# Phase III Study of ASP015K

# −A Randomized, Double-Blind, Placebo-Controlled Confirmatory Study of Efficacy and Safety of ASP015K in Patients with Rheumatoid Arthritis (RA) Who Had an Inadequate Response to MTX−

**ISN/Protocol 015K-CL-RAJ4**

## ClinicalTrials.gov Identifier: NCT02305849

## Date of Protocol: Version 5.0, dated 03 March 2017

**Sponsor: Astellas Pharma Inc. (API)**

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Created 3 March 2017 (Ver. 5.0)

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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, ICH Guidelines 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) inscribe in the bipartite agreement.

# II. CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL

Contact Information for the Sponsor

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Location: [redacted]

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[redacted]

# III. LIST OF ABBREVIATIONS AND DEFINITION OF 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 plasma 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 |
| anti-CCP antibody | anti-cyclic citrullinated peptide antibody |
| $C_{max}$ | 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 |
| DIP | Distal interphalangeal joint |
| DILI | Drug-induced liver injury |
| 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 |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GFR | Glomerular filtration rate |
| GMP | Good Manufacturing 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 |

| Abbreviations | Description of abbreviations |
|---|---|
| HDL | High-density lipoprotein |
| 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 |
| IL | Interleukin |
| IND | Investigational new drug |
| INR | International normalized ratio |
| IP | Interphalangeal joint |
| IR | Inadequate response |
| IRB | Institutional review board |
| ISN | International study number |
| JAK | Janus kinase |
| LAtest | Latex agglutination test |
| LA-CRF | Liver abnormality - CRF |
| LC-MS | Liquid chromatography- mass spectrometry |
| LDL | Low-density lipoprotein |
| LOCF | Last observation carried forward |
| MCP | Metacarpophalangeal joint |
| MDRD | Modification of diet in renal disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMF | Mycophenolate mofetil |
| MMP-3 | Matrix metalloproteinase 3 |
| MPA | Mycophenolic acid |
| MPAG | Mycophenolic acid glucuronide |
| MTP | Metatarsophalangeal joint |
| mTSS | Modified Total Sharp Score |
| 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 |
| PDAS | Pharmacodynamic analysis set |
| PGA | Physician's Global Assessment of Arthritis |
| PGx | Pharmacogenomics |
| PIP | Proximal interphalangeal joint |
| PK | Pharmacokinetic |
| PKAS | Pharmacokinetic analysis set |
| PPS | Per protocol set |
| QOL | Quality of life |
| RA | Rheumatoid arthritis |
| RF | Rheumatoid factor |
| SAE | Serious adverse event |

| Abbreviations | Description of abbreviations |
|---|---|
| SAF | Safety analysis set |
| SDAI | Simplified Disease Activity Index |
| SF-36v2® | Short Form Health Survey – 36 questions, version 2 |
| 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 |
| $t_{½}$ | Apparent terminal elimination half-life |
| $t_{max}$ | Time to attain $C_{max}$ |
| TYK | Tyrosine kinase |
| ULN | Upper limit of normal |
| VAS | Visual analog scale |
| VEGF | Vascular endothelial growth factor |
| WBC | White blood cell |
| WPAI | Work Productivity and Activity Impairment Questionnaire |

## Definition of Key Study Terms

| Terms | Definition of terms |
|---|---|
| Adverse event | An adverse event is defined as any untoward medical occurrence in a subject administered a study drug that does not necessarily have a causal relationship with this treatment. |
| Baseline | 1) Values/findings observed prior to the initiation of study treatment, which are regarded as the starting point for comparison.<br>2) The time point at which those reference values/findings were observed. |
| 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: discontinuation of participation without notice or action by the subject; d) sponsor-initiated discontinuation.<br>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, which precedes or is contemporaneous with randomization. |
| Investigational period | The period of time where major interests of protocol objectives are observed. In general, the subject will receive a test drug or comparative drug (possibly without randomization) during this period, which extends until the last post-treatment assessment is completed. |
| Follow-up period | The follow-up period will be 4 weeks (on a per-protocol basis) starting after the early-termination visit for withdrawn subjects and after the Week 52 visit for subjects who completed the study but are not willing to enroll into the extension study. For subjects who completed the study and wish to enroll into the extension study, the follow-up period will last for a maximum of 4 weeks starting after the Week 52 visit and ending at the initiation of the extension study treatment. |
| Randomization | Action to allocate a subject to the treatment group or treatment cohort. Depending on the type of rules for handling for study drugs, 'Randomization' is usually executed just before entering the 'investigational period.' |
| Screening | 1) Process of searching for candidates for the study<br>2) Process of checking the eligibility of subjects, usually done during the "pre-investigational period" |
| Screening failure | Screened subject, but did not fulfill protocol inclusion and/or exclusion criteria and failed to receive randomized or open label study treatment, or decided not to participate anymore (withdrew consent) prior to completing pre-investigational period. |

| Terms | Definition of terms |
|---|---|
| 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. |
| Study period | The period of time from obtaining informed consent from the subject 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 | A characteristic under study that varies: any attribute, phenomenon, or event that can have different qualitative or quantitative values. |

# IV. SYNOPSIS

| | |
|---|---|
| **Title of Study** | Phase III Study of ASP015K<br>–A randomized, double-blind, placebo-controlled confirmatory study of efficacy and safety of ASP015K in patients with rheumatoid arthritis (RA) who had an inadequate response to MTX–<br>(Protocol No.: 015K-CL-RAJ4) |
| **Planned Study Period** | From July 2014 to January 2018 |
| **Study Objectives** | The objective of this study is to evaluate the efficacy of ASP015K (100 and 150 mg/day) versus placebo administered in combination with methotrexate (MTX) in rheumatoid arthritis (RA) patients who had an inadequate response to MTX. The primary variables are the American College of Rheumatology (ACR) 20 response rate at Week 12 and suppression of joint destruction [change from baseline in Modified Total Sharp Score (mTSS)] at Week 28. This study will also investigate pharmacokinetic, pharmacodynamic, and safety profiles. Furthermore, this study will examine the long-term efficacy and safety (52 weeks). |
| **Planned Total Number of Study Centers and Locations** | Approximately 150 centers<br>Japan |
| **Design and Methodology** | This study is a multi-center, randomized, placebo-controlled, double-blind, parallel-group, confirmatory study to evaluate the efficacy and safety of ASP015K (100 and 150 mg) administered in combination with MTX in patients with RA who had an inadequate response to MTX. After the screening period, subjects will be randomly assigned at a 1:1:1 ratio to receive ASP015K 100 mg, ASP015K 150 mg, or placebo once daily (QD) in combination with MTX. Subjects will orally receive the study drug after breakfast for 52 weeks. At Week 12, inadequate responders in the placebo group, as determined by a < 20% improvement from baseline (i.e., treatment initiation day) in tender or painful joint count (TJC) and swollen joint count (SJC), will be switched to either ASP015K 100 mg or ASP015K 150 mg, and the dosage will be maintained until the end of treatment. In addition, subjects receiving placebo at Week 28 will be switched to either ASP015K 100 mg or ASP015K 150 mg, and the dosage will be maintained until the end of treatment. The ASP015K dose that will be started for placebo group subjects at Week 12 or Week 28 (100 or 150 mg) will be randomly chosen at baseline. The dose will be switched under the blinded condition.<br>Subjects who complete this study will be eligible for participation in the open-label extension study (015K-CL-RAJ2). Subjects will make a follow-up visit after the Week 52 visit if they do not enroll into the extension study on the day of the Week 52 visit. |
| **Number of Subjects to Be Enrolled/Randomized** | A total of 510 treated patients, with 170 in each treatment group |

| | |
|---|---|
| **Inclusion/Exclusion Criteria** | <Inclusion Criteria><br>Subject is eligible for the study if all of the following apply:<br>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.<br>2. Subject is a man or woman aged ≥ 20 years at the time of informed consent.<br>3. Subject has RA of < 10 years duration at baseline that was diagnosed according to the 1987 American College of Rheumatology (ACR) criteria or the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria.<br>4. Subject who did not receive the following drugs, or received the drugs with stable dosage for at least 28 days prior to the baseline (start of treatment) for RA treatment:<br>Non-steroidal anti-inflammatory drugs (NSAIDs; excluding topical formulations with a local action), oral morphine or equivalent opioid analgesics (≤ 30 mg/day), acetaminophen, or oral corticosteroids (≤ 10 mg/day in prednisolone equivalent).<br>5. At screening subject has active RA as evidenced by both of the following:<br>• ≥ 6 tender/painful joints (using 68-joint assessment)<br>• ≥ 6 swollen joints (using 66-joint assessment)<br>6. CRP (latex agglutination test) of ≥ 1.00 mg/dL at screening.<br>7. Subject meets the ACR 1991 Revised Criteria for the Classification of Global Functional Status in RA Class I, II, or III at screening.<br>8. Inadequate responders to MTX which was continuously administered for at least 90 days prior to screening and MTX ≥ 8 mg/week for at least 28 days prior to baseline. However, inadequate responder to MTX < 8 mg/week is eligible if intolerance precludes dose increase and defined as MTX-IR.<br>9. Subject is able to continue stable dose of MTX (a maximum of 16 mg/week) from at least 28 days prior to screening until the end of treatment.<br>10. Subjects has bone erosion at the joint (as evidenced by x-rays of hands and feet) assessed in mTSS and any of the following apply at screening. Bone erosion may be evidenced by x-rays within 90 days prior to baseline.<br>• Positive anti-CCP antibody: ≥ 4.5 U/mL<br>• Positive rheumatoid factor: > 15 IU/mL<br>11. Subject must be willing and able to comply with the study requirements. |

| | |
|---|---|
| **Inclusion/Exclusion Criteria** | <Exclusion Criteria><br>Subject will be excluded from participation if any of the following applies:<br>1. Subject has received a biologic DMARD within the specified period:<br>• Etanercept: within 28 days prior to baseline<br>• Adalimumab, infliximab: within 56 days prior to baseline<br>• Golimumab, certolizumab pegol: within 70 days prior to baseline<br>• Abatacept, tocilizumab: within 84 days prior to baseline<br>• Denosumab: within 150 days prior to baseline<br>• Rituximab: within 180 days prior to baseline<br>2. Inadequate responders to biologic DMARD as determined by investigator/sub-investigator.<br>3. Subject has received a non-biologic DMARD listed below or other drugs used in the treatment of RA within 28 days prior to baseline. Leflunomide is prohibited within 180 days prior to baseline. Alternatively, leflunomide is prohibited within 28 days prior to baseline if washout with cholestyramine for at least 17 days is completed at least 28 days prior to baseline. However, topical drugs other than those for the treatment of RA may be used concomitantly.<br>• Salazosulfapyridine<br>• Lobenzarit<br>• Gold<br>• Iguratimod<br>• *D*-penicillamine<br>• Bucillamine<br>• Actarit<br>• Leflunomide<br>• Tacrolimus<br>• Cyclosporine<br>• Cyclophosphamide<br>• Azathioprine<br>• Minocycline<br>• Mizoribine<br>4. Subject has received tofacitinib and other JAK inhibitors (including other investigational drugs).<br>5. Subject has received intra-articular, intravenous, intramuscular, or endorectal (excluding suppositories in patients with anal diseases) corticosteroid within 28 days prior to baseline.<br>6. Subject has participated in any study of ASP015K and has received ASP015K and placebo.<br>7. Subject received other investigational drug within 90 days or within 5 half-lives, whichever is longer, prior to baseline.<br>8. Subject has received plasma exchange therapy within 60 days prior to baseline.<br>9. Subject has undergone joint drainage, has received local anesthesia and nerve block, or has received articular cartilage protectant at the assessed joint within 28 days prior to baseline.<br>10. Subject has undergone surgery and has residual effects in the assessed joints at the discretion of investigator/sub-investigator, or is scheduled to undergo surgery that may affect the study evaluation of the assessed joints at the discretion of investigator/sub-investigator. |

