficacy

Efficacy analysis will be conducted on the FAS. The efficacy results will be summarized with sample size, mean, standard deviation, minimum, median and maximum by time point for continuous variables, and frequency and percentage for categorical variables. Subgroup analyses for sex and age categories may be explored. Unless otherwise specified, data will be tallied by each preceding study (RAJ1, RAJ3, and RAJ4) and for the entire population of RAJ2. When needed, analyses will take into consideration the treatment groups in the preceding studies as well as the regions (i.e. Japan, Korea, and Taiwan).

7.5 Analysis of Safety

Unless otherwise specified, data will be tallied by each preceding study (RAJ1, RAJ3, and RAJ4). When needed, analyses will take into consideration the treatment groups in the preceding studies as well as the regions (i.e. Japan, Korea, and Taiwan).

7.5.1 Adverse Events

AEs will be coded using the MedDRA. The incidence of AEs, SAEs, AEs leading to treatment discontinuation, and AEs whose relationship to the study drugs could not be ruled out will be summarized by system organ class and preferred term. The incidence of AEs by severity will also be summarized. All AEs will be listed.

7.5.2 Laboratory Measurements

Descriptive statistics will be used to summarize clinical laboratory measurements and change from baseline if quantitative, by time point. Laboratory data will be displayed in listings.

7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign measurements and change from baseline by time point.

7.5.4 12-lead ECG

The frequency of each category of 12-lead ECG results will be summarized by time point.

7.5.5 Body Weight

Descriptive statistics will be used to summarize the body weight measurements by time point.

7.6 Other Analyses

Any other analyses, including disposition of subjects, exposure to study drug and etc., will be specified in a statistical analysis plan (SAP).

7.6.1 Analysis of Pharmacodynamics

Analysis of pharmacodynamics will be conducted on the PDAS. Descriptive statistics will be used to summarize the pharmacodynamics measurements and change from baseline by time point. Unless otherwise specified, data will be tallied by each preceding study (RAJ1, RAJ3, and RAJ4) and for the entire population of RAJ2. When needed, analyses will take into consideration the treatment groups in the preceding studies as well as the regions (i.e. Japan, Korea, and Taiwan).

7.7 Interim Analysis (and Early Discontinuation of the Clinical Study)

Not applicable. However, while the study is ongoing, safety data review and evaluation of safety will be performed according to the operating procedures developed separately by the Data and Safety Monitoring Board (DSMB; see Section 10.1).

7.8 Handling of Missing Data, Outliers, Visit Windows, and Other Information

Final judgments on handling of missing data, outliers, visit windows, and other information will be made at the Case Review Meeting based on the opinions and advice from a medical expert prior to data lock and included in the SAP.

The acceptable time ranges of the efficacy and safety examinations, observations, etc. from the date of initial study treatment (Day 1) are defined as follows. If there are multiple data available over the same period of time, the data obtained on the day closest to the reference date will be utilized; the later date will be applied if the number of days from the reference date is equal. Missing data at the end or discontinuation of treatment will be imputed using the LOCF method.

Since the study period of this study differs depending on the subject, the timing for the required visits to the study center will also differ from subject to subject. Only subjects who transferred from study RAJ1, but not those who transferred from studies RAJ3 or RAJ4, are required to come for visits at Week 2, Week 4, Week 8, Week 16, Week 20, Week 28, Week 32, Week 40, and Week 44. Therefore, these time points defined in the analysis are set only for the subjects from study RAJ1.

7.8.1 Handling of Schedule of Assessments of Efficacy Variables

For data obtained after the end of treatment, the data obtained within +2 days after the last dose will be included in analysis, except for the data at the end of the study (at time of follow-up).

(1) RA disease activity (TJC, SJC, PGA, SGA, subject's assessment of pain), CRP, ESR

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 2	Day 15	Day 12 to Day 18
Week 4	Day 29	Day 22 to Day 36
Week 8	Day 57	Day 50 to Day 64
Week 12	Day 85	Day 78 to Day 92
Week 16	Day 113	Day 106 to Day 120
Week 20	Day 141	Day 134 to Day 148
Week 24	Day 169	Day 162 to Day 176
Week 28	Day 197	Day 190 to Day 204
Week 32	Day 225	Day 218 to Day 232
Week 36	Day 253	Day 246 to Day 260
Week 40	Day 281	Day 274 to Day 288
Week 44	Day 309	Day 302 to Day 316
Week 48	Day 337	Day 330 to Day 344
Week 60	Day 421	Day 407 to Day 435
Week 72	Day 505	Day 491 to Day 519
Week 84	Day 589	Day 575 to Day 603
Week 96	Day 673	Day 659 to Day 687
Week 108	Day 757	Day 743 to Day 771
Week 120	Day 841	Day 827 to Day 855
Week 132	Day 925	Day 911 to Day 939
Week 132 + 12 × x	Day 7 × (132 + 12 × x) + 1	Day 7 × (132 + 12 × x) − 13 to Day 7 × (132 + 12 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose
End of the study (at time of follow-up)	28 days after the last dose	21 to 35 days after the last dose

*: Day 1 represents the first day of study treatment.

(2) Patient Questionnaires (HAQ-DI, FACIT-Fatigue)

The schedule for FACIT-Fatigue applies only to subjects who transferred from study RAJ1.

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 2	Day 15	Day 12 to Day 18
Week 4	Day 29	Day 22 to Day 36
Week 8	Day 57	Day 50 to Day 64
Week 12	Day 85	Day 78 to Day 92
Week 16	Day 113	Day 106 to Day 120
Week 20	Day 141	Day 134 to Day 148
Week 24	Day 169	Day 162 to Day 176
Week 28	Day 197	Day 190 to Day 204
Week 32	Day 225	Day 218 to Day 232
Week 36	Day 253	Day 246 to Day 260
Week 40	Day 281	Day 274 to Day 288
Week 44	Day 309	Day 302 to Day 316
Week 48	Day 337	Day 330 to Day 344
Week 60	Day 421	Day 407 to Day 435
Week 72	Day 505	Day 491 to Day 519
Week 84	Day 589	Day 575 to Day 603
Week 96	Day 673	Day 659 to Day 687
Week 108	Day 757	Day 743 to Day 771
Week 120	Day 841	Day 827 to Day 855
Week 132	Day 925	Day 911 to Day 939
Week 132 + 12 × x	Day 7 × (132 + 12 × x) + 1	Day 7 × (132 + 12 × x) − 13 to Day 7 × (132 + 12 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose
End of the study (at time of follow-up)**	28 days after the last dose	21 to 35 days after the last dose

*: Day 1 represents the first day of study treatment.

**: The assessment at the end of the study (at the time of follow-up) will be scheduled only for HAQ-DI.

(3) Patient Questionnaires (SF-36v2®)

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 4**	Day 29	Day 22 to Day 36
Week 8**	Day 57	Day 50 to Day 64
Week 12**	Day 85	Day 78 to Day 92
Week 16**	Day 113	Day 106 to Day 120
Week 20**	Day 141	Day 134 to Day 148
Week 24	Day 169	Day 162 to Day 176
Week 28**	Day 197	Day 190 to Day 204
Week 32**	Day 225	Day 218 to Day 232
Week 36**	Day 253	Day 246 to Day 260
Week 40**	Day 281	Day 274 to Day 288
Week 44**	Day 309	Day 302 to Day 316
Week 48	Day 337	Day 330 to Day 344
Week 60**	Day 421	Day 407 to Day 435
Week 72	Day 505	Day 491 to Day 519
Week 84**	Day 589	Day 575 to Day 603
Week 96	Day 673	Day 659 to Day 687
Week 108**	Day 757	Day 743 to Day 771
Week 120	Day 841	Day 827 to Day 855
Week 120 + 12 × x**	Day 7 × (120 + 12 × x) + 1	Day 7 × (120 + 12 × x) − 13 to Day 7 × (120 + 12 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose

*: Day 1 represents the first day of study treatment.

**: Scheduled only for subjects who transferred from study RAJ1. For subjects who transferred from studies RAJ3 or RAJ4, the survey is administered every 24 weeks after Week 120. Starting at the first visit after the revision of the study protocol, the survey will be administered to subjects who transferred from study RAJ1 also every 24 weeks.

(4) Patient Questionnaires (WPAI [subjects from RAJ3 or RAJ4])

Scheduled only for subjects who transferred from studies RAJ3 or RAJ4.

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 24	Day 169	Day 162 to Day 176
Week 48	Day 337	Day 330 to Day 344
Week 72	Day 505	Day 491 to Day 519
Week 96	Day 673	Day 659 to Day 687
Week 120	Day 841	Day 827 to Day 855
Week 120 + 24 × x	Day 7 × (120 + 24 × x) + 1	Day 7 × (120 + 24 × x) − 13 to Day 7 × (120 + 24 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose

*: Day 1 represents the first day of study treatment.