**Inclusion/Exclusion Criteria**

11. A diagnosis of inflammatory arthritis (psoriatic arthritis, ankylosing spondylitis, SLE, sarcoidosis, etc.) other than RA.
12. Any of the following laboratory values during the screening test period:
    - Hemoglobin < 9.0 g/dL
    - Absolute neutrophil count < 1000/μL
    - Lymphocyte count < 800/μL
    - Platelet count < 75000/μL
    - ALT ≥ 2 ×ULN
    - AST ≥ 2 × ULN
    - Total bilirubin (TBL) ≥ 1.5 × ULN
    - Estimated GFR ≤ 40 mL/min as measured by the MDRD method
    - β-D-glucan ≥ 11 pg/mL
    - Positive HBs antigen, HBc antibody, HBs antibody, or HBV-DNA quantitation (However, subject with negative HBs antigen and HBV-DNA quantitation, and positive HBc antibody and/or HBs antibody is eligible if HBV-DNA is monitored by HBV-DNA quantitation at every scheduled visit after initiation of study drug administration.)
    - Positive HCV antibody
13. Subject has a history of or concurrent active tuberculosis (TB). Eligibility criteria for TB are tabulated below:

| History of active TB | Chest x-ray (for TB) | TB infection[b)] | Exposure to patients with infective TB (interview) | Eligibility |
|---|---|---|---|---|
| Present | - | - | - | Not eligible |
| Absent | Abnormal (active) | - | - | Not eligible |
| | Abnormal (old)[a)] | - | Eligible | Eligible if prophylaxis is given[c)] |
| | Normal | Positive | Eligible | Eligible if prophylaxis is given[c)] |
| | | Negative | Exposed | Eligible if prophylaxis is given[c)] |
| | | | Not exposed | Eligible |

a) Old TB is evidenced if chest x-ray reveals pleural thickening, band-like shadow, and calcification ≥ 5 mm. Chest x-ray within 90 days prior to baseline may substitute the screening test.

b) T-spot or Quantiferon Gold test is of first priority. When the result is equivocal or invalid, retest including other test methods may be allowed. If a retest is not performed, criteria for positive results will be followed. When T-spot or Quantiferon Gold test is not feasible, tuberculin test will be performed. Tuberculin is defined as positive with a red spot covering an area of 20 mm or more or induration. Tests conducted within 90 days prior to baseline may be used for diagnosis.

c) Subject must receive or have received prophylaxis with isoniazid or rifampicin. Prophylaxis will be administered for 6 to 9 months, starting from at least 21 days prior to baseline.

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| **Inclusion/Exclusion Criteria** | 14. Subject meets any of the following in terms of infections except for TB:<br>• History of or concurrent severe herpes zoster (associated with Hunt syndrome or having ulcerative lesions) or disseminated herpes zoster<br>• History of multiple recurrences (at least twice) of localized herpes zoster<br>• Serious infection requiring hospitalization within 90 days prior to baseline<br>• Subject received intravenous antibiotics within 90 days prior to baseline. (However, prophylactic antibiotics are allowed.)<br>• Subject with high risk of infection (e.g., subject with urinary catheter) at the discretion of investigator/sub-investigator<br>15. Subject has a history of or concurrent interstitial pneumonia and investigator/sub-investigator judges that it is inappropriate for the subject to participate in this study.<br>16. Subject has a history of or concurrent malignant tumor (except for successfully treated basal cell carcinoma).<br>17. Subject has received live or live attenuated virus vaccination within 56 days prior to baseline. (Inactivated vaccines including influenza and pneumococcal vaccines are allowed.)<br>18. Subject has any ongoing severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, infectious, or autoimmune disease except for RA (excluding Sjogren's syndrome and chronic thyroiditis), or any ongoing illness which would make the subject unsuitable for the study as determined by the investigator/sub-investigator.<br>19. Subject has a history of clinically significant allergy. (Clinically significant allergy includes allergies such as systemic urticaria induced by specific antigens and drugs, anaphylaxis, and allergy associated with shock necessitating hospitalized treatment.)<br>20. Subject has received medications that are CYP3A substrates with narrow therapeutic range within 14 days prior to baseline. These medications include: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, and disopyramide.<br>21. Subject has concurrent cardiac failure, defined as NYHA classification Class III or higher, or a history of it.<br>22. Subject has concurrent prolonged QT syndrome or a history of it. Subject has prolonged QT interval (defined as QTc $\geq$ 500 msec. Subject has QTc $\geq$ 500 msec at retest will be excluded) at screening.<br>23. Subject has a history of positive HIV infection.<br>24. 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 serum pregnancy test given at the time of screening.<br>25. Subject is a man who cannot practice at least 2 types of contraception from the time of informed consent to 90 days after the end of treatment, or subject is a woman with childbearing potential who cannot practice at least 2 types of contraception from the time of informed consent to 60 days after the end of treatment. |

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| **Inclusion/Exclusion Criteria** | 26. Male subject who do not agree not to donate sperm starting at informed consent and through the treatment period and for at least 90 days after final study drug administration. Female subject who do not agree not to donate ova starting at informed consent through the treatment period and for 60 days after final study drug administration.<br>27. The subject has been judged unsuitable to participate in the study for other reasons by the investigator/sub-investigator.<br>28. Subject has a history or complication of lymphatic diseases such as lymphoproliferative disorder, lymphoma, and leukemia.<br>29. Subject has congenital short QT syndrome or a history of it. Subject has shortened QT interval (defined as QTc < 330 msec. Subject has QTc < 330 msec at retest will be excluded) at screening. |

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| **Discontinuation Criteria** | The investigator/sub-investigator should discontinue the study if any of the following occur:<br><br>1. The subject withdraws consent.<br>2. The investigator/sub-investigator judges that the study drug is not sufficiently effective and the treatment method needs to be changed.<br>3. Symptomatic CPK elevation (> 1.5 × ULN accompanied with severe and unusual episodes of myalgia, muscular weakness, or muscle twitching).<br>4. Any case of myopathy involving severe and unusual episodes of myalgia, muscular weakness, or muscle twitching that persists for no less than, or aggravates rapidly within, 2 weeks, regardless of the CPK level.<br>5. A previously HBV-infected patient with positive HBc antibody, positive HBs antibody, or both has been shown positive for HBV-DNA during the study.<br>Attention should be paid that abrupt discontinuation of immunotherapy may cause fulminant or severe liver failure. Therefore, if the subject manifests HBV reactivation, the investigator/sub-investigator will administer nucleoside analogs without delay according to the "Proposal for Management of Rheumatic Disease Patients with Hepatitis B Virus Infection Receiving Immunosuppressive Therapy" (Japan College of Rheumatology). The investigator/sub-investigator will carefully decide whether to continue or discontinue the study drug and concomitant DMARDs in consultation with the hepatology specialist.<br>6. Malignant tumor<br>7. The subject develops a serious infection or other adverse events (AEs), and continued administration of the study drug is not deemed appropriate in the subject's best interest by the investigator/sub-investigator.<br>8. The subject has been treated with a prohibited concomitant drug or therapy (including another investigational product) that may impact efficacy evaluation. The subject has been, or needs to be, treated with a rescue medication for a period extending beyond its allowable time. Otherwise, the subject has been, or needs to be, treated with a live or live attenuated vaccine.<br>9. The subject has been judged by the investigator/sub-investigator to be non-compliant to the medication requirements for the study drug or MTX.<br>10. The subject is deemed incapable of continuing the follow-up based on the opinion of the investigator/sub-investigator (subject can no longer come to the study center; subject can no longer be contacted, etc.).<br>11. It comes to light after the administration of the first dose of study drug that 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.<br>12. The subject needs the study drug to be interrupted beyond its allowable time limit.<br>13. Investigator/sub-investigator decides it is in the subject's best interest.<br>14. The sponsor has requested that the study be discontinued because of a safety problem in a particular subject, or the sponsor has decided to discontinue the study altogether.<br>15. The subject shows QTc interval < 300 msec at Central ECG, or the subject shows QTc interval < 300 msec at the study site's ECG and also shows QTc interval < 300 msec at retest of study site's ECG. |

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| **Suspension, Interruption, and Resumption of the Study Drug** | If the subject meets during the treatment period any of the criteria provided in "Criteria for Suspension or Interruption of the Study Drug," the investigator/sub-investigator will immediately suspend or interrupt the treatment. The investigator/sub-investigator can resume the study treatment only if re-examinations and other assessments performed after the suspension or interruption confirm that none of the conditions listed below are applicable to the subject and the investigator/sub-investigator considers it desirable for the interest of the subject on the basis of risk–benefit analysis.<br><br>The maximum allowable time for "suspension" is 7 days. If the study treatment is halted beyond the suspension period, i.e., longer than 7 days, the period of no treatment is categorized as an "interruption."<br>Upper limits have been set to the number of interruptions 1 subject can have and to the duration of 1 interruption. One interruption period may last for 28 days. One subject is allowed to have a maximum of 2 interruptions, which must be separated by 16 or more weeks.<br>The investigator will consult the sponsor regarding the handling of a subject who repeatedly requires treatment suspension.<br>The subject must be withdrawn from the study, if he or she requires either a third interruption or a second interruption within 16 weeks from the first one.<br><br><u>Criteria for Suspension or Interruption of the Study Drug</u><br>The investigator/sub-investigator will suspend or interrupt the study drug if any of the following becomes applicable during the treatment period:<br><br>1. Clinical laboratory tests yielded any of the following results:<br>• Hemoglobin < 8.0 g/dL<br>• Absolute neutrophil count < 500/μL<br>• Absolute lymphocyte count < 500/μL<br>• Platelet count < 50000/μL<br>• Creatinine (serum) levels measured at 2 consecutive hospital visits: above 150% of the baseline level<br>• CPK > 10 × ULN<br>2. β-D-glucan test result of 11 pg/mL or higher.<br>3. The subject requires a medication whose concomitant administration is prohibited in the protocol because of possible drug–drug interaction.<br>4. The subject is suspected to be pregnant.<br>5. The investigator/sub-investigator judged it appropriate in the interest of the subject to suspend or interrupt the study drug.<br>6. The sponsor made a request to suspend or interrupt the study drug out of safety concerns for the subject. |
| **Participation in Open-Label Extension Study** | Subjects who complete this study will be eligible for participation in the open-label extension study (Protocol No.: 015K-CL-RAJ2). |
| **Test Drugs:**<br>**Mode of Administration:**<br>**Dose:**<br>**Duration of Treatment:** | Test drugs: ASP015K 100 mg and 150 mg tablets<br>Dose: 100 mg/day, 150 mg/day<br>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 baseline visit after all the necessary assessments and tests have been completed.<br>Duration of treatment: 52 weeks |