7.8.2 Handling of Schedule of Assessments of Pharmacodynamics Variables

For data obtained after the end of study treatment, the data obtained within +2 days after the last dose will be included in analysis, except for the data at the end of the study (at time of follow-up).

(1) Lymphocyte subsets

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 48	Day 337	Day 330 to Day 344
Week 96	Day 673	Day 659 to Day 687
Week 96 + 48 × x	Day 7 × (96 + 48 × x) + 1	Day 7 × (96 + 48 × x) − 13 to Day 7 × (96 + 48 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose
End of the study (at time of follow-up)	28 days after the last dose	21 to 35 days after the last dose

*: Day 1 represents the first day of study treatment.

7.8.3 Handling of Schedule of Assessments of Safety Variables

For data obtained after the end of study treatment, the data obtained within +2 days after the last dose will be included in analysis, except for the data at the end of the study (at time of follow-up).

(1) Vital Signs

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 2	Day 15	Day 12 to Day 18
Week 4	Day 29	Day 22 to Day 36
Week 8	Day 57	Day 50 to Day 64
Week 12	Day 85	Day 78 to Day 92
Week 16	Day 113	Day 106 to Day 120
Week 20	Day 141	Day 134 to Day 148
Week 24	Day 169	Day 162 to Day 176
Week 28	Day 197	Day 190 to Day 204
Week 32	Day 225	Day 218 to Day 232
Week 36	Day 253	Day 246 to Day 260
Week 40	Day 281	Day 274 to Day 288
Week 44	Day 309	Day 302 to Day 316
Week 48	Day 337	Day 330 to Day 344
Week 60	Day 421	Day 407 to Day 435
Week 72	Day 505	Day 491 to Day 519
Week 84	Day 589	Day 575 to Day 603
Week 96	Day 673	Day 659 to Day 687
Week 108	Day 757	Day 743 to Day 771
Week 120	Day 841	Day 827 to Day 855
Week 132	Day 925	Day 911 to Day 939
Week 132 + 12 × x	Day 7 × (132 + 12 × x) + 1	Day 7 × (132 + 12 × x) − 13 to Day 7 × (132 + 12 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose
End of the study (at time of follow-up)	28 days after the last dose	21 to 35 days after the last dose

*: Day 1 represents the first day of study treatment.

(2) Laboratory Tests (Hematology, Biochemistry [including Fasting Lipid Profile Test], Urinalysis)

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 2	Day 15	Day 12 to Day 18
Week 4	Day 29	Day 22 to Day 36
Week 8	Day 57	Day 50 to Day 64
Week 12	Day 85	Day 78 to Day 92
Week 16	Day 113	Day 106 to Day 120
Week 20	Day 141	Day 134 to Day 148
Week 24	Day 169	Day 162 to Day 176
Week 28	Day 197	Day 190 to Day 204
Week 32	Day 225	Day 218 to Day 232
Week 36	Day 253	Day 246 to Day 260
Week 40	Day 281	Day 274 to Day 288
Week 44	Day 309	Day 302 to Day 316
Week 48	Day 337	Day 330 to Day 344
Week 60	Day 421	Day 407 to Day 435
Week 72	Day 505	Day 491 to Day 519
Week 84	Day 589	Day 575 to Day 603
Week 96	Day 673	Day 659 to Day 687
Week 108	Day 757	Day 743 to Day 771
Week 120	Day 841	Day 827 to Day 855
Week 132	Day 925	Day 911 to Day 939
Week 132 + 12 × x	Day 7 × (132 + 12 × x) + 1	Day 7 × (132 + 12 × x) − 13 to Day 7 × (132 + 12 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose
End of the study (at time of follow-up)	28 days after the last dose	21 to 35 days after the last dose

*: Day 1 represents the first day of study treatment.

(3) 12-lead ECG, Chest Radiography

Time points defined in analysis	Reference date*	Acceptable time range
Week 0**	Day 1	Day 1
Week 48	Day 337	Day 330 to Day 344
Week 96	Day 673	Day 659 to Day 687
Week 96 + 48 × x	Day 7 × (96 + 48 × x) + 1	Day 7 × (96 + 48 × x) − 13 to Day 7 × (96 + 48 × x) + 15
End/discontinuation of treatment***	Day of the last dose	Day 2 to 2 days after the last dose

*: Day 1 represents the first day of study treatment.

**: Regarding chest radiography, it is allowed to use data obtained within 28 days prior to the Week 0 visit.

***: Chest radiography at the end/discontinuation of treatment is unnecessary if one has been taken within 24 weeks from the day of discontinuation.

(4) Body weight

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 2	Day 15	Day 12 to Day 18
Week 4	Day 29	Day 22 to Day 36
Week 8	Day 57	Day 50 to Day 64
Week 12	Day 85	Day 78 to Day 92
Week 24	Day 169	Day 162 to Day 176
Week 36	Day 253	Day 246 to Day 260
Week 48	Day 337	Day 330 to Day 344
Week 60	Day 421	Day 407 to Day 435
Week 72	Day 505	Day 491 to Day 519
Week 84	Day 589	Day 575 to Day 603
Week 96	Day 673	Day 659 to Day 687
Week 108	Day 757	Day 743 to Day 771
Week 120	Day 841	Day 827 to Day 855
Week 132	Day 925	Day 911 to Day 939
Week 132 + 12 × x	Day 7 × (132 + 12 × x) + 1	Day 7 × (132 + 12 × x) − 13 to Day 7 × (132 + 12 × x) + 15
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose
End of the study (at time of follow-up)	28 days after the last dose	21 to 35 days after the last dose

*: Day 1 represents the first day of study treatment.

8 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

8.1 Procedure for Clinical Study Quality Control

8.1.1 Data Collection

The investigator is responsible to ensure that all data in the eCRFs and queries are accurate and complete and that all entries are verifiable with source documents. These source documents should be appropriately maintained by the study center.

The investigator, sub-investigator, or collaborator will enter data collected using an EDC system. The investigator, sub-investigator, and collaborator will enter the data within 5 working days from the day of their occurrence (e.g., day of the subject's visit, day of receipt of information) as a general rule.

In case of an AE, the name of the AE is to be entered within 5 working days from the day on which the event was confirmed, and in case of concurrent medications/therapies, the name of the medication or therapy is to be entered within 5 working days from the day on which the concurrent use was started or became known. Other information to be entered into the eCRF is to be entered without delay as soon as they become known.

The monitor should verify the data in the eCRFs with source documents and confirm that there are no inconsistencies between them.

For screening failures, the minimum demographic data (sex and informed consent date as well as study region and birth date of subjects who transferred from studies RAJ3 or RAJ4) and reason for screening failure will be collected from SFL.

Laboratory tests and pharmacodynamics measurements are performed at a central laboratory. At predefined intervals during the study, the Data Science Department of the sponsor will obtain the laboratory test results and measurement results of pharmacodynamics parameters and records with verified quality from the central laboratory.

8.1.2 Specification of Source Documents

Source data must be available at the study center to document the existence of the study subjects and substantiate the integrity of study data collected. Source data must include the original documents relating to the study as well as those relating to the medical treatment and medical history of the subject.

The following information should be included in the source medical records:

- Demographic data [birth date (subjects who transferred from studies RAJ3 or RAJ4), study region (subjects who transferred from studies RAJ3 or RAJ4), sex, height, and body weight]
- Inclusion and exclusion criteria details
- Participation in study and signed and dated informed consent forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data
- AEs and symptomatic treatment
- Results of relevant examinations (e.g., ECG charts, X-ray films etc.)
- Laboratory test slips/reports
- Dispensing and return of study drug details
- Reason for premature discontinuation
- Records of RA diagnosis and evaluation, patient questionnaires (e.g., HAQ-DI, SF-36v2®, FACIT-Fatigue, WPAI)
- Patient questionnaire administered during CPK monitoring
- Herpes Zoster (shingles) Worksheet

If the following data are not included in medical records, the entries in the eCRFs are treated as source data.

- Dates of AE occurrence and resolution, its severity, seriousness, outcome, causality to the study drug, and rationale for the causality
- Route of administration, treatment dates, and reason for use for previous and concomitant drugs
- Type, treatment dates, and reason for use for previous and concomitant therapies
- Presence or absence of abnormal 12-lead ECG readings, abnormal findings
- Date, reason, and background/details for discontinuation
- Other comments

8.1.3 Clinical Study Monitoring

The sponsor or delegated CRO is responsible for monitoring the clinical study to ensure that subject's human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol and GCP, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with planned monitoring procedures.

8.1.4 Direct Access to Source Data/Documents

The investigator and the study center must accept monitoring and auditing by the sponsor or delegated CRO as well as inspections from the IRB/Independent Ethic Committee (IEC) and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (see Section 8.1.2, Specification of Source Documents) when they are requested by the sponsor monitors and auditors, the IRB/IEC, or regulatory authorities. The confidentiality of the subject's identities shall be well protected consistent with local and national laws/regulations when the source documents are subject to direct access.

8.1.5 Data Management

Data management will be coordinated by the Data Science Department of the sponsor in accordance with the SOPs for data management. All study specific processes and definitions will be documented by Data Management. CRF retrieval and correction process will be referenced in the CRF instructions. Coding of medical terms will be performed using MedDRA.

8.2 Ethics and Protection of Subject Confidentiality

8.2.1 Institutional Review Board (IRB)/Independent Ethic Committee (IEC)

Prior to a conclusion of study contracts for the present study, the protocol and documents used to obtain patient consent shall be reviewed and approved by the IRBs/IECs of each study center in order to ensure that subject's human rights, safety, and well-being are protected.

8.2.2 Ethical Conduct of the Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to GCP, ICH Guidelines, and the applicable laws/regulations.

8.2.3 Informed Consent of Subjects

8.2.3.1 Subject Information and Consent

Prior to execution of the clinical study, the investigator should prepare the written informed consent form and other written information in collaboration with the sponsor and revise the information whenever necessary. The written and revised informed consent form and any

other written information should be submitted to the sponsor and be subject to prior approval by the IRB/IEC.

- The investigator or other responsible personnel is responsible for explaining the nature and purpose of the study as well as other study-related matters to subjects, using the written information, and for obtaining their full understanding and written consent to participate in the study of their own free will.
- The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign, [unique to Japan: seal,] and date the written information.
- Informed consent must be obtained by the time that the first observations/examinations of the present study, before the initial administration, are performed.
- The investigator or other responsible personnel must give a copy of the signed [unique to Japan: or sealed] consent form to the subject with the written information and store the original appropriately in accordance with the rules at the study center concerned.
- The investigator or other responsible personnel should note the following when obtaining consent from subjects:
  - No subject may be subjected to undue influence, such as compulsory enrollment into a study.
  - The language and expressions used in the written information should be as plain and understandable as possible for subjects. Subjects should be given the opportunity to ask questions and receive satisfactory answers to the inquiry, and should have adequate time to decide whether or not to participate in the study. Written information should not contain any language or contents that causes the subject to waive or appears to waive any legal rights, or that releases/mitigates or appears to release/mitigate the study center, the investigator/sub-investigator, collaborators, or the sponsor from liability for negligence.

The signed consent forms will be retained by the investigator and made available (for review only) to the study monitor and auditor upon request.

8.2.3.2 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information

1. The investigator or other responsible personnel will immediately inform the subject orally whenever new information becomes available that may be relevant to the subject's consent or may influence the subject's willingness to continue participation in the study (e.g., report of serious adverse drug reactions). The communication should be documented in the subject's medical records, and it should be confirmed whether the subject is willing to remain in the study or not.
2. If the investigator recognizes the necessity to revise the written information in the terms and conditions applicable to paragraph 1, the written information should be revised immediately based upon the newly available information, and be re-approved by the IRB/IEC.

3. The investigator or other responsible personnel should obtain written informed consent to continue participation in the study with the revised written information defined in paragraph 2, even if subjects are already informed of the relevant information orally. The investigator or other responsible personnel who provided explanations (including collaborators who gave supportive information, if applicable) and the subject should sign [unique to Japan: or seal] and date the informed consent form, or write down his/her name, place a personal seal, and date the form. The investigator or other responsible personnel should give a copy of the signed or sealed informed consent form to the subject who had given consent with the written information and store the original appropriately as done for the previous informed consent.

8.2.4 Subject Confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Such medical information may be given only after approval of the subject to the subject's physician or to other appropriate medical personnel responsible for the subject's well-being.

The sponsor, its board members or its employee shall not disclose any confidential information on subjects obtained during the performance of their duties in the clinical study without justifiable reasons.

All individuals and organizations involved in the study must pay very careful attention to protect subjects' privacy with appropriate measures, for example, by prohibiting the use of any private information that may identify a subject (e.g., name or address). These details shall be processed in accordance with the applicable laws such as Personal Information Protection Law and regulatory requirement(s).

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to subject's privacy due to direct access to source documents, or from other sources, they may not leak the content to third parties.

8.3 Administrative Matters

8.3.1 Arrangement for Use of Information and Publication of the Clinical Study

Information concerning the study drug, patent applications, processes, unpublished scientific data, the Investigator's Brochure and other pertinent information is confidential and remains the property of the sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The investigator or other responsible personnel may use this information for the purpose of the study only. It is understood by the investigator that the sponsor will use the information obtained during the clinical study in connection with the clinical development of the study drug and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he/she has an obligation to provide the sponsor with all data obtained during the study.

The study will be considered for publication or presentation at (scientific) symposia and congresses. The investigator or other responsible personnel will be entitled to publish or disclose the data generated at their respective study center only after having all transcripts, texts of presentations, and abstracts related to the study reviewed by sponsor at least 90 days prior to the intended submission for publication or any other disclosure. This is necessary to prevent proprietary information and/or knowledge protected by a patent from undue premature disclosure. In addition, this is in no way intended to restrict publication of facts or opinions formulated by the investigator or other responsible personnel. The sponsor will inform the investigator in writing of any objection or question arising within 30 days of receipt of the proposed publication material. After agreement between investigator or other responsible personnel and sponsor, the manuscript is free for publication.

8.3.2 Retaining Documents and Records Related to the Clinical Study

The sponsor will provide the investigator or other responsible personnel and/or study center with the following:

- Study protocol (and amendments, where applicable)
- Investigator's Brochure (and amendments, where applicable)
- eCRFs and other related documents, SAE report
- Study drug with all necessary documentation
- Study contract

In order to start the study, the investigator and/or study center is required to provide the following documentation to the sponsor:

- Signed Investigator's Statement in this protocol and eCRF
- Current curricula vitae (CVs) of all investigators
- List of sub-investigators and collaborators
- IRB/IEC approval of the protocol, protocol supplement (if applicable) including a membership list with names and qualification (copy)
- Instruction and decision of the head of the study center (if applicable)
- Study contract and memorandum
- Laboratory normal reference ranges (including modification and amendment)

At the end of the study, the sponsor is responsible for the collection of:

- Unused CRFs (laboratory test slips) and other study documentation,
- Unused study drug (if applicable)

The investigator will archive all study data (e.g., subject identification code list, source documents, CRFs (laboratory test slips), and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

The sponsor will notify the investigator or other responsible personnel if the NDA/ marketing authorization application (MAA)/NDA is approved or if the IND/IMPD/NDA is discontinued.

The investigator or other responsible personnel agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

Data generated by the methods described in the protocol will be recorded in the subjects' medical records and/or study progress notes. All data will be entered into CRFs supplied for each subject.

In Japan:

The records to be retained at the study centers are the ones listed as essential documents in GCP. These records shall be retained by the head of the study center or the record keeper designated by the head until notice issued by the sponsor on completion of the retention period is received. These documents are also subject to direct access and should be provided upon request from the sponsor or regulatory authorities.

The following are the major documents to be retained at the study center.

Source documents (clinical data, documents, and records for preparing the eCRF)

1. Hospital records, medical records, test records, memoranda, or check lists for evaluation, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, subject files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as subject registration forms, laboratory test slips including central measurement, worksheets/forms specified by the sponsor [e.g., patient questionnaire administered during CPK monitoring, Herpes Zoster (shingles) Worksheet], records of clinical coordinators, and records related to the clinical study selected from those verified in other departments or hospitals.
2. Contracts, written informed consent forms, written information, and other documents or their copies prepared by the study personnel.
   A letter of request for clinical study (including a request for continuation/amendment), letter of request for review, notice of clinical study contract, clinical study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), CVs of investigators, list of sub-investigators, list of signatures and print of seals (copy), and electronic media storing the eCRF data, etc.
3. The protocol, documents obtained from the IRB related to the adequacy of conducting the clinical study by the head of the study centers, documents obtained from the IRB related to the adequacy of conducting a clinical study whose period exceeds one year or the adequacy of continuously conducting the clinical study from which information on adverse drug reactions is obtained, and other documents obtained.
   An agreed-upon protocol (including revisions), Investigator's Brochure (including revisions), SAP for the investigator, materials and information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE

reports, etc.), SOP for the IRB/IEC, the list of names of the IRB/IEC members, materials for IRB/IEC review (including continuous deliberation), IRB/IEC review records (including continuous deliberation), and the review result report of the IRB/IEC (including continuous deliberation), etc.