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| **Comparative Drugs:**<br>**Mode of Administration:**<br>**Dose:**<br>**Duration of Treatment:** | ASP015K placebo tablets<br>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 baseline visit after all the necessary assessments and tests have been completed.<br>Duration of treatment: 52 weeks (placebo will be administered for a maximum of 28 weeks. Subjects in the placebo group will be switched to either ASP015K 100 mg or ASP015K 150 mg at Week 12 or Week 28.) |
| **Concomitant Medication** | 1) Necessary concomitant medications<br><u>MTX</u><br>• MTX will be initiated 90 or more days prior to screening. The same dosage and administration schedule (≤ 16 mg/week) must be followed at least 28 days prior to screening and during the screening and treatment periods.<br>• If MTX is temporarily interrupted or its dose is reduced within 28 days prior to the baseline visit in a subject eligible at screening for the study based on inclusion and exclusion criteria, the screening period will be extended to allow for the same dosage and administration schedule to be observed for 28 days prior to the baseline visit.<br>• In the case of AEs, administration may be temporarily interrupted, or the dose may be temporarily reduced. The period of interruption is up to 28 days. When resuming administration, the dose may be increased with the baseline dose as the upper limit. Administration may only be interrupted once.<br>• 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.<br>• If ALT/AST becomes ≥ 3 × ULN, MTX must be interrupted, or the dose must be reduced, and daily administration of folic acid should be considered.<br><br>2) Prohibited concomitant medications and therapies<br>• Biologic DMARDs<br>The following biologic DMARDs will be prohibited during the period shown below and during the treatment period:<br>➢ Etanercept: within 28 days prior to baseline<br>➢ Adalimumab, infliximab: within 56 days prior to baseline<br>➢ Golimumab, certolizumab pegol: within 70 days prior to baseline<br>➢ Abatacept, tocilizumab: within 84 days prior to baseline<br>➢ Denosumab: within 150 days prior to baseline<br>➢ Rituximab: within 180 days prior to baseline<br><br>• Non-biologic DMARD<br>Non-biologic DMARDs, excluding MTX, will be prohibited within 28 days prior to baseline and during the treatment period. In addition, the use of leflunomide is prohibited within 180 days prior to baseline. However, if washout with cholestyramine for at least 17 days is completed before 28 days prior to baseline, the use of leflunomide will be prohibited within 28 days prior to baseline. However, topical drugs other than those for the treatment of RA may be used concomitantly.<br>• Other drugs used in the treatment of RA<br>Cyclosporine, cyclophosphamide, azathioprine, minocycline, and other drugs indicated for the treatment of RA will be prohibited within 28 days prior to baseline and during the treatment period. |

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| **Concomitant Medication** | • Corticosteroids<br>Oral corticosteroids at doses exceeding 10 mg per day in the prednisolone equivalent will be prohibited within 28 days prior to baseline and during the treatment period.<br>The intra-articular, intravenous, intramuscular, and endorectal corticosteroid administration will also be prohibited within 28 days prior to baseline and during the treatment period. However, suppositories for anal diseases may be used concomitantly.<br>• Oral morphine<br>Oral morphine at doses exceeding 30 mg per day (or equivalent doses of other opioid analgesics) will be prohibited within 28 days prior to baseline and during the treatment period.<br>• Other study drugs<br>Other study drugs will be prohibited within 90 days or 5 half-lives, whichever is longer, prior to baseline. In addition, the use of other study drugs will be prohibited during the study period.<br>• CYP3A substrates<br>The following CYP3A substrate drugs with a narrow therapeutic range will be prohibited within 14 days prior to baseline and during the treatment and follow-up periods: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide, etc.<br>• Vaccines<br>Live and live attenuated vaccines will be prohibited within 56 days prior to baseline and during the treatment and follow-up periods. Inactivated vaccines may be administered (influenza, pneumococcal vaccines, etc.)<br>• Plasma exchange therapy<br>Plasma exchange therapy will be prohibited within 60 days prior to baseline and during the treatment period.<br>• Surgical treatment methods<br>Surgery involving the target joint will be prohibited from the time of informed consent to the end of the treatment period.<br>• Effusion drainage, local anesthesia, and nerve block of the target joint<br>Effusion drainage, local anesthesia, and nerve block of the target joint will be prohibited within 28 days prior to baseline and during the treatment period.<br>• Articular cartilage protective agents<br>The use of articular cartilage protective agents in the target joint will be prohibited within 28 days prior to baseline and during the treatment period.<br><br>3) Restricted concomitant medications<br>Regarding the drugs listed below, changes to the dosage, administration schedule, or route of administration will not be allowed within 28 days prior to baseline and during the treatment period, unless the specific conditions for the change are met.<br>• The drugs listed below will be prohibited within 28 days prior to baseline and during the treatment period if they are discontinued before the initiation of study treatment [except in cases where NSAIDs and non-NSAID analgesics (e.g., acetaminophen, opioid analgesics, all-in-one flu and cold medications) are used as rescue medication]. |

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| **Concomitant Medication** | • In the case of AEs, administration may be temporarily interrupted, or the dose may be temporarily reduced. The period of interruption is up to 28 days. When resuming administration, the baseline dose is the upper limit.<br>• From the visit at Week 28, the drugs below may be discontinued, new drugs may be used, and the dosage, administration schedule, or route of administration of the concomitant drugs may be changed. However, with the exception of oral corticosteroids, after changing the conditions, administration must be continued under the same conditions for 12 weeks or longer.<br><br>➢ NSAIDs (excluding topical drugs with a local action)<br>➢ Oral morphine (not more than 30 mg per day, or equivalent doses of other opioid analgesics)<br>➢ Acetaminophen<br>➢ Oral corticosteroids (however, at 10 mg per day or less in the prednisolone equivalent and from the visit at Week 28, the dose may be reduced or increased within the range not exceeding the baseline dose.)<br>4) Rescue medications<br>The drugs listed below may be administered only if they are necessary for treating an untoward medical occurrence, AEs, comorbid conditions, or acute aggravation of the primary disease within 28 days prior to baseline and during the treatment period. However, these medications may not be taken within 24 hours before joint assessment at each visit.<br>➢ NSAIDs: For 3 days or less<br>➢ Analgesics other than NSAIDs (acetaminophen, opioid analgesics, all-in-one flu and cold medications, etc.): For 7 consecutive days or less |

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| **Major Outcome Variables Efficacy** | <Primary Variables><br>• ACR20 response rate at Week 12<br>• Change from baseline in mTSS at Week 28 (suppression of joint destruction)<br><Secondary Variables><br>• ACR20 response rate<br>• ACR50 response rate<br>• ACR70 response rate<br>• Change from baseline in mTSS<br>• Change in joint space narrowing score<br>• Change in erosion score<br>• Percentage of subjects showing no progression of joint damage ($\Delta$mTSS $\leq$ 0.5)<br>• Change from baseline in DAS28-CRP and DAS28-ESR scores<br>• Change from baseline in TJC (68 joints)<br>• Change from baseline in SJC (66 joints)<br>• Percentage of subjects achieving DAS28-CRP and DAS28-ESR scores for remission<br>• Percentage of subjects achieving low disease activity by DAS28-CRP and DAS28-ESR<br>• Change from baseline in CRP and ESR<br>• Percentage of subjects with good EULAR response<br>• Percentage of subjects with good or moderate EULAR response<br>• Percentage of subjects achieving ACR/EULAR remission<br>If all of the following 4 parameters are fulfilled, it is defined as remission:<br>➢ TJC $\leq$ 1<br>➢ SJC $\leq$ 1<br>➢ CRP $\leq$ 1 mg/dL<br>➢ SGA $\leq$ 1 cm (on a VAS of 0-100 mm)<br>• Change from baseline in the percentage of subjects achieving ACR/EULAR remission<br>• Percentage of subjects achieving SDAI remission (SDAI score $\leq$ 3.3)<br>• Change from baseline in SDAI score<br>• Change from baseline in Physician's Global Assessment of Arthritis (PGA) (VAS)<br>• Change from baseline in Subject's Global Assessment of Arthritis (SGA) (VAS)<br>• Change from baseline in subject's assessment of pain (VAS)<br>• Incidence of subject withdrawal due to lack of efficacy<br>• Change from baseline in HAQ-DI score<br>• Change from baseline in SF-36v2® score<br>• Change from baseline in WPAI score |
| **Variables (Safety)** | • AEs<br>• Vital signs (body temperature, pulse rate and blood pressure in sitting position)<br>• Body weight<br>• 12-lead electrocardiogram (ECG)<br>• Central electrocardiogram<br>• Chest radiography<br>• Laboratory assessments |
| **Variables (Pharmacokinetics)** | Plasma ASP015K concentration on each day of the study visit |

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| **Variables (Pharmacodynamics)** | • Change from baseline in VEGF level<br>• Change from baseline in MMP-3 level<br>• Change from baseline in lymphocyte subset assays (CD3, CD4, CD8, CD16, CD19, CD56, CD56/16)<br><br>Additional analysis may be performed for biomarkers for efficacy and safety assessments based on study results using blood samples that have been collected during the study and biobanked (i.e., residual sample stored for retrospective analysis). These could include biomarkers of inflammation, bone or cartilage metabolism, or inhibitory activity of JAK, but other biomarkers may also be subject to analysis. |
| **Pharmacogenomics (Bio-Banking)** | To prepare for future research to analyze the relationship between genes and the efficacy, safety, or pharmacokinetics of the study drug, blood sample will be collected and stored with the consent of the subject. |
| **Statistical Methods** | [Sample Size Calculation]<br>The sample size calculation was based on ASP015K Japanese Phase IIb study (015K-CL-RAJ1) result and other Japanese studies for patients with RA [XELJANZ®, tablet, 5 mg CTD (2013)] [CIMZIA, sc, 200 mg, Syringe, CTD (2012)]. In the 015K-CL-RAJ1 study, the primary efficacy endpoint, which was Percentage of Subjects achieving ACR 20 response at Week 12/ET, was 54.5% in the 100 mg, and 65.5% in the 150 mg. Therefore, in the 015K-CL-RAJ4 study, it can be assumed to achieve same magnitude of ACR20 response at Week 12/ET for both 100 mg and 150 mg. For ACR20 response at Week 12/ET in the placebo group, it was assumed 25% based on other Japanese drugs for RA.<br>On the other hand, for the modified Total Sharp Score (mTSS) change from baseline at Week 28/ET, it was assumed that mTSS change from baseline at Week 28/ET would be at least 0.5 in the 150 mg. For mTSS change from baseline at Week 28/ET in the placebo, it was assumed 2.0. Standard deviation for difference between groups in mTSS change from baseline at Week 28/ET was assumed 4.0.<br>Under these assumptions, Fisher's exact test for ACR20 response at Week 12/ET and t-test for mTSS change from baseline at Week 28/ET were used for sample size calculation in consideration for the multiplicity adjustment by closed testing procedure which is described in the Primary Efficacy Variable Analysis. As a result, 151 patients per group were needed to reach 90% power to detect the treatment difference which was assumed in the Step 3 at a two-sided 0.05 significance level. By considering about 10% drop-out, this study will enroll 170 patients in each treatment group.<br>[Primary Efficacy Variable Analysis]<br>For ACR20 response at Week 12/ET, pairwise comparisons to placebo will be performed at each ASP015K dose level using Fisher's exact test in the primary analysis. For mTSS change from baseline at Week 28/ET, pairwise comparisons to placebo will be performed at each ASP015K dose level using rank analysis of covariance (ANCOVA) with treatment group (Placebo, ASP015K 100 mg, ASP015K 150 mg) as factor and baseline rank mTSS as covariate in the primary analysis.<br>Closed testing procedure shown below will be used for multiplicity adjustment in the primary analysis. |