4. Records of control for study drugs and other duties related to the clinical study
   Procedure for controlling the study drugs, drug inventory and accountability record, vouchers for the receipt and return of the study drugs, and other records of the prescriptions for concomitant medications
5. The documents of the Independent DSMB (minutes, SOP and others) shall be retained by the sponsor.

Unique to Korea and Taiwan: The investigator and the study center will retain the documents and records related to the clinical study in compliance with the applicable laws and regulations. The investigator and the study center should take measures to prevent loss or disposal of these records during the period when the records must be retained.

8.3.3 Protocol Amendment and/or Revision

Any changes to the study that arise after approval of the protocol must be documented as protocol amendments and/or revisions. Depending on the nature of the amendment and/or revisions, either IRB/IEC (if applicable) approval or notification is required. The changes will become effective only after the approval of the sponsor, the investigator, and the IRB/IEC (if applicable) [unique to Japan: followed by the approval of the head of the study center].

8.3.4 Insurance of Subjects and Others

If a subject suffers any study-related injury, the sponsor will compensate appropriately according to the severity and duration of the damage. However, if it was caused intentionally or was due to gross negligence by the study center, the sponsor will consult with the study center about handling the injury, based on the agreed study contract.

Compensation for study-related injury is provided by the following procedures:

1. If a subject incurs an injury as a result of participation in the clinical study, the study center should provide medical treatment and other necessary measures. The sponsor/delegated CRO should be notified of the injury.
2. When the subject claims compensation from the study center for the above study-related injury, or such compensation may be claimed, the study center should immediately communicate the fact to the sponsor/delegated CRO. Both parties should work together towards compensation settlement.
3. The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the clinical contract.

4. The sponsor shall make an arranging for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

8.3.5 Signatory Investigator for Clinical Study Report

ICH E3 guidelines recommend and EU Directive 2001/83/EC requires that a final study report which forms part of a marketing authorization application be signed by a coordinating (principal) investigator. The coordinating investigator will have the responsibility to review the final study results to confirm to the best of his/her knowledge it accurately describes the conduct and results of the study. A coordinating investigator will be selected from the participating investigators by the sponsor prior to database lock.

9 QUALITY ASSURANCE

The sponsor is implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that studies are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

The Sponsor or Sponsor's designee may arrange to inspect/audit the clinical study at any or all study centers. The auditor is independent from the clinical monitoring and project management team at the Sponsor. The audit may include on-site review of study-related documents/records, eCRFs, and source documents. Direct access to these documents will be required by the auditors.

10 STUDY ORGANIZATION

10.1 Independent Data and Safety Monitoring Board (DSMB)

An independent DSMB will review safety data, make a decision from the safety perspective on whether to continue or stop the study or modify the protocol, and provide the sponsor with recommendations. The DSMB should follow the procedures separately defined in details, including the frequency of meetings and data review.

10.2 Other Evaluation Committee(s)

Not applicable.

10.3 Other Study Organization

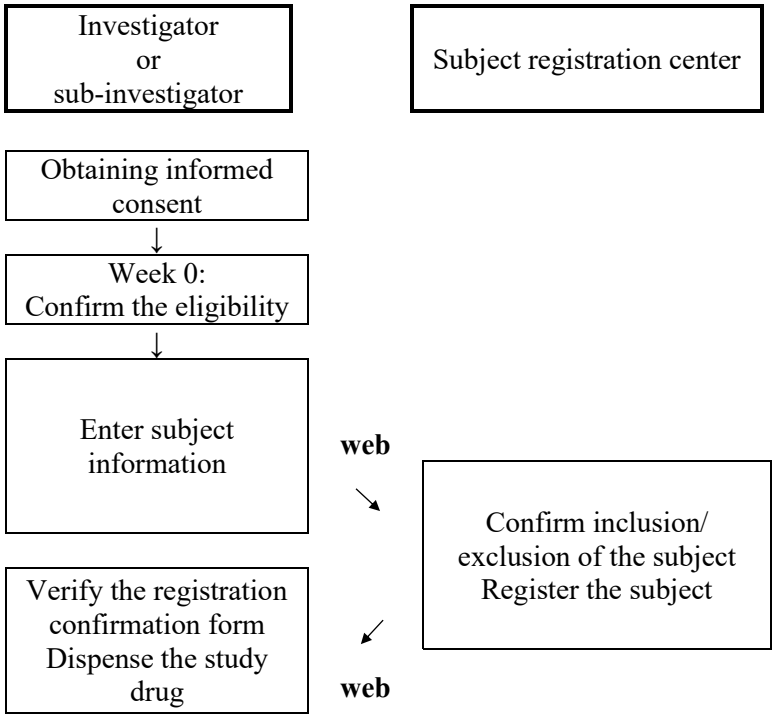
See the Appendix.

10.4 Registration of Subjects

[Subjects who transferred from study RAJ1]

The investigator or sub-investigators are responsible for conducting survey on demographics of the candidate subjects and obtaining their written consent. The investigator or sub-investigators should confirm whether inclusion/exclusion criteria are met, and make necessary entries in the case registration form on the web-based registration system. The registration center will confirm the fulfillment of inclusion/exclusion criteria based on the case registration information received and inform the study centers of the case inclusion or exclusion via the web-based registration system. The investigator or sub-investigators will dispense the study drug to the subject who is considered "eligible" for the study registration.

Flow Chart of Subject Registration (for subjects who transferred from study RAJ1):



<Subject registration center>
In Japan:
URL: [redacted]
Service available: Everyday (365 days, 24 hours)
Help desk TEL: [redacted], FAX: [redacted]
(Monday to Friday: 9:00-18:00, except national holidays, and 29 December to 4 January)

[Subjects who transferred from studies RAJ3 or RAJ4]

The investigator or sub-investigators are responsible for conducting survey on demographics of the candidate subjects and obtaining their written consent. The investigator or sub-investigator should confirm whether inclusion/exclusion criteria are met, and make necessary entries in the case registration form on the web-based registration system for the Week 52 visit of the studies RAJ3 or RAJ4. After the registration is confirmed, the investigator or sub-investigator will dispense the study drug to the subject who has completed tests and observations scheduled for Week 0.

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12 APPENDICES

APPENDIX <1>: LIST OF PROHIBITED CONCOMITANT MEDICATION

- ✓ **Biologic DMARDs**

  Etanercept, anakinra, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab, certolizumab pegol, denosumab, sarilumab

- ✓ **Non-biologic DMARDs***

  Subjects who transferred from study RAJ1

  MTX, salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib

  Subjects who transferred from study RAJ3

  Non-biologic DMARDs other than those used concomitantly in study RAJ3

  Subjects who transferred from study RAJ4

  Salazosulfapyridine, gold, *D*-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib, baricitinib

  *: Topical drugs other than those for the treatment of RA may be used concomitantly.

- ✓ **Other drugs used in the treatment of RA**

  Cyclosporine, cyclophosphamide, azathioprine, minocycline, etc.

- ✓ **Corticosteroids****

  Prednisolone, hydrocortisone, hydrocortisone succinate, methylprednisolone, methylprednisolone succinate, triamcinolone, triamcinolone acetonide, dexamethasone, betamethasone, etc.

  **: It is prohibited to use oral corticosteroids at doses that exceed the amount used from the initiation of studies RAJ1, RAJ3, or RAJ4 to the initiation of administration of the study drug in this extension study at a daily dose of prednisolone equivalent. Intra-articular, intravenous, intramuscular, or endorectal administration is prohibited. However, suppositories for anal diseases may be used concomitantly.

- ✓ **Oral morphine*****

  Morphine hydrochloride, morphine sulfate

  ***: Oral morphine at doses exceeding 30 mg/day (or equivalent amount of opioid analgesics)

- ✓ **CYP3A substrates with narrow therapeutic range**

  Dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide, etc

- ✓ **Live or live attenuated virus vaccines**

  Freeze-dried live attenuated measles vaccine, freeze-dried live attenuated mumps vaccine, freeze-dried BCG vaccine, freeze-dried live attenuated varicella vaccine, freeze-dried live attenuated rubella vaccine, live oral poliomyelitis vaccine, etc.