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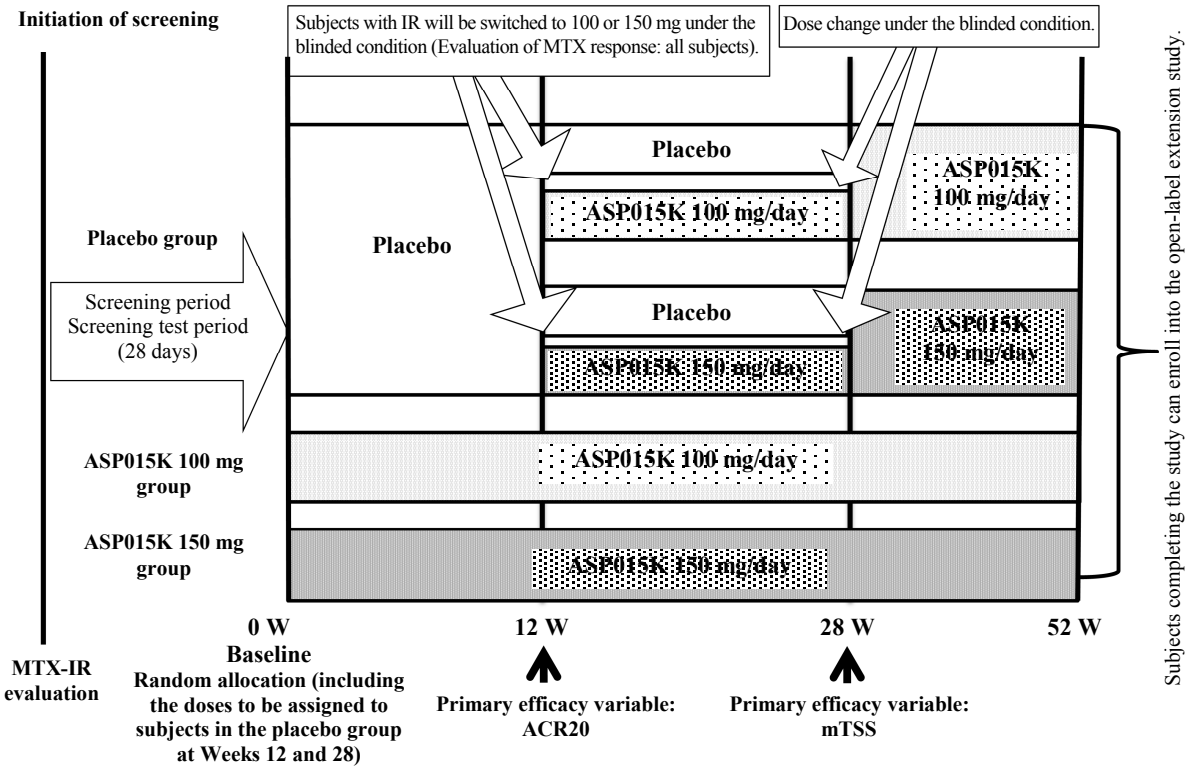
| | Step 1. ACR20 response at Week 12/ET: ASP015K 150 mg vs. Placebo<br>Step 2. ACR20 response at Week 12/ET: ASP015K 100 mg vs. Placebo<br>Step 3. mTSS change from baseline at Week 28/ET: ASP015K 150 mg vs. Placebo<br>Step 4. mTSS change from baseline at Week 28/ET: ASP015K 100 mg vs. Placebo<br>The null hypothesis at Step 1 will be tested at a significance level of 0.05. If it is statistically significant, the next step will be initiated. Otherwise, it is completion of the hypothesis test. These hypothesis tests continue up to Step 4 unless it is rejected.<br>For the missing imputation of ACR20 at Week 12/ET, Last Observation Carried Forward (LOCF) methodology will be used.<br>For the missing imputation of mTSS at Week 28/ET, Linear Extrapolation (LEP) methodology will be applied using baseline value and post Week 12 value.<br>[Secondary Efficacy Variable Analysis]<br>For secondary efficacy endpoints, binary variables such as Percentage of subjects achieving ACR50 response at Week 12/ET, Percentage of subjects achieving ACR70 response at Week 12/ET will be analyzed using Fisher's exact test, and continuous variables, such as Change from baseline/Day 1 to Week 12/ET in DAS28-CRP and DAS28-ESR scores, will be analyzed using ANCOVA with treatment group as factor and baseline as covariate. Each ASP015K group will be compared with placebo group and multiplicity for the secondary efficacy variables will not be adjusted.<br>[Safety and Other Variables Analyses]<br>Summary statistics will be calculated for trough levels and biomarker concentrations by dose and time point.<br>AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs, serious AEs (SAEs), AEs leading to discontinuation, and AEs related to study drug will be summarized. All AEs will be listed. Descriptive statistics for laboratory values, vital signs, ECG results, QT variables (including QTc), body weight, and their changes from baseline if quantitative, will be provided by treatment group and time. |

# V. FLOW CHART AND SCHEDULE OF ASSESSMENTS

## Flow Chart

| Obtain informed consent | → | Screening period (The screening test period must be within 28 days prior to the baseline visit.)<br><br>Confirmation of inclusion/exclusion criteria<br>Preliminary registration | → | Baseline<br><br>Confirmation of inclusion/exclusion criteria<br>Enrollment & randomization | → | Treatment period: maximum of 52 weeks, ranging from the start of the study treatment to the completion of tests/assessments schedule at the end of treatment (Week 52 or early termination)<br><br>See figure below. | → | Entry into the extension study<br><br>Subjects not enrolling into the extension study will undergo follow-up observation 4 weeks after the end of the study treatment. |
|---|---|---|---|---|---|---|---|---|



## Table 1 Schedule of Assessments

| Visit | Initiation of Screening[1)] | Screening Test Period | 0 W | 4 W | 8 W | 12 W | 16 W | 20 W | 24 W | 28 W | 32 W | 36 W | 40 W | 44 W | 48 W | 52 W | Early Termination | Follow-up[2)] | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit day** | **−1 at latest** | **−28 to −1** | **1** | **29** | **57** | **85** | **113** | **141** | **169** | **197** | **225** | **253** | **281** | **309** | **337** | **365** | **Within 2 days of withdrawal** | **28 days after Week 52 or early termination visit** | **-** |
| Allowable range from specified date | | | | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | +2 | ±7 | - |
| Informed consent | ○ | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion criteria | ○ | ○ | ○ | | | | | | | | | | | | | | | | |
| Subject registration | ○ | | ○ | | | ○ | | | | ○ | | | | | | ○ | ○ | ○ | |
| Inadequate response to MTX | ○ | | ○ | | | | | | | | | | | | | | | | |
| Demographics | ○ | ○ | ○ | | | | | | | | | | | | | | | | |
| Medical history | ○ | ○ | ○ | | | | | | | | | | | | | | | | |
| Height | | ○ | | | | | | | | | | | | | | | | | |
| TB | | ○ | | | | | | | | | | | | | | | | | |
| Anti-CCP antibody, RF | | ○ | | | | | | | | | | | | | | | | | |
| **Safety** | | | | | | | | | | | | | | | | | | | |
| Physical examination | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| Body weight | | ○ | | | | ○ | | | | ○ | | | ○ | | | ○ | ○ | ○ | ▲ |
| Vital signs | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| Hepatitis examination | | ○ | | | | | | | | | | | | | | | | | ▲ |
| Hematology[3)] | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| Serum biochemistry[3)] | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| Urinalysis[3)] | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| Fasting lipid profile test | | | ○ | | | ○ | | ○ | | ○ | | | ○ | | | ○ | ○ | ○ | ▲ |
| Chest radiography | | ○ | | | | | | | | ○ | | | | | | ○ | ▲ | | ▲ |
| 12-lead ECG | | ○ | | | | | | | | ○ | | | | | | ○ | ○ | | ▲ |
| Central ECG[6)] | | | ○ | ○ | | | | | | | | | | | | | | | |

| Visit | Initiation of Screening[1)] | Screening Test Period | 0 W | 4 W | 8 W | 12 W | 16 W | 20 W | 24 W | 28 W | 32 W | 36 W | 40 W | 44 W | 48 W | 52 W | Early Termination | Follow-up[2)] | Unscheduled Visit |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit day** | **−1 at latest** | **−28 to −1** | **1** | **29** | **57** | **85** | **113** | **141** | **169** | **197** | **225** | **253** | **281** | **309** | **337** | **365** | **Within 2 days of withdrawal** | **28 days after Week 52 or early termination visit** | **-** |
| Allowable range from specified date | | | | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | +2 | ±7 | - |
| Pregnancy test[5)] | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| Adverse event | | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| **Efficacy** | | | | | | | | | | | | | | | | | | | |
| Hand and foot radiography | | ○ | ○ | | | ○[4)] | | | | ○ | | | | | | ○ | ○ | | |
| CRP and ESR | | ○ (CRP only) | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| TJC/SJC (68/66 joints) | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| PGA (VAS), SGA (VAS), and subject's assessment of pain (VAS) | | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| SF-36 v2® | | | ○ | ○ | ○ | ○ | | | | ○ | | | | | | ○ | ○ | ○ | ▲ |
| WPAI | | | ○ | ○ | ○ | ○ | | | | ○ | | | | | | ○ | ○ | ○ | ▲ |
| HAQ-DI | | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ▲ |
| **PK/PD** | | | | | | | | | | | | | | | | | | | ▲ |
| Blood sampling for trough concentration | | | ○ | ○ | ○ | ○ | | ○ | | ○ | | | ○ | | | ○ | ○ | | |
| Blood sampling for post-dose drug concentration | | | | ○ | | | | | | | | | | | | | | | |
| Blood sampling for PD (biomarkers) | | | ○ | ○ | ○ | ○ | | | | ○ | | | | | | ○ | ○ | ○ | ▲ |
| Blood sampling for PD (lymphocyte subset) | | | ○ | ○ | ○ | ○ | | | | ○ | | | | | | ○ | ○ | ○ | ▲ |
| Informed consent for PGx research (relevant sites only) | | | ○ | | | | | | | | | | | | | | | | |

| **Visit** | **Initiation of Screening[1)]** | **Screening Test Period** | **0 W** | **4 W** | **8 W** | **12 W** | **16 W** | **20 W** | **24 W** | **28 W** | **32 W** | **36 W** | **40 W** | **44 W** | **48 W** | **52 W** | **Early Termination** | **Follow-up[2)]** | **Unscheduled Visit** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit day** | **−1 at latest** | **−28 to −1** | **1** | **29** | **57** | **85** | **113** | **141** | **169** | **197** | **225** | **253** | **281** | **309** | **337** | **365** | **Within 2 days of withdrawal** | **28 days after Week 52 or early termination visit** | **-** |
| Allowable range from specified date | | | | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | ±7 | +2 | ±7 | - |
| Blood sampling for PGx (relevant sites only) | | | ○ | | | | | | | | | | | | | | | | |
| **Study drug** | | | | | | | | | | | | | | | | | | | |
| Confirmation of remaining unused drug | | | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | | |
| Prescription | | | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | | | | |

The symbol "○" designates mandatory items, whereas the symbol "▲" denotes the optional items to be investigated on the basis of the clinical judgment of the investigator/sub-investigator.

For details, see the respective sections of the protocol.

1) Subjects who have signed the informed consent will undergo evaluation of MTX response at the screening visit.

2) Follow-up will not be performed for subjects starting the extension study immediately after the Week 52 visit.

3) For details of the test parameters, refer to Section 5.4.4.

4) At Week 12, subjects with < 20% improvement from baseline in TJC and SJC will be required to undergo radiographic examination of their hands and feet.

5) For pregnancy tests, serum samples will be used at the screening visit, and urine samples will be used at and after the baseline visit.

6) Central ECG should be performed on the same day as blood sampling for post-dose drug concentration at Week 4 or Week 8 before and after study drug administration.

# VI. ACCEPTABLE RANGE OF SCHEDULE OF ASSESSMENTS

The paragraphs that follow describe the allowable time windows on scheduled test and observation dates.

Reasonable efforts must be made to perform the tests and observations specified for early termination and follow-up, even if they cannot be conducted within the allowable time frame.