- ✓ **Articular cartilage protective agents**

  Purified sodium hyaluronate (intra-articular injection), chondroitin sulfate (excluding eye drops)

APPENDIX <2>: LABORATORY TESTS

	Visit*	Collecting tube (unique to Japan**)	Parameters to be analyzed
Hematology	[Subjects who transferred from RAJ1] Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits [Subjects who transferred from RAJ3 or RAJ4] Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	2 mL vacutainer tube containing EDTA-2K	Hemoglobin, hematocrit, RBC, WBC, differential WBC, platelet count
Biochemistry	[Subjects who transferred from RAJ1] Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits [Subjects who transferred from RAJ3 or RAJ4] Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	9 mL vacutainer tube containing separating medium For glucose: 2 mL vacutainer tube containing NaF+EDTA-2Na For β-D glucan: 3 mL container for blood endotoxin/β-D-glucan	Na, K, Ca, Cl, Mg, HCO_3, BUN, phosphorus, glucose, creatinine, ALP, AST (GOT), ALT (GPT), γ-GTP, TBL, total protein, albumin, uric acid, CPK, LDH, serum amylase, β-D-glucan, eGFR
Biochemistry (during CPK monitoring)	At the time of CPK monitoring	4 mL vacutainer tube containing the separating medium	CK-MB, troponin T, aldolase

Fasting lipid profile test	[Subjects who transferred from RAJ1] Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits [Subjects who transferred from RAJ3 or RAJ4] Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	(Included among biochemical tests)	Total cholesterol, LDL, HDL, TGs
Hepatitis DNA test	[Subjects who transferred from RAJ3 or RAJ4] Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	5 mL vacutainer tube containing the separating medium	HBV-DNA assay
Urinalysis	[Subjects who transferred from RAJ1] Week 0, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits [Subjects who transferred from RAJ3 or RAJ4] Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	For urinalysis: 10 mL light-blocking urine collection tubes For urine microscopic analysis: 10 mL urine collection tubes	pH, specific gravity, protein, glucose, keton bodies, bilirubin, occult blood, sediment

Pregnancy testing	Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	Urine pregnancy testing kit (in-hospital testing) As necessary, serum pregnancy testing (included among biochemistry tests)	Human chorionic gonadotropin (hCG)
Acute phase reactants	[Subjects who transferred from RAJ1] Week 0, Week 2, Week 4, Week 8, Week 12, Week 24, Week 28, Week 32, Week 36, Week 40, Week 44, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits [Subjects who transferred from RAJ3 or RAJ4] Week 0, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, Week 132/end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	(Included among biochemistry tests)	CRP
		In-hospital testing	ESR
Pharmacodynamics	Week 0, Week 48, Week 96 /end of treatment/early termination, end of study (at time of follow-up), Unscheduled Visits	2 mL vacutainer tube containing EDTA-2K	Lymphocyte subsets

* Necessary hospital visits will differ from subject to subject because the duration of participation in this study will differ depending upon the subject. After Week 132, tests will be performed every 12 weeks (only the pharmacodynamics tests will be performed every 48 weeks after Week 96.)

** Types of collecting tube used at Korea and Taiwan are described in the laboratory handling manual.

APPENDIX <3>: EVENTS ALWAYS CONSIDERED TO BE SERIOUS

If any of the following events occurs during the study, it should be regarded as a SAE and must be reported in accordance with Section 5.5.5, Reporting of Serious Adverse Events (SAEs).

- Acute hepatic failure
- Renal failure acute
- Acute respiratory failure
- Agranulocytosis
- Anaphylactic reaction, anaphylactic shock
- Malignant tumor
- Aplastic anaemia
- Endotoxic shock (confirmed or suspected)
- Confirmed or suspected transmission of infectious agents by marketed product
- Congenital anomalies
- Hepatic necrosis
- Malignant hypertension
- Pulmonary fibrosis
- Pulmonary hypertension
- Sclerosing syndromes
- Convulsion (only central neurological seizure)
- Torsades de pointes
- Toxic epidermal necrolysis
- Ventricular fibrillation

Note: Hy's Law cases are considered as SAEs.

See Appendix 6 "Liver Safety Monitoring and Assessment."

APPENDIX <4>: CRITERIA FOR THE CLASSIFICATION OF GLOBAL FUNCTIONAL STATUS IN RA (1991 REVISED CRITERIA)

[Classification of Global Functional Status in RA: Class]

Class I	Complete functional capacity with ability to carry on all usual duties without handicaps
Class II	Functional capacity adequate to conduct normal activities despite handicap or discomfort or limited mobility of one or more joints
Class III	Functional capacity adequate to perform only few or none of the duties of usual occupation or of self-care
Class IV	Largely or wholly incapacitated with patient bedridden or confined to wheelchair, permitting little or no self-care

[Hochberg et al, 1992]

APPENDIX <5>: CLASSIFICATION OF DISEASE STAGE/PROGRESSION OF RA

Stage I: Early	1. X-rays do not show destruction of bone. 2. X-rays may show radiological osteoporosis.
Stage II: Intermediate	1. X-rays show osteoporosis which may or may not be accompanied by mild destruction of subchondral bone. Mild bone destruction may be observed. 2. Joint mobility may be limited, but there is no joint deformation. 3. Muscle atrophy surround the joint is present. 4. Lesions in extra-articular soft tissue, such as nodules and tenosynovitis, may be present.
Stage III: Advanced/Progressive	1. In addition to osteoporosis, X-rays show destruction of bone and cartilage. 2. Joint deformities such as subluxation, ulnar displacement, or hyperextension are present, unaccompanied by fibrous or bony ankylosis. 3. Exaggerated muscle atrophy is present. 4. Lesions in extra-articular soft tissue, such as nodules and tenosynovitis, may be present.
Stage IV: Late Stage	1. Fibrous or bony ankylosis is present. 2. Other symptoms meet criteria for Stage III.

[Steinbrocker O. 1949]

APPENDIX <6>: LIVER SAFETY MONITORING AND ASSESSMENT

If laboratory testing for a subject enrolled in a study and receiving the study drug reveals > 3 × ULN elevation in serum aminotransferases (ALT, AST) or TBL elevation to > 2 × ULN, the investigator/sub-investigator should repeat the liver function test including at least the 4 parameters ALT, AST, ALP, and TBL. The retest is to be performed between 48 hours and 72 hours after notification of the test results. For studies for which a central laboratory is used, alerts will be generated by the central lab regarding moderate and marked liver abnormality to inform the investigator or other responsible personnel, and sponsor. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction by the investigator or sub-investigator.

Definition of Hepatic Function Abnormal

Confirmed hepatic function abnormal will be characterized as moderate (hepatocellular failure type or cholestasis type) or marked (mixed type) based on the ULN as follows:

	ALT or AST		Total bilirubin
Moderate **Hepatocellular failure type or cholestasis type**	>3 × ULN	or	>2 × ULN
Marked **Mixed type**	>3 × ULN	and	>2 × ULN

In addition, the subject with any of the following should be considered to have marked (severe) hepatic function abnormal.

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and INR > 1.5
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, pyrexia, rash and/or eosinophilia (> 5%).

If the investigator or sub-investigator may determine that abnormal liver function results, other than as described above, quality as moderate or marked abnormalities, he/she should conduct additional monitoring and follow-up.

Follow-up Procedures

Confirmed moderate and marked hepatic function abnormal should be thoroughly characterized by obtaining appropriate expert consultations, detailed pertinent history, physical examination, and laboratory tests by the investigator or sub-investigator. The investigator should complete the liver abnormality case report form (LA-CRF) or an appropriate document. Subjects with confirmed abnormal liver function testing should be followed as described below by the investigator or sub-investigator.

If moderate liver abnormality is confirmed, re-testing should be performed every 2 to 3 times a week. If the abnormal test values stabilize or the patient is asymptomatic after the study drug is withdrawn, re-testing should be performed at a frequency of once a week or less.

Marked hepatic function abnormal, in the absence of another etiology, may be considered an important medical event and reported as a SAE by the investigator. The sponsor should be contacted and informed of all subjects for whom marked hepatic function abnormal possibly attributable to study drug is observed.

To further assess the findings of hepatic function abnormal, the investigator or sub-investigator is expected to:

- Obtain a more detailed history of symptoms and prior or concurrent diseases. Symptoms and new-onset diseases should be recorded as “AEs” on the AE page of CRF. Illnesses and conditions such as hypotensive events, and decompensated cardiac disease that may lead to secondary liver abnormalities should be noted. Non-alcoholic steatohepatitis (NASH) is seen in obese hyperlipoproteinemic and/or diabetic patients and may be associated with fluctuating serum aminotransferase (ALT, AST) levels. The investigator or sub-investigator should ensure that the medical history form captures any illness that pre-dates study enrollment that may be relevant in assessing hepatic function.
- Obtain a history of concomitant drug use (including non-prescription medication, complementary and alternative medications), alcohol intake, drug abuse, and special diets. Medications, including dose, should be entered on the concomitant medication page of CRF. Information on alcohol, other substance use, and diet should be entered into the LA-CRF or an appropriate document.
- Obtain a history of exposure to environmental chemical agents.
- Based on the subject’s history, other testing may be appropriate, including:
  - Acute viral hepatitis subtypes (A, B, C, D, E, or other infectious agents)
  - Ultrasound or other imaging to assess biliary tract disease
  - Other laboratory tests including INR and direct bilirubin
- Consider gastroenterology or hepatology consultations.
- Enter results for any additional testing and possible etiology into the LA-CRF or an appropriate document.