**[Acceptable Time Ranges for Efficacy Tests]**

Hand and foot radiography

| | |
|---|---|
| Screening | From 1 to 90 days prior to the baseline visit. Radiographs taken before the informed consent will be acceptable as long as they satisfy the abovementioned time frame. |
| Baseline | On the day of the baseline visit. If re-examination is requested by the third-party evaluator, new radiographs must be taken within 30 days of the baseline visit. Only the radiographs taken on the day of the baseline visit will be acceptable if no re-examination is required. |
| Weeks 12, 28, and 52<br><br>At Week 12, hand and foot radiographs will be required for subjects with < 20% improvement from baseline in TJC and SJC. | Within ± 7 days of the protocol-specified date. If re-examination is requested by the third-party evaluator, new radiographs must be taken within 30 days of the previous measurement date. Radiographs taken within ± 7 days of the specified date will be acceptable if no re-examination is required. |
| Early termination | Within 2 days of the early termination visit. If re-examination is requested by the third-party evaluator, new radiographs must be taken within approximately 30 days of the previous measurement date. Radiographs taken within 2 days of withdrawal will be acceptable if no re-examination is required. |

TJC/SJC (68/66 joints) and CRP

| | |
|---|---|
| Screening | From 1 to 28 days prior to the baseline visit. |
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day. |
| Study visits from Week 4 to Week 48 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. |
| Follow-up | Within ± 7 days of the date 28 days after the Week 52 **OR** early termination visit. |

PGA (VAS), SGA (VAS), Subject's Assessment of Pain (VAS), HAQ-DI, and ESR

| | |
|---|---|
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day. |
| Study visits from Week 4 to Week 48 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. |
| Follow-up | Within ± 7 days of the date 28 days after the Week 52 **OR** early termination visit. |

SF-36 v2®, WPAI

| | |
|---|---|
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day. |
| Weeks 4, 8, 12, and 28 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. |
| Follow-up | Within ± 7 days of the date 28 days after the Week 52 **OR** early termination visit. |

**[Acceptable Time Ranges for Safety Tests]**

Physical Examination, Vital Signs, Laboratory Tests [Hematology, Serum Biochemistry, Urinalysis, Pregnancy Test (serum/urine)]

| | |
|---|---|
| Screening | From 1 to 28 days prior to the baseline visit. |
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day. |
| Study visits from Week 4 to Week 48 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. |
| Follow-up | Within ± 7 days of the date 28 days after the Week 52 **OR** early termination visit. |

Body Weight

| | |
|---|---|
| Screening | From 1 to 28 days prior to the baseline visit. |
| Weeks 12, 28, and 40 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. |
| Follow-up | Within ± 7 days of the date 28 days after the Week 52 **OR** early termination visit. |

Fasting Lipid Profile Test

| | |
|---|---|
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day **AND** 8 or more hours after the last meal. |
| Weeks 12, 20, 28, and 40 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day **AND** 8 or more hours after the last meal. |
| Week 52 | Within ± 7 days of the protocol-specified date **AND** 8 or more hours after the last meal. |
| Early termination | Within 2 days after withdrawal **AND** 8 or more hours after the last meal (the nutritional condition is recommended but not compulsory). |
| Follow-up | Within ± 7 days of the date 28 days after the Week 52 **OR** early termination visit. |

Chest Radiography

| | |
|---|---|
| Screening | From 1 to 28 days prior to the baseline visit. Radiographs taken before the informed consent will be acceptable as long as they were taken within 90 days before the baseline visit. |
| Weeks 28 and 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. Not mandatory; may be required at the discretion of the investigator/sub-investigator. |

12-lead ECG

| | |
|---|---|
| Screening | From 1 to 28 days prior to the baseline visit. |
| Week 28 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. |

Central ECG

| | |
|---|---|
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day. |
| Week 4 or Week 8 (before study drug administration) | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 4 or Week 8 (after study drug administration) | Within ± 7 days of the protocol-specified date **AND** 2-hour post-dose on the visit day (Recommended time point. Sampling from 1 hour to 4 hours post-dose will be acceptable.) |

**[Acceptable Time Ranges for PD Tests: Biomarker and Lymphocyte Subset Measurements]**

| | |
|---|---|
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day. |
| Weeks 4, 8, 12, and 28 | Within ± 7 days of the protocol-specified date **AND** before the initiation of treatment with the study drug on the baseline visit day. |
| Week 52 | Within ± 7 days of the protocol-specified date. |
| Early termination | Within 2 days of withdrawal. |
| Follow-up | Within ± 7 days of the date 28 days after the Week 52 **OR** early termination visit. |

**[Acceptable Time Ranges for Blood Sampling for Plasma Drug Concentration]**

Trough Concentration

| | |
|---|---|
| Baseline | Before the initiation of treatment with the study drug on the baseline visit day. |
| Weeks 4, 8, 12, 20, 28, 40, and 52 | Within ± 7 days of the protocol-specified date **AND** within 19 to 29 hours between the time of treatment with the study drug before blood collection and the time of blood collection. |
| Early termination | Within 2 days after withdrawal. |

Post-Dose Drug Concentration

| | |
|---|---|
| Week 4 or 8 | The recommended time point is 2 hours post-dose. Sampling from 1 hour to 4 hours post-dose will be acceptable. |

# 1 INTRODUCTION

## 1.1 Background

Rheumatoid arthritis (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 decreased 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 disease-modifying antirheumatic drugs (DMARDs) have been combined [Nakajima, 2009]. After the approval of methotrexate (MTX) and biologics, RA treatment improved greatly, shifting its goal from pain control to induction and maintenance of remission. In more recent years, the ultimate goal of RA therapy evolved to include clinical, structural, and functional remission. Now, researchers are attempting to achieve drug-free remission.

In Japan, MTX has been established as the standard first-line therapy for RA. The combination of tumor necrosis factor (TNF) inhibitors and other biological agents with MTX has paved the way for the treat-to-target (T2T) approach aimed at clinical and structural remission.

However, it has been that such combination therapies induced clinical remission in approximately 30% to 50% of treated patients [Y. Tanaka, 2009; K. Yamaoka, 2008], failing to control disease in most cases. In addition, MTX, a non-specific inhibitor of cellular proliferation, frequently causes adverse drug reactions in proliferative tissues such as the gastrointestinal epithelium and bone marrow, and these reactions lead to premature discontinuation in a certain proportion of patients. TNF inhibitors (e.g., etanercept, infliximab, adalimumab), selective T-cell co-stimulation modulators (e.g., abatacept), and other biologics are very expensive and require intravenous or subcutaneous administration; the issues of cost, cumbersome dosing procedure, and other factors are a hindrance to their application. Under these circumstances, low-molecular-weight DMARDs acting on a novel molecular target have captured increasing interest from drug companies.

ASP015K is an oral Janus kinase (JAK) inhibitor discovered by Astellas Pharma. *In vitro* kinase assays demonstrated that this agent effectively inhibited JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). In particular, JAK3 was suppressed in a relatively selective manner. The binding of the ligand to the cytokine receptor triggers JAK activation, and activated JAK molecules in turn phosphorylate the receptor. The phosphorylation of the cytokine receptor creates a site for interaction with the signal transducer and activator of transcription (STAT). Upon JAK-induced phosphorylation, STAT forms a dimer complex and enters into the nucleus, where the STAT dimer binds with DNA to regulate gene

transcription. Because JAK3 expression is restricted to primarily hematopoietic cells, JAK3 inhibition is a desirable therapeutic target for immunosuppression in human organ transplantation and immunomodulation in autoimmune disorders [Papageorgiou and Wikman, 2004], without significantly affecting other organ systems [Kremer et al, 2009].

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) 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 015K-CL-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. In a study using a rat model of adjuvant-induced arthritis, prophylactic use of ASP015K significantly suppressed the swelling of the injected limb and prevented the worsening of the bone destruction score assessed by radiography. 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 ether-a-go-go related gene (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 [electrocardiogram (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 orally administered a single $^{14}$C-ASP015K dose, 25.2% and 46.7% of the administered radioactivity was eliminated into urine and bile at 72 hours, respectively, suggesting an excellent oral absorption profile of ASP015K. In monkeys orally administered a single $^{14}$C-ASP015K dose, 22.3% and 26.4% of the administered radioactivity was eliminated into urine and bile at 72 hours, 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 (MMP-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/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/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/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.

### 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).

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 subject and mild in 6 subjects); mild, tension headache (3 subjects); flatulence (3 subjects; moderate in 1 subject and mild in 2 subjects); 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 WBC 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 (possibly 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, ASP015K 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, ASP015K 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 increased CPK 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, triglycerides, and total cholesterol were observed, there was no change from baseline in LDL.

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

## 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), CPK elevations 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 hour 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, have 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.

One can also expect that long-term use of ASP015K will improve QOL of RA patients by successfully controlling the RA disease activity over an extended period.

# 2 STUDY OBJECTIVE(S), DESIGN, AND VARIABLES

## 2.1 Study Objectives

The main objective of this study is to evaluate the efficacy of ASP015K (100 and 150 mg/day) versus placebo administered in combination with MTX in RA patients who had an inadequate response to MTX. The primary efficacy variables are the ACR20 response rate at Week 12 and suppression of joint destruction (change from baseline in mTSS) at Week 28. This study will also investigate pharmacokinetic, pharmacodynamic, and safety profiles. Furthermore, this study will examine the long-term efficacy and safety (52 weeks).

## 2.2 Study Design and Dose Rationale

### 2.2.1 Study Design

This study is a multi-center, randomized, placebo-controlled, double-blind, parallel-group, confirmatory study to evaluate the efficacy and safety of ASP015K (100 and 150 mg/day) administered in combination with MTX in patients with RA who had an inadequate response to MTX. The geographical scope of this study will be confined to Japan. MTX response is evaluated at the initiation of screening and then after the screening period, subjects will be randomly assigned at a 1:1:1 ratio to receive ASP015K 100 mg, ASP015K 150 mg, or placebo QD in combination with MTX. Subjects will orally receive the study drug after breakfast for 52 weeks. The target number of subjects is 170 patients per group.

Re-screening is allowed only in situations in which a subject underwent the screening procedures (i.e., scans and laboratory work) and owing to logistical circumstances, the allocated time window for these tests has expired. Re-screening is not permitted in cases in which the initial test results do not support eligibility based on inclusion and exclusion criteria. The subject must be classified as a screening failure at that time point.

Any subject found not to meet the inclusion criterion (CRP) is permitted to undergo retest only once during the screening period. This however only applies to cases in which the CRP value measured at screening exceeds 0.50 mg/dL and the most resent CRP value measured at least 28 days before the screening procedures is 1.0 mg/dL or greater.

Based on the consideration of the ethical issues related to long-term placebo use, inadequate responders in the placebo group, as determined by < 20% improvement from baseline in tender or painful joint count (TJC) and swollen joint count (SJC), will be switched at Week 12 to either ASP015K 100 mg or ASP015K 150 mg, and the dosage will be maintained until the end of treatment. In addition, subjects receiving placebo at Week 28 will be switched to either ASP015K 100 mg or ASP015K 150 mg, and the dosage will be maintained until the end of treatment. The ASP015K dose that will be started for placebo group subjects at Week 12 or Week 28 (100 or 150 mg) will be randomly chosen at baseline. The dose will be switched under the blinded condition.

Subjects who complete this study will be eligible for participation in the open-label extension study (015K-CL-RAJ2). Subjects will make a follow-up visit after the Week 52 visit if they do not enroll into the extension study on the day of the Week 52 visit.

Safety data obtained from this study will be reviewed by the Independent Data and Safety Monitoring Board (DSMB), which will make recommendations on study continuation, termination, or protocol revision from the safety perspective.

[Study Design Rationale]

According to "Guidelines on methodology for clinical assessment of antirheumatic drugs" (PFSB/ELD Notification No. 0217001, dated 17 February 2006), the appropriate treatment period for clinical studies including a group taking a placebo alone is generally held to be 12 weeks or less, and the Guidelines state that the study should be planned so that a sufficient investigation can be performed within this time frame. Taking note that 015K-CL-RAJ1 and clinical trials of similar drugs documented treatment responses sufficient for efficacy evaluation within 12 weeks of treatment, this study was designed to assess the ACR20 response rate, a primary efficacy variable, at 12 weeks of treatment.

For the other primary efficacy variable, change from baseline in mTSS (suppression of joint destruction), published guidelines recommended at least 6 months of treatment for mTSS and other radiographic assessments. In the case of similar drugs, approximately 6 months were required to monitor treatment responses for efficacy evaluation. Consequently, this study was designed to evaluate mTSS at 28 weeks of treatment, and this design required that subjects assigned to receive placebo would remain on placebo during the period, where possible. Taking into consideration the ethical issues related to long-term placebo use, this study was designed to enable switching to the active drug for subjects showing inadequate response (< 20% improvement from baseline in TJC and SJC) at Week 12. In addition, this study was designed such that all placebo group subjects would receive the active drug no later than Week 28. Because subjects of this clinical trial will receive MTX in combination with the investigational product, 28-week treatment with placebo will be ethically acceptable as long as inadequate responders of the placebo group switch to the active drug at Week 12.

Moreover, taking note of the "Guidelines on methodology for clinical assessment of antirheumatic drugs" (PFSB/ELD Notification No. 0217001, dated 17 February 2006), the duration of treatment was set at 52 weeks to evaluate the 1-year efficacy and safety as secondary endpoints.

### 2.2.2 Dose Rationale

[Dose Rationale]

Study 015K-CL-RAJ1 evaluated the efficacy, safety, and dose response of ASP015K as single-agent therapy in RA patients. This study employed 25, 50, 100, and 150 mg doses. The primary efficacy variable of this study, the ACR20 response rate at Week 12 (or early termination), showed statistically significant improvements for 50 mg and higher doses relative to placebo, and dose-dependent improvements were noted up to 150 mg. Compared

with placebo, statistically significant dose-dependent decreases in the DAS28-CRP score were observed for 50 mg, 100 mg, and 150 mg groups at Week 12 (or early termination).

When the effect size between ASP015K versus placebo for the ACR20 response rate was compared with the effect sizes reported from clinical trials of a similar design (12- to 14-week, double-blind, single-agent studies) conducted in Japan for other drugs, ASP015K 100 mg or higher doses were likely to provide levels of efficacy comparable with those of other agents.

AEs reported from 1 or more groups of Study 015K-CL-RAJ1 at ≥ 5% incidence rates were nasopharyngitis, rheumatoid arthritis aggravated, diarrhoea, constipation, blood creatine phosphokinase increased, stomatitis, dyspepsia, lipids increased, and blood triglycerides increased. Compared with placebo, the incidence rates of AEs were not significantly elevated for the ASP015K groups. The reported AEs were mostly Grade 1 or Grade 2 by severity (NCI-CTCAE), involving a high proportion of events known as the class effect of JAK inhibitors. The ASP015K 150 mg group had the highest incidence rate of study-related AEs. This group had a particularly high incidence rate of blood creatine phosphokinase increased, reported in 7 subjects. AEs of increased CPK levels were mostly transient; in all the cases, the subjects recovered completely, including 1 subject who prematurely discontinued the study owing to logistic issues. No collateral symptoms suggestive of rhabdomyolysis or myopathy were detected. Although careful monitoring of CPK levels will be necessary for individual subjects of this Phase III study, currently available data suggest that ASP015K-induced changes in CPK are reversible and that subject safety associated with CPK changes can be properly monitored. The mean changes in CPK levels reported for the ASP015K and placebo groups were comparable with those reported from tofacitinib clinical trials.

Ten SAEs were reported from 7 subjects; there was no characteristic pattern of occurrence, and no dose–response relationship was noted.

Thus, the results of Study 015K-CL-RAJ1 raised no safety concerns with the use of 100 and 150 mg/day doses in this Phase III study.

With regard to efficacy, ACR20 response rate and DAS28 score, the primary variables of the Phase II study, showed dose-dependent improvements up to 150 mg, and the observed effects were statistically significant in comparison with placebo for 50 mg and higher doses. Comparison of published data [Enbrel® Pharmaceutical Interview Form, Simponi® Pharmaceutical Interview Form, Xeljanz® Pharmaceutical Interview Form, Humira® Pharmaceutical Interview Form] showed that 100 mg and higher doses of ASP015K could provide efficacy comparable with that of the approved doses of similar drugs, supporting the validity of using 100 mg and higher doses in this Phase III study. From the safety perspective, the results of Study 015K-CL-RAJ1 confirmed the tolerability of ASP015K doses up to 150 mg.

Based on the abovementioned discussion, 100 and 150 mg/day doses were selected for this Phase III clinical trial.

[Rationale for the Mode of Administration]

Nonclinical study results showed that AUC was the most important pharmacokinetic parameter for characterizing the therapeutic effect of ASP015K. While admitting that 015K-CL-PS01 focused on a clinical condition different from that of this Phase III study, this clinical trial conducted in patients with psoriasis demonstrated no significant differences between 50 mg QD and 25 mg BID doses of ASP015K.

In Study 015K-CL-RAJ1, ASP015K was administered once daily after breakfast. This method of administration was based on the idea that the desired efficacy could be achieved regardless of the differences in the mode of administration, as long as the target AUC is attained. In addition, this method of administration was favorable from the view point of subject convenience, medication adherence, and other aspects of study implementation. Study 015K-CL-RAJ1 showed excellent medication adherence and demonstrated the efficacy of ASP015K in terms of the ACR20 response rate and other outcome measures. Therefore, administration once daily after breakfast was also adopted in this clinical trial.

## 2.3 Variables

### 2.3.1 Primary Variables

- ACR20 response rate at Week 12
- Change from baseline in mTSS at Week 28 (suppression of joint destruction)

[Rationale]

Taking note of the "Guidelines on methodology for clinical assessment of antirheumatic drugs," the ACR20 response rate, an indicator of RA disease activity and response to treatment, was chosen as a primary variable. The evaluation time point was set at Week 12 of treatment on the basis of the guidelines.

The assessment of mTSS using radiographs of the hand and foot, a measure of joint destruction suppression, was also included as a primary endpoint on the basis of the guidelines. This variable has been commonly used for clinical evaluation of similar drugs. The evaluation time point was set at 28 weeks of treatment or half a year after the start of therapy. This was chosen taking note of the longest possible duration of placebo treatment, study designs for similar drugs, and published guidelines.

### 2.3.2 Secondary Variables

#### 2.3.2.1 Secondary Efficacy Variables

- ACR20 response rate
- ACR50 response rate
- ACR70 response rate
- Change from baseline in mTSS
- Change in joint space narrowing score
- Change in erosion score

- Percentage of subjects showing no progression of joint damage ($\Delta$mTSS $\leq$ 0.5)
- Change from baseline in DAS28-CRP and DAS28-ESR scores
- Change from baseline in TJC (68 joints)
- Change from baseline in SJC (66 joints)
- Percentage of subjects achieving DAS28-CRP and DAS28-ESR scores for remission
- Percentage of subjects achieving low disease activity by DAS28-CRP and DAS28-ESR
- Change from baseline in CRP and ESR
- Percentage of subjects with good EULAR response
- Percentage of subjects with good or moderate EULAR response
- Percentage of subjects achieving ACR/EULAR remission
  If all of the following 4 parameters are fulfilled, it is defined as remission:
  - TJC $\leq$ 1
  - SJC $\leq$ 1
  - CRP $\leq$ 1 mg/dL
  - SGA $\leq$ 1 cm (on a VAS of 0-100 mm)
- Percentage of subjects achieving SDAI remission (SDAI score $\leq$ 3.3)
- Change from baseline in SDAI score
- Change from baseline in Physician's Global Assessment of Arthritis (PGA) (VAS)
- Change from baseline in Subject's Global Assessment of Arthritis (SGA) (VAS)
- Change from baseline in subject's assessment of pain (VAS)
- Incidence of subject withdrawal due to lack of efficacy
- Change from baseline in HAQ-DI score
- Change from baseline in SF-36v2® score
- Change from baseline in WPAI score

#### 2.3.2.2 Safety Variables

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

#### 2.3.2.3 Pharmacokinetics Variables

Plasma ASP015K concentration

#### 2.3.2.4 Pharmacodynamics Variables

- Change from baseline in MMP-3 level
- Change from baseline in vascular endothelial growth factor (VEGF) level
- Change from baseline in lymphocyte subset assays (CD3, CD4, CD8, CD16, CD19, CD56, CD56/16)

#### 2.3.2.5 Pharmacogenomics (Bio-Banking)

To prepare for future research to analyze the relationship between genes and the efficacy, safety, or pharmacokinetics of the study drug, blood sample will be collected and stored with the consent of the subject.

### 2.3.3 Other Variables

Not applicable.

# 3 STUDY POPULATION

## 3.1 Selection of Study Population

The target population for this study is patients with RA who had an inadequate response to MTX.

## 3.2 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 is a man or woman aged ≥ 20 years at the time of informed consent.
3. Subject has RA of < 10 years duration at baseline that was diagnosed according to the 1987 American College of Rheumatology (ACR) criteria or the 2010 American College of Rheumatology/European League against Rheumatism (ACR/EULAR) criteria.
4. Subject who did not receive the following drugs, or received the drugs with stable dosage for at least 28 days prior to the baseline (start of treatment) for RA treatment: Non-steroidal anti-inflammatory drugs (NSAIDs; excluding topical formulations with a local action), oral morphine or equivalent opioid analgesics (≤ 30 mg/day), acetaminophen, or oral corticosteroids (≤ 10 mg/day in prednisolone equivalent).
5. At screening subject has active RA as evidenced by both of the following:
   - ≥ 6 tender/painful joints (using 68-joint assessment)
   - ≥ 6 swollen joints (using 66-joint assessment)
6. CRP (latex agglutination test) of ≥ 1.00 mg/dL at screening.
7. Subject meets the ACR 1991 Revised Criteria for the Classification of Global Functional Status in RA Class I, II, or III at screening.
8. Inadequate responders to MTX which was continuously administered for at least 90 days prior to screening and MTX ≥ 8 mg/week for at least 28 days prior to baseline. However, inadequate responder to MTX < 8 mg/week is eligible if intolerance precludes dose increase and defined as MTX-IR.
9. Subject is able to continue stable dose of MTX (a maximum of 16 mg/week) from at least 28 days prior to screening until the end of treatment.
10. Subjects has bone erosion at the joint (as evidenced by x-rays of hands and feet) assessed in mTSS and any of the following apply at screening. Bone erosion may be evidenced by x-rays within 90 days prior to baseline.
    - Positive anti-CCP antibody: ≥ 4.5 U/mL
    - Positive rheumatoid factor: > 15 IU/mL
11. 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 ensure ethical and safe conduct of the study.

3: Established to select RA patients relevant for this study. Taking note of the recent changes in RA diagnostic criteria and current practices in clinical settings, patients conforming to either the 1987 ACR or the 2010 ACR/EULAR criteria have been defined eligible for inclusion.

4: Established because these drugs are used to improve QOL of RA patients and may possibly impact the efficacy evaluation of ASP015K.

5 and 6: Established to define the range of RA disease activity pertinent to this study.

7: Established to identify patients appropriate for evaluation using the classification criteria for functional status.

8: Established to select patients who had an inadequate response to, and require concomitant administration of, MTX.

9: Established to choose patients who can maintain the same dosage and administration schedule from before baseline and throughout the treatment period.

10: Established to include patients who have poor prognostic factors for joint destruction for the evaluation of joint damage prevention.

11: Established to ensure the integrity of the study evaluation.