Study Discontinuation

In the absence of an explanation for liver function test raised, such as viral hepatitis, pre-existing or acute liver disease or exposure to other agents associated with liver injury, the subject may be discontinued from the study by the investigator. The investigator may determine that it is not in the subject's best interest to continue study enrollment. Discontinuation of treatment should be considered if any of the following applies:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5)
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

In addition, if close monitoring of a subject with moderate or marked hepatic function abnormal is not possible, the study drug should be discontinued by the investigator.

Reference

See "Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation," published by the FDA in July 2009.

APPENDIX <7>: STUDY PROTOCOL VER. 1.3 (EXCERPT)

This study has been conducted as an extension study of the Phase IIb Study (RAJ1). After completion of study RAJ1, Phase III studies (studies RAJ3 and RAJ4) were planned based on the results of study RAJ1. In association with these studies, the dosages of the study drug in this study were reconsidered, and the protocol was revised to make it possible for subjects who have completed the Phase III studies to also participate in the study.

The study protocol before the revision (ver. 1.3, supplements 1 to 6 of protocol ver. 1.3) is shown below.

SYNOPSIS

Title of Study	Phase IIb Extension Study of ASP015K – Open-Label Extension Study in Rheumatoid Arthritis Patients Who Have Completed Phase IIb Study of ASP015K – (Protocol Number: 015K-CL-RAJ2)
Study Objectives	This is an extension study conducted in RA patients who have completed the Phase IIb Study of ASP015K [015K-CL-RAJ1] (hereinafter referred to as study RAJ1) to investigate the safety and efficacy of long-term administration of ASP015K. Another objective of this study is to devise rescue measures for providing the active drug to patients who participated in the Phase IIb Study of ASP015K, as described in "Guidelines on methodology for clinical assessment of antirheumatic drugs" (PFSB Notification No. 0217001, dated 17 February, 2006).
Design and Methodology	This study is an extension of study RAJ1 conducted as an open-label multicenter study in RA patients who completed study RAJ1. Patients who meet all of the inclusion criteria and do not fall under any of the exclusion criteria will be registered and will receive oral ASP015K 50 mg QD after breakfast as the starting dose. Subjects who have no safety problems but show lack of efficacy may later increase the dose to 100 mg/day. After the dosage increase, the dosage may be reduced from 100 mg/day to 50 mg/day at the discretion of the investigator or sub-investigator. The dose level will be redetermined after the results of the dose finding study (study RAJ1) have been obtained. Because this study will end at the point in time where the Phase III study begins, the duration of treatment with the study drug will differ depending upon the subject (planned maximum duration of treatment: 132 weeks). To prevent purposeless continuation of dosing without effect, the investigator or sub-investigator will assess each subject for efficacy and safety at each visit, confirm the appropriateness of continued administration for each individual, and decide whether or not to continue dosing.
Selection Criteria	<Inclusion Criteria> Subject is eligible for the study if all of the following apply: 1. Subject has received a full explanation of the study drug and this study in advance, and written informed consent to participate in the study has been obtained from the subject himself/herself. 2. Subject has completed treatment with the study drug in study RAJ1 as specified in the protocol and has also completed the tests and assessment performed at the study visit in Week 16. 3. The subject himself/herself wishes to continue taking the study drug, and the investigator or sub-investigator deems continued administration to be necessary or appropriate.

	4. Subject must be willing and able to comply with the study requirements. <Exclusion Criteria> Subject will be excluded from participation if any of the following apply: 1. Subject has developed an adverse reaction related to the study drug in study RAJ1 and the risks of continuing treatment with this drug are expected to outweigh the benefits. 2. There were abnormal findings in the x-ray taken at Week 0, and an acute or chronic infection, tuberculosis infection, or malignant tumor is suspected. 3. Subject has received live or live attenuated virus vaccination within 30 days prior to the first dose of study drug. 4. Subject is a hepatitis B virus or hepatitis C virus carrier or has a history of a positive test for HIV infection. 5. Subject has concurrent autoimmune disease (except Sjogren's syndrome) other than RA or a history of it. 6. Subject has a clinically significant infection or disease (requiring hospitalization or parenteral therapy). 7. Subject has a history of any malignant tumor, except for successfully treated basal or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix, or subject has a concurrent malignant tumor. 8. Subject has taken one of the following drugs between the end of the assessments at Week 12 of study RAJ1 and the start of treatment with the study drug in this extension study. • Biologic DMARD (biologic for the treatment of RA): Etanercept, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab • Non-biologic DMARD: MTX, salazosulfapyridine, gold, D-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib (However, topical drugs other than those for the treatment of RA may be used concomitantly.) • Other drugs used in the treatment of RA: Cyclosporine, cyclophosphamide, azathioprine, minomycin, etc. 9. Subject has received plasma exchange therapy between the end of the assessments at Week 12 of study RAJ1 and the start of treatment with the study drug in this extension study. 10. Subject has received any of the following CYP3A substrates with narrow therapeutic range within 14 days prior to starting treatment with the study drug: Dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, and temsirolimus 11. Subject has any of the following laboratory values at the study visit in Week 12 of study RAJ1: • Hemoglobin < 10 g/dL • WBC count < 3000/μL • Absolute neutrophil count (ANC) < 2000/μL • Absolute lymphocyte count < 800/μL • Platelet count < 100000/μL • ALT ≥ 2 × ULN • AST ≥ 2 × ULN • TBL ≥ 1.5 ×ULN • Estimated glomerular filtration rate (GFR) ≤ 40 mL/min, as measured by the Modification of Diet in Renal Disease (MDRD) method • CPK > 1.5 ×ULN • β-D-glucan ≥ 11 pg/mL 12. Subject has symptomatic CPK elevation (CPK > 1.5 × ULN with myalgia, muscular weakness, or severe unusual muscle twitching) at the study visit in Week 12 of study RAJ1.

	13. Subject is found to have symptoms of myopathy such as myalgia, muscular weakness, and severe unusual muscle twitching regardless of CPK level that persist for at least 2 weeks or that worsen rapidly in less than 2 weeks, at study visit in Week 12 of study RAJ1. 14. Subject has concurrent cardiac failure with NYHA classification of Class III or higher, or a history of it. 15. Subject has concurrent long QT syndrome or history of it. Subject exhibits QT interval prolonged at the study visit in Week 0. 16. Subject has any ongoing severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, or infectious disease, or any ongoing illness which would make the subject unsuitable for the study as determined by the investigator/sub-investigator. 17. Subject has any condition possibly affecting oral absorption (e.g., gastrectomy or clinically significant diabetic gastroenteropathy). 18. Subject has received surgical treatment and the investigator/sub-investigator judges there to be residual effects of surgical stress. Or, the subject plans to have surgical treatment that will require hospitalization during the study period or surgery on the joints. 19. The subject is a woman who is pregnant or might be pregnant, is nursing, wishes to conceive within 60 days after end of treatment drug, or for whom the possibility of pregnancy cannot be ruled out as a result of the pregnancy test given at Week 0. 20. The subject is a man who cannot practice proper contraception with a condom from the time informed consent is given until 90 days after end of treatment, or the subject is a woman who could become pregnant and cannot practice proper contraception with a condom from the time informed consent is given until 60 days after end of treatment. 21. The subject has been judged unsuitable to participate in the study for other reasons by the investigator/sub-investigator.
Discontinuation Criteria	The investigator/sub-investigator should discontinue administration of the study drug if any of the following occurs: 1. Subject develops an AE, where continued administration of the study drug is deemed not in the subject's best interest by the investigator and/or the sub-investigator. 2. Any of the following laboratory values as confirmed by a re-test within 72 hours of the initial observation: • Hemoglobin < 8.0 g/dL • WBC count < 2000/μL • ANC < 1000/μL • Absolute lymphocyte count < 500/μL • Platelet count < 50000/μL • CPK > 2000 IU/L 3. Symptomatic CPK elevation, defined as CPK > 1.5 × ULN with myalgia, muscular weakness, or severe unusual muscle twitching. 4. Any event of myopathy defined as myalgia, muscular weakness, and severe unusual muscle twitching regardless of CPK level that persists for at least 2 weeks or that worsens rapidly within 2 weeks. 5. If a β-D-glucan test shows a value of 11 pg/mL or higher during the treatment period. (However, if further testing shows there to be no problem, administration of the study drug can be continued.). 6. Subject withdraws consent. 7. The study drug is not sufficiently effective (ACR20 response rate based on baseline value for study RAJ1 is not reached in 12 weeks of continuous treatment) and a change in treatment method is deemed by the physician to be in the subject's best interest.