## 3.3 Exclusion Criteria

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

1. Subject has received a biologic DMARD within the specified period:
    - Etanercept: within 28 days prior to baseline
    - Adalimumab, infliximab: within 56 days prior to baseline
    - Golimumab, certolizumab pegol: within 70 days prior to baseline
    - Abatacept, tocilizumab: within 84 days prior to baseline
    - Denosumab: within 150 days prior to baseline
    - Rituximab: within 180 days prior to baseline
2. Inadequate responders to biologic DMARD as determined by investigator/sub-investigator.
3. Subject has received a non-biologic DMARD listed below or other drugs used in the treatment of RA within 28 days prior to baseline. Leflunomide is prohibited within 180 days prior to baseline. Alternatively, leflunomide is prohibited within 28 days prior to baseline if washout with cholestyramine for at least 17 days is completed at least 28 days prior to baseline. However, topical drugs other than those for the treatment of RA may be used concomitantly.
    - Salazosulfapyridine
    - Lobenzarit
    - Gold

- Iguratimod
- *D*-penicillamine
- Bucillamine
- Actarit
- Leflunomide
- Tacrolimus
- Cyclosporine
- Cyclophosphamide
- Azathioprine
- Minocycline
- Mizoribine

4. Subject has received tofacitinib and other JAK inhibitors (including other investigational drugs).
5. Subject has received intra-articular, intravenous, intramuscular, or endorectal (excluding suppositories in patients with anal diseases) corticosteroid within 28 days prior to baseline.
6. Subject has participated in any study of ASP015K and has received ASP015K and placebo.
7. Subject received other investigational drug within 90 days or within 5 half-lives, whichever is longer, prior to baseline.
8. Subject has received plasma exchange therapy within 60 days prior to baseline.
9. Subject has undergone joint drainage, has received local anesthesia and nerve block, or has received articular cartilage protectant at the assessed joint within 28 days prior to baseline.
10. Subject has undergone surgery and has residual effects in the assessed joints at the discretion of investigator/sub-investigator, or is scheduled to undergo surgery that may affect the study evaluation of the assessed joints at the discretion of investigator/sub-investigator.
11. A diagnosis of inflammatory arthritis (psoriatic arthritis, ankylosing spondylitis, SLE, sarcoidosis, etc.) other than RA.
12. Any of the following laboratory values during the screening test period:
    - Hemoglobin < 9.0 g/dL
    - Absolute neutrophil count < 1000/μL
    - Lymphocyte count < 800/μL
    - Platelet count < 75000/μL
    - ALT ≥ 2 × ULN
    - AST ≥ 2 × ULN
    - Total bilirubin (TBL) ≥ 1.5 × ULN
    - Estimated GFR ≤ 40 mL/min as measured by the MDRD method
    - β-D-glucan ≥ 11 pg/mL
    - Positive HBs antigen, HBc antibody, HBs antibody or HBV-DNA quantitation (However, subject with negative HBs antigen and HBV-DNA quantitation, and positive HBc antibody and/or HBs antibody is eligible if HBV-DNA is monitored

by HBV-DNA quantitation at every scheduled visit after initiation of study drug administration.)

- Positive HCV antibody

13. Subject has a history of or concurrent active tuberculosis (TB). Eligibility criteria for TB are tabulated below:

| History of active TB | Chest x-ray (for TB) | TB infection[b)] | Exposure to patients with infective TB (interview) | Eligibility |
|---|---|---|---|---|
| Present | - | - | - | Not eligible |
| Absent | Abnormal (active) | - | - | Not eligible |
| | Abnormal (old)[a)] | - | Eligible | Eligible if prophylaxis is given[c)] |
| | Normal | Positive | Eligible | Eligible if prophylaxis is given[c)] |
| | | Negative | Exposed | Eligible if prophylaxis is given[c)] |
| | | | Not exposed | Eligible |

a) Old TB is evidenced if chest x-ray reveals pleural thickening, band-like shadow, and calcification ≥ 5 mm. Chest x-ray within 90 days prior to baseline may substitute the screening test.

b) T-spot or Quantiferon Gold test is of first priority. When the result is equivocal or invalid, retest including other test methods may be allowed. If a retest is not performed, criteria for positive results will be followed. When T-spot or Quantiferon Gold test is not feasible, tuberculin test will be performed. Tuberculin is defined as positive with a red spot covering an area of 20 mm or more or induration. Tests conducted within 90 days prior to baseline may be used for diagnosis.

c) Subject must receive or have received prophylaxis with isoniazid or rifampicin. Prophylaxis will be administered for 6 to 9 months, starting from at least 21 days prior to baseline.

14. Subject meets any of the following in terms of infections except for TB:
    - History of or concurrent severe herpes zoster (associated with Hunt syndrome or having ulcerative lesions) or disseminated herpes zoster
    - History of multiple recurrences (at least twice) of localized herpes zoster
    - Serious infection requiring hospitalization within 90 days prior to baseline
    - Subject received intravenous antibiotics within 90 days prior to baseline. (However, prophylactic antibiotics are allowed.)
    - Subject with high risk of infection (e.g., subject with urinary catheter) at the discretion of investigator/sub-investigator
15. Subject has a history of or concurrent interstitial pneumonia and investigator/sub-investigator judges that it is inappropriate for the subject to participate in this study.
16. Subject has a history of or concurrent malignant tumor (except for successfully treated basal cell carcinoma).
17. Subject has received live or live attenuated virus vaccination within 56 days prior to baseline. (Inactivated vaccines including influenza and pneumococcal vaccines are allowed.)
18. Subject has any ongoing severe, progressive, or uncontrolled renal, hepatic, hematological, gastrointestinal, metabolic, endocrine, pulmonary, cardiac, neurological, infectious, or autoimmune disease except for RA (excluding Sjogren's syndrome and

chronic thyroiditis), or any ongoing illness which would make the subject unsuitable for the study as determined by the investigator/sub-investigator.

19. Subject has a history of clinically significant allergy. (Clinically significant allergy includes allergies such as systemic urticaria induced by specific antigens and drugs, anaphylaxis, and allergy associated with shock necessitating hospitalized treatment.)
20. Subject has received medications that are CYP3A substrates with narrow therapeutic range within 14 days prior to baseline. These medications include: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, and disopyramide.
21. Subject has concurrent cardiac failure, defined as NYHA classification Class III or higher, or a history of it.
22. Subject has concurrent prolonged QT syndrome or a history of it. Subject has prolonged QT interval (defined as QTc ≥ 500 msec. Subject has QTc ≥ 500 msec at retest will be excluded) at screening.
23. Subject has a history of positive HIV infection.
24. 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 serum pregnancy test given at the time of screening.
25. Subject is a man who cannot practice at least 2 types of contraception from the time of informed consent to 90 days after the end of treatment, or subject is a woman with childbearing potential who cannot practice at least 2 types of contraception from the time of informed consent to 60 days after the end of treatment.
26. Male subject who do not agree not to donate sperm starting at informed consent and through the treatment period and for at least 90 days after final study drug administration. Female subject who do not agree not to donate ova starting at informed consent through the treatment period and for 60 days after final study drug administration.
27. The subject has been judged unsuitable to participate in the study for other reasons by the investigator/sub-investigator.
28. Subject has a history or complication of lymphatic diseases such as lymphoproliferative disorder, lymphoma, and leukemia.
29. Subject has congenital short QT syndrome or a history of it. Subject has shortened QT interval (defined as QTc < 330 msec. Subject has QTc < 330 msec at retest will be excluded) at screening.

[Rationale for exclusion criteria]

1, 2, 4, 5, 6, 7: Established to eliminate confounding factors affecting evaluation.

3, 8, 9, 10, 11: Established to eliminate confounding factors affecting efficacy evaluation.

12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 28, 29: Established out of safety concerns.

29: The QTc criterion is quoted from Expert Consensus [Silvia G. Priori, 2014] of HRS/EHRA/APHRS.

27: Established in anticipation for a case where the investigator/sub-investigator judges a patient to be inappropriate for participation in the study.

## 3.4 Discontinuation Criteria for Individual Subjects

A discontinuation is a subject who enrolled in the study and for whom study treatment is permanently prematurely discontinued for any reason.

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 the subject's clinical condition warrants it.

The Appendix 4 entitled "Liver Safety Monitoring and Assessment" describes liver function tests raised that provide grounds for discontinuation. Refer to Appendix 4 concerning the measures to take for increases in liver function test parameters.

The investigator/sub-investigator should discontinue the study if any of the following occurs:

1. The subject withdraws consent.
2. The investigator/sub-investigator judges that the study drug is not sufficiently effective and the treatment method needs to be changed.
3. Symptomatic CPK elevation (> 1.5 × ULN accompanied with severe and unusual episodes of myalgia, muscular weakness, or muscle twitching).
4. Any case of myopathy involving severe and unusual episodes of myalgia, muscular weakness, or muscle twitching that persists for no less than, or aggravates rapidly within, 2 weeks, regardless of the CPK level.
5. A previously HBV-infected patient with positive HBc antibody, positive HBs antibody, or both has been shown positive for HBV-DNA during the study.
   Attention should be paid that abrupt discontinuation of immunotherapy may cause fulminant or severe liver failure. Therefore, if the subject manifests HBV reactivation, the investigator/sub-investigator will administer nucleoside analogs without delay according to the "Proposal for Management of Rheumatic Disease Patients with Hepatitis B Virus Infection Receiving Immunosuppressive Therapy" (Japan College of Rheumatology). The investigator/sub-investigator will carefully decide whether to continue or discontinue the study drug and concomitant DMARDs in consultation with the hepatology specialist.
6. Malignant tumor
7. The subject develops a serious infection or other AEs, and continued administration of the study drug is not deemed appropriate in the subject's best interest by the investigator/sub-investigator.

8. The subject has been treated with a prohibited concomitant drug or therapy (including another investigational product) that may impact efficacy evaluation. The subject has been, or needs to be, treated with a rescue medication for a period extending beyond its allowable time. Otherwise, the subject has been, or needs to be, treated with a live or live attenuated vaccine.
9. The subject has been judged by the investigator/sub-investigator to be non-compliant to the medication requirements for the study drug or MTX.
10. The subject is deemed incapable of continuing the follow-up based on the opinion of 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. The subject needs the study drug to be interrupted beyond its allowable time limit.
13. Investigator/sub-investigator decides it is in the subject's best interest.
14. The sponsor has requested that the study be discontinued because of a safety problem in a particular subject, or the sponsor has decided to discontinue the study altogether.
15. The subject shows QTc interval < 300 msec at Central ECG, or the subject shows QTc interval < 300 msec at the study site's ECG and also shows QTc interval < 300 msec at retest.

Subjects who discontinue early from the study should be given the necessary tests and assessments specified for early termination within 2 days of withdrawal. They should also undergo follow-up tests and assessments. Subjects with early termination will be treated as discontinuations, and the investigator/sub-investigator must make clear the reason for discontinuation and the day of early termination (the date on which the investigator/sub-investigator has decided to discontinue the subject) as well as retain all clinical study data on the discontinuations and submit them to the sponsor in eCRF, etc.

### 3.4.1 Suspension, Interruption, and Resumption of the Study Drug

If the subject meets during the treatment period any of the criteria provided in Section 3.4.1.1 Criteria for Suspension or Interruption of the Study Drug, the investigator/sub-investigator will immediately suspend or interrupt the treatment. The investigator/sub-investigator can resume the study treatment only if re-examinations and other assessments performed after the suspension or interruption confirm that none of the conditions listed below are applicable to the subject and the investigator/sub-investigator considers it desirable for the interest of the subject on the basis of risk–benefit analysis.

The maximum allowable time for "suspension" is 7 days. If the study treatment is halted beyond the suspension period, i.e., longer than 7 days, the period of no treatment is categorized as an "interruption."

Upper limits have been set to the number of interruptions 1 subject can have and to the duration of 1 interruption. One interruption period may last for 28 days. One subject is allowed to have a maximum of 2 interruptions, which must be separated by 16 or more weeks.