	8. Subject uses or requires a prohibited concomitant medication during the study. Subject uses or requires a prohibited concomitant therapy during the study. 9. Subject has been an interruption in treatment with the study drug (drug holiday) exceeding the following criteria: • The maximum possible drug holiday will be for 4 consecutive weeks or less. • Up to 2 drug holidays per year may be taken. Moreover, they must be separated by an interval of 16 weeks or more. 10. Subject has missed doses of the study drug in excess of the following criteria (excepting suspension of dosing at the physician's discretion): • Subject has missed 7 or more daily doses in the 4 weeks prior to the study visit, up to Week 48 visit (excluding the Week 2 visit). • Subject has missed 21 or more daily doses in the 12 weeks prior to the study visit in or after Week 60. 11. Subject is deemed lost to follow-up by the investigator/sub-investigator (subject can no longer come to the study center; subject can no longer be contacted, etc.). 12. It comes to light after the administration of the first dose of study drug that the inclusion criteria were not met at the time of case enrollment or that criteria for exclusion were met. It comes to light that there was some other major deviation from the protocol. 13. Investigator or sub-investigator decides it is in the subject's best interest to discontinue. 14. The sponsor has requested that administration of the study drug be discontinued because of a safety problem in a particular subject, or the sponsor has decided to discontinue the study altogether. The Appendix 6 entitled "Liver Safety Monitoring and Assessment" describes liver function tests raised providing grounds for considering discontinuation. Refer to this if liver function tests raised is observed.
Test Drug **Mode of Administration:** **Dose:** **Duration of Treatment:**	Test drug: ASP015K 10 mg and 30 mg tablets Dose: (starting dose) 50 mg/day, (escalated dose) 100 mg/day The starting dose will be 50 mg/day. The dose may be increased to 100 mg QD will be permitted at the point in time as the following 2 conditions are met. 1) When the DAS28-ESR score is 3.2 or higher (corresponding to moderate disease activity or high disease activity) on the study visit day specified in the protocol (at 2 or more consecutive visit days up to Week 12) 2) When the investigator or sub-investigator judges there to be no problem with safety for the subject in the assessment performed on the study visit day on which the DAS28-ESR of 3.2 score or higher was exhibited Moreover, after dose escalation, the dose may again be reduced from 100 mg/day to 50 mg/day at the discretion of the investigator or sub-investigator on the visit day specified in the protocol. The investigator or sub-investigator will decide whether or not to reduce the dosage on the basis of the following criterion. • If an AE with an NCI-CTCAE grade classification of Grade 2 or higher has developed. Mode of administration: To be orally administered QD after breakfast. The first dose should be given at each study center on the day of the Week 0 visit after all of the necessary assessments and tests have been completed. Duration of treatment: Because this study will end at the point in time where the Phase III study begins, the duration of treatment will differ depending upon the subject (planned maximum duration of treatment: 132 weeks). To

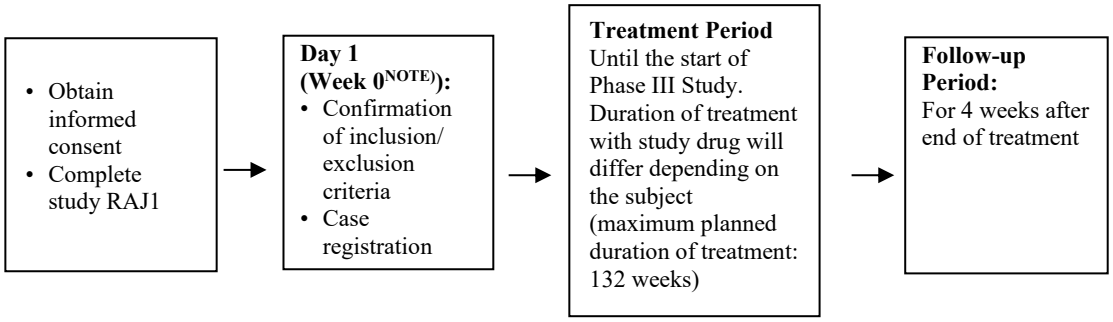
	prevent purposeless continuation of dosing without effect, the investigator or sub-investigator will assess each subject for efficacy and safety at each visit, confirm the appropriateness of continued administration for each individual, and decide whether or not to continue dosing.
Comparative drug **Mode of Administration:** **Dose:** **Duration of Treatment:**	Not applicable.
Concomitant Treatment	(1) The following concomitant medications and complimentary alternative treatments are prohibited as described. ➢ Administration or use of the following drugs and therapies will be prohibited from the end of the assessments in Week 12 of study RAJ1 until the start of administration of the study drug in this extension study, as well as throughout the treatment period. 1) Biologic DMARDs: etanercept, adalimumab, golimumab, infliximab, tocilizumab, abatacept, rituximab, certolizumab pegol 2) Non-biologic DMARDs: MTX, salazosulfapyridine, gold, D-penicillamine, leflunomide, lobenzarit, actarit, tacrolimus, mizoribine, bucillamine, iguratimod, tofacitinib (However, topical drugs other than those for the treatment of RA may be used concomitantly.) 3) Other drugs used in the treatment of RA: cyclosporine, cyclophosphamide, azathioprine, minomycin, etc. 4) Plasma exchange therapy ➢ Administration or use of the following medications and therapies will be prohibited from the end of the assessments in Week 12 of study RAJ1 until the start of study drug administration in this extension study, as well as throughout the treatment period and follow-up period. 5) Live or live attenuated virus vaccines ➢ Administration of the following medications is prohibited within 14 days prior to the start of treatment with the study drug, as well as throughout the treatment period and follow-up period. 6) CYP3A substrates with narrow therapeutic range: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, and temsirolimus. ➢ Concomitant use of the following drugs and therapies will be prohibited throughout the treatment period. 7) Oral corticosteroids in doses that exceed the amount used from the start of study RAJ1 to the start of administration of the study drug in this extension study, in daily dose of prednisolone or equivalent 8) Intra-articular, intravenous, intramuscular, or endorectal corticosteroids (However, suppositories for anal diseases may be used concomitantly.) 9) Oral morphine in doses exceeding 30 mg per day (or equivalent amount of opioid analgesics) 10) Intra-articular administration of articular cartilage protective agents 11) Drainage of fluid accumulated in joint, local anesthesia of joint, and nerve block 12) St. John's wort and food products (including beverages) containing it ➢ Concomitant use of the following medications and therapies is prohibited throughout the treatment period and follow-up period. 13) Other study drugs, study drugs from post-marketing clinical studies, or medical devices being studied in clinical studies 14) Surgeries requiring hospitalization or surgical treatment of the joints.

	(2) Limited concomitant medications During the treatment period, the following medications may be used concomitantly at the discretion of the investigator or sub-investigator if they meet the following conditions for concomitant use (Both new administration and change in dosage/administration are permitted). 1) NSAIDs 2) Oral morphine (≤ 30 mg/day, or equivalent amount of opioid analgesics) 3) Acetaminophen – Conditions for concomitant use – • No changes in the dosage/administration of the drug are allowed within the period of 12 weeks. However, this shall exclude cases where the medication has caused an AE. Moreover, if, after discontinuation of the concomitant medication, it becomes apparent that the suspected medication was not the offending drug that caused the AE, administration may be resumed with the dose prior to discontinuation as the maximum dose. • The limited concomitant medications may not be used within 12 hours prior to the joint assessment performed at each study visit. (3) Rescue medications The following medications may be used only when needed to treat AEs or worsening of the primary disease. However, these medications may not be taken within 24 hours prior to the joint assessment at each study visit. 1) NSAIDs: Single use as needed, for a period of 3 days or less 2) Analgesics other than NSAIDs (acetaminophen, all-in-one cold and flu medications, etc.): For 7 consecutive days or less 3) Intra-articular administration of corticosteroids, intra-articular administration of articular cartilage protective agents, drainage of fluid accumulated in joint, local anesthesia of joint, and nerve block: Performed once every 24 weeks (on up to 2 joints), starting at or after the Week 12 study visit. However, joints on which intra-articular drug administration or rescue procedure has been performed will be assessed as showing disease activity (pain [tenderness]/swelling) after administration of the medication/therapy.
Endpoints (Safety)	• AEs • Vital signs (body temperature, pulse and blood pressure in sitting position) • 12-lead ECG • Laboratory Assessments
Endpoints (Efficacy)	The following items at each study visit • ACR 20 response rate • ACR 50 response rate • ACR 70 response rate • TJC (68 joints) • SJC (66 joints) • DAS28-CRP and DAS28-ESR • Percentage of subjects achieving DAS28-CRP score for remission • Percentage of subjects achieving ACR/EULAR score for remission ACR/EULAR remission is defined as meeting all 4 of the following criteria: o Tender Joint Count ≤ 1 o Swollen Joint Count ≤ 1 o CRP ≤ 1 mg/dL o SGA ≤ 1 cm (0-100 mm on a VAS scale) • Percentage of subjects with a SDAI score of ≤ 3.3 (SDAI remission) • PGA (VAS) • SGA (VAS) • Subject's assessment of pain (VAS) • FACIT-Fatigue score (excluding scores from Week 2 study visit and at end of