The investigator will consult the sponsor regarding the handling of a subject who repeatedly requires treatment suspension.

The subject must be withdrawn from the study, if he or she requires either a third interruption or a second interruption within 16 weeks from the first one.

#### 3.4.1.1 Criteria for Suspension or Interruption of the Study Drug

The investigator/sub-investigator will immediately suspend or interrupt the study drug if any of the following becomes applicable during the treatment period:

1. Clinical laboratory tests yielded any of the following results:
   - Hemoglobin < 8.0 g/dL
   - Absolute neutrophil count < 500/μL
   - Absolute lymphocyte count < 500/μL
   - Platelet count < 50000/μL
   - Creatinine (serum) levels measured at 2 consecutive hospital visits: above 150% of the baseline level
   - CPK > 10 × ULN
2. β-D-glucan test result of 11 pg/mL or higher.
3. The subject requires a medication whose concomitant administration is prohibited in the protocol because of possible drug–drug interaction.
4. The subject is suspected to be pregnant.
5. The investigator/sub-investigator judged it appropriate in the interest of the subject to suspend or interrupt the study drug.
6. The sponsor made a request to suspend or interrupt the study drug out of safety concerns for the subject.

# 4 STUDY DRUGS

## 4.1 Description of Study Drugs

The test drugs for this study are ASP015K tablets of 100 mg and 150 mg, and the comparative drugs are placebo tablets for ASP015K of 100 mg and 150 mg.

### 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 100 mg: An elliptical, pale-red, film-coated tablet containing the ASP015K drug substance at 100 mg (as free form)<br>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)

| | |
|---|---|
| Code name | ASP015K |
| Content and dosage form | ASP015K tablet 100 mg placebo: An elliptical, pale-red, film-coated tablet indistinguishable from the ASP015K tablet 100 mg<br>ASP015K tablet 150 mg placebo: An elliptical, yellow, film-coated tablet indistinguishable from the ASP015K tablet 150 mg |
| 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 |

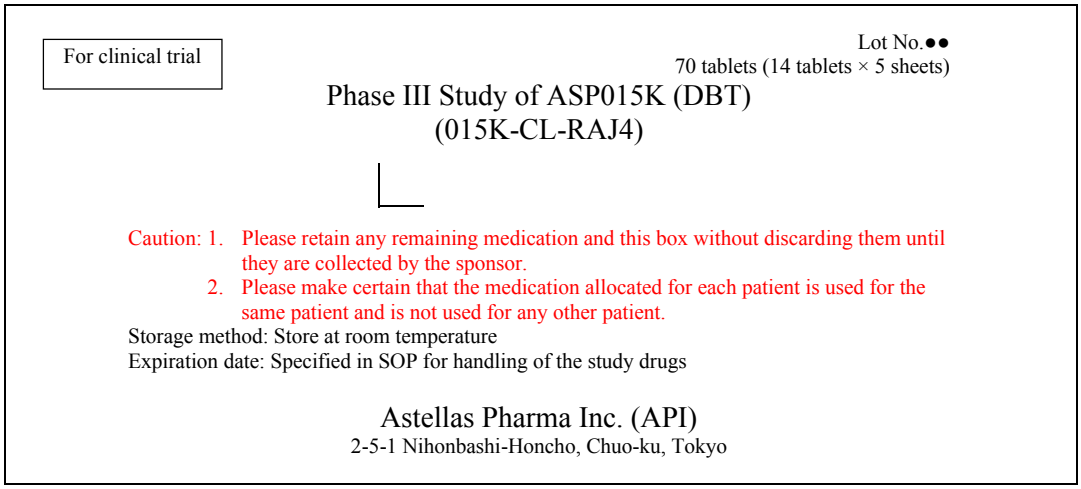
## 4.2 Packaging and Labeling

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

(Packaging form)

The study drugs will be packaged in a small box containing 28 day's worth of medication and 7 day's worth of spare medication. One PTP sheet (aluminium/aluminium) holds a total of 14 tablets: 7 tablets of ASP015K at 100 mg or placebo for ASP015K at 100 mg and 7 tablets of ASP015K at 150 mg or placebo for ASP015K at 150 mg. Five PTP sheets (including 1 spare sheet) will be packaged in the small box.

(Small box)




Lot No. is noted in SOP for handling of study drugs.

## 4.3 Study Drug Handling

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

- The study drug storage manager should store and take accountability of the study drugs in conforming to the procedures for handling the study drugs written 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 by the protocol, and reconcile all the study drugs supplied from the sponsor.

## 4.4 Blinding

### 4.4.1 Blinding Method

Treatment allocation to the ASP015K 100 mg, ASP015K 150 mg, or placebo groups is double-blinded. The ASP015K tablet 100 mg, ASP015K tablet 100 mg placebo, or ASP015K tablet 150 mg, ASP015K tablet 150 mg placebo are indistinguishable from each other in appearance, and the packaging for each treatment group (100 mg, 150 mg, and placebo) is also indistinguishable from that for other groups in appearance. The treatment code will only be known to the person responsible for assigning study drugs, person appointed at the

institution performing measurements of plasma drug concentrations, persons in the Safety Control Division when necessary for Suspected Unexpected Serious Adverse Reaction (SUSAR) handling, and independent Data and Safety Monitoring Board (DSMB).

### 4.4.2 Confirmation of the Indistinguishability of the Study Drugs

The appearance and the form of both the drug and packaging of the ASP015K tablet 100 mg and ASP015K tablet 150 mg are identical to those of their matching placebo. The person responsible for assigning study drugs will confirm the indistinguishability of the study drugs and their packaging in appearance before the assignment of the study drugs and during the period from collection of the study drugs to the breaking of the treatment code.

### 4.4.3 Retention of the Assignment Schedule and Procedures for Treatment Code Breaking

The person responsible for assigning study drugs will create a randomization list (original document) plus 3 copies (reproductions) in advance of the assignment of the study drug and seal each separately. The person responsible for assigning study drugs will retain the original randomization list. One copy of the randomization list (reproduction) will be retained by the sponsor in a sealed state even after the breaking of the treatment code, one copy will be prepared for use by DSMB, and the third copy will be provided to the institution performing measurements of plasma drug concentrations by the person responsible for assigning study drugs to be used as a sample measurement instruction sheet bearing treatment code information.

The person responsible for assigning study drugs will also create a treatment code for emergency and provide it to the person responsible for managing the treatment code for emergency. The person responsible for managing the treatment code for emergency will manage individual treatment code for emergency with code breaking permission in the web-based system. The web treatment code system can only be accessed by the person responsible for managing treatment code for emergency, the sponsor's responsible personnel (or sponsor), and the person in charge of the Safety Control Division when necessary for SUSAR handling. The "SOPs for the Phase III Study of ASP015K DSMB" should be followed for treatment code retention, breaking, and code information conservation at the time of safety data review and safety evaluation.

### 4.4.4 Breaking the Treatment Code for Emergency

In the event of a medical emergency requiring knowledge of the treatment assigned to the subject, the investigator/sub-investigator can ask the sponsor to break the treatment code for emergency for the subject in question. The sponsor will make the decision as to whether or not to break the treatment code for emergency. The "SOPs for breaking the treatment code for emergency in Phase III study of ASP015K (015K-CL-RAJ4)" should be followed when the treatment code is broken. The investigator/sub-investigator, sponsor, and the person responsible for managing the treatment code for emergency should maintain contact so that the treatment code can be broken immediately in an emergency. When a sub-investigator requests that the treatment code be broken in an emergency, the consent of the investigator

should in principle be obtained in advance. However, in cases where it is difficult to obtain the understanding of the investigator in advance, the sub-investigator should immediately report the request to break the treatment code for an emergency to investigator after the fact. After the treatment code has been broken by the investigator or other responsible personnel, the study center must report the breaking of the treatment code and the reason for doing so to the contacts listed in the "Section II CONTACT DETAILS OF KEY SPONSOR'S PERSONNEL."

### 4.4.5 Breaking the Treatment Code by the Sponsor

The sponsor may break the treatment code for subjects who experience SUSAR if regulatory reporting is considered necessary. An individual emergency code will be provided to the limited staff who are empowered to break the code for all SUSAR cases for reporting purposes.

## 4.5 Assignment and Allocation

The person responsible for assigning study drugs will randomly assign the study drugs and retain the treatment code under secrecy until the breaking of the treatment code.

The Case Registration Center will assign subjects who have been found to be eligible for enrollment in accordance with the case registration procedures to 1 of the following groups: ASP015K 100 mg, ASP015K 150 mg, or placebo groups at baseline in 1:1:1 ratio. At Week 12, subjects in the placebo group whose tender and swollen joint counts have not improved by 20% from baseline will be assessed as having an inadequate response, and they will be switched to receiving either ASP015K at a dose of 100 mg or ASP015K at a dose of 150 mg. Subjects who are continuing to receive placebo at Week 28 will be switched to receiving either ASP015K at a dose of 100 mg or ASP015K at a dose of 150 mg.

The dose of ASP015K (100 mg or 150 mg) to be administered to the placebo group from Week 12 or Week 28 is decided randomly at baseline, and study drugs must always be switched under double-blind conditions.

All drug numbers are assigned randomly by the Case Registration Center under blind conditions.

# 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) Dose and administration period

The following 3 treatment groups will be set up: ASP015K 100 mg group, ASP015K 150 mg group, and placebo group. The dose for each treatment group is shown in the table below.

The administration period will be 52 weeks. Two tablets of the drug described in the table below will be administered QD. Subjects in the placebo group who are showing an inadequate response at Week 12 will be switched to receiving either ASP015K at a dose of 100 mg or ASP015K at a dose of 150 mg under blind conditions. Subjects who are continuing to receive placebo at Week 28 will be switched to receiving either ASP015K at a dose of 100 mg or ASP015K at a dose of 150 mg. The dose of ASP015K to be administered to the placebo group after the switching at Week 12 or Week 28 will be determined in advance at baseline and will be continued until Week 52.

- Confirmation of inadequate response at Week 12
  The investigator/sub-investigator will confirm the numbers of tender joints (of 68) and swollen joints (of 66) at Week 12 and confirm the rate of improvement from baseline. Subjects in the placebo group whose rate of improvement in tender and swollen joint counts is less than 20% will receive a different dose from Week 12. The rate of improvement will be confirmed for all subjects to maintain the blindness of the placebo group during the dose change at Week 12.

Table Treatment Periods and Doses by Treatment Period (Administered Drug) in Study 015K-CL-RAJ4

<table>
<tr><th></th><th>Baseline–Week 12</th><th>Week 12–Week 28[1)]</th><th>Week 28–Week 52[2)]</th></tr>
<tr><td rowspan="4">Placebo group</td><td rowspan="4">ASP015K placebo<br>(ASP015K tablet 100 mg placebo and<br>ASP015K tablet 150 mg placebo</td><td rowspan="2">ASP015K placebo<br>(ASP015K tablet 100 mg placebo and<br>ASP015K tablet 150 mg placebo)</td><td>100 mg/day as ASP015K<br>(ASP015K tablet 100 mg and<br>ASP015K tablet 150 mg placebo)</td></tr>
<tr><td>150 mg/day as ASP015K<br>(ASP015K tablet 100 mg placebo<br>and ASP015K tablet 150 mg)</td></tr>
<tr><td colspan="2">100 mg/day as ASP015K<br>(ASP015K tablet 100 mg and<br>ASP015K tablet 150 mg placebo)</td></tr>
<tr><td colspan="2">150 mg/day as ASP015K<br>(ASP015K tablet 100 mg placebo and<br>ASP015K tablet 150 mg)</td></tr>
<tr><td>ASP015K 100 mg group</td><td colspan="3">100 mg