	study [at time of follow-up]) • HAQ-DI • SF-36v2® score (excluding scores from Week 2 study visit and at end of study [at time of follow-up]) • Percentage of subjects in EULAR response criterion of "Good Response" • Percentage of subjects in EULAR response criterion of "Moderate Response" • Percentage of subjects in EULAR response criterion of "Good Response" or "Moderate Response" • Incidence of subject withdrawal due to lack of efficacy
Statistical Methods	• In the assessment of efficacy and safety, the following will be calculated for continuous variables: number of subjects, mean, standard deviation, minimum, median, and maximum; categorical variables will be expressed as frequency and percentage. • AEs will be coded using the MedDRA. AEs occurring after administration of the study drug will be tallied for the entire study period and for each 3-month sub-period. • Laboratory test values (actual measured values and change from baseline), vital signs (actually measured values and diagram of change from baseline), and results of ECG assessment will be tallied at each time point. • Incidence of subject withdrawal due to lack of efficacy will be tallied for the entire study period and each 3-month sub-period. Other efficacy variables will be tallied at each time point.

FLOW CHART AND SCHEDULE OF ASSESSMENTS

Flow Chart



NOTE) The study visit in Week 0 in this extension study will coincide with the day of the visit in Week 16/end of study (follow-up) in study RAJ1.

Start and End of Study

Start of Study:	Point in time where informed consent is obtained from the first subject
End of Study:	Point in time where final assessment specified in protocol has been performed in the last subject
Treatment Period:	Period from the start of treatment to the end of the tests and assessments

Table 1. Schedule of Assessments

Schedule		**Treatment Period[c]**																				**Follow-up Period**	**Unscheduled Visit**
Visit Timing	**Week 0[b]**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**	**Week 108**	**Week 120**	**Week 132/ end of treatment /early termination[d]**	**End of study (Follow-up)[e]**	
Visit Day [r]	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**421**	**505**	**589**	**673**	**757**	**841**	**-[p]**	**28 days after end of treatment**	
Allowable range from specified date	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-[p]**	**±7**	
Assessment																							
Informed consent[a]	X																						
Inclusion/exclusion criteria	X																						
Demographics/ medical history	X																						
Weight	X	X	X	X	X			X			X			X	X	X	X	X	X	X	X	X	X[q]
Physical examination [f]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Vital signs	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Laboratory test (blood/urine) [g]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Fasting lipid profile test [h]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
CRP and ESR [i]	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Pregnancy test [j]	X*				X			X			X			X	X	X	X	X	X	X	X	X	X[q]
12-Lead ECG [k]	X													X				X			X		X[q]
Chest X-ray [l]	X																						X[q]
Disease activity assessment [m]																							
TJC/SJC	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
PGA and SGA (VAS)	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]

Schedule		**Treatment Period[c]**																				**Follow-up Period**	**Unscheduled Visit**
Visit Timing	**Week 0[b]**	**Week 2**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	**Week 48**	**Week 60**	**Week 72**	**Week 84**	**Week 96**	**Week 108**	**Week 120**	**Week 132/ end of treatment /early termination[d]**	**End of study (Follow-up)[e]**	
Visit Day [r]	**1**	**15**	**29**	**57**	**85**	**113**	**141**	**169**	**197**	**225**	**253**	**281**	**309**	**337**	**421**	**505**	**589**	**673**	**757**	**841**	**-[p]**	**28 days after end of treatment**	
Allowable range from specified date	**-**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±14**	**±14**	**±14**	**±14**	**±14**	**±14**	**-[p]**	**±7**	
Assessment																							
FACIT-Fatigue, SF-36®	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X[q]
HAQ-DI	X*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Assessment of AEs and SAEs [n]	X	→																			X	X	X
Confirm study drug prescriptions/ remaining drug residues[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Record concomitant medications and therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a. Be sure to obtain informed consent before beginning any of the procedures involved in the study. In principle, informed consent should be obtained at the Week 12 visit in study RAJ1.

b. Assessments and tests performed at Week 0 should be performed on the same day as the Week 16 at end of study (day of follow-up) in study RAJ1. For items marked with the * symbol, the results of the assessments and tests performed at Week 16/end of study (at time of follow-up) in study RAJ1 may be used.

c. From the time of the Week 48 visit onward, the subject should be contacted once a month to confirm the status of compliance with study drug dosing and the safety of the subject. Moreover, because this study will end at the point in time where the Phase III Study begins, the duration of the treatment period will differ depending upon the subject. Accordingly, the timing for the required visits to the study center will also differ from subject to subject. When administration of the study drug has ended, the assessments and tests scheduled to be performed at end of treatment and end of study (at time of follow-up) will be performed.

d. The assessments and tests to be performed at end of treatment should be performed promptly after administration of the study drug has ended. If administration of the study drug has been terminated early, the assessments and tests specified to be performed at end of treatment/early termination should

be performed within 2 days of the last dose of the study drug if possible. Moreover, even subjects who have had early termination during the scheduled treatment period should in principle visit the study center at end of study (at time of follow-up).

e. The assessments and tests scheduled for end of study (at time of follow-up) should be performed 28 days after the visit at end of treatment.

f. Confirmation of physical findings by questioning the subject during the physical examination should be performed at all study visits. A symptom directed physical examination for RA should also be performed at all study visits. See NOTE m with regard to the confirmation of RA symptoms.

g. **Hematology:** Hemoglobin, hematocrit, RBC, WBC, WBC with differential, platelet count; **Biochemistry:** Na, K, Ca, Cl, Mg, HCO_3, BUN, phosphorus, glucose, creatinine, ALP, AST (GOT), ALT (GPT), γ-GTP, TBL, total protein, albumin, uric acid, CPK, LDH, serum amylase, β-D-glucan (see Section 5.4.4.1 for procedure at time of CPK elevation); **Urinalysis:** pH, specific gravity, protein, glucose, keton bodies, bilirubin, occult blood, and sediment

h. Subject must fast for at least 8 hours prior to blood sampling for lipid profile (total cholesterol, low density lipoprotein [LDL], high density lipoprotein [HDL] and triglycerides [TGs]).

i. CRP and ESR tests will be performed at each study visit. CRP test will be performed by the Central Laboratory; ESR test should be performed by each study center.

j. A urine pregnancy test should be performed at the study visits every 12 weeks from Week 0 onward, as well as at end of treatment/early termination and end of study (at time of follow-up). If a urine pregnancy test is positive at any time, a negative serum pregnancy test is required for the subject to continue participation in the study. The pregnancy tests need not be performed if the possibility of pregnancy can clearly be ruled out, such as if the woman is postmenopausal and has not had a menstrual period for 1 year or more, or has had a hysterectomy, bilateral oophorectomy, etc.

k. The 12-lead ECG exams must be performed at the study visits every 48 weeks from Week 0 onward, as well as at end of treatment/early termination. If a cardiovascular AE is observed, a 12-lead ECG may be performed at any time as necessary, even in an unscheduled visit. Clinical interpretation of the results of the 12-lead ECG at Week 0 must be completed prior to the first dose of the study drug.

l. A chest X-ray will be taken during the study visit in Week 0. If a respiratory AE is observed, a chest X-ray may be taken at any time as necessary, even in an unscheduled visit.

m. Assessment of disease activity: **Physician** – TJC (68 joints), SJC (66 joints), PGA (VAS); **Subject** – SGA (VAS), subject's assessment of pain (VAS), Health Assessment Questionnaire – Disease Index (HAQ-DI), FACIT-Fatigue, and SF-36®.

n. AEs must be collected from the time of the administration of the first dose of study drug to the end of all assessments at end of study (at time of follow-up).

o. After all of the assessments and tests scheduled for Week 0 have been completed, the subjects will receive the first dose of the study drug at each study center.

p. If the study is terminated before the Week 48 visit, the specified date for the study visit at end of treatment will be the date of the previous study visit + 28 days (allowable range ±7 days). If the study is terminated in or after the Week 48 visit, the specified date for the study visit at end of treatment will be the date of the previous visit ±84 days (allowable range ±14 days).

q. For unscheduled visits, these assessments and tests should be performed only if clinically indicated as determined by the investigator.

r. In principle, the subject should visit the study center on the specified date. If it is not possible for subjects to visit the study center on the specified date, the date of the visit should be adjusted to the date closest to the reference date as possible.

(GPF 2.02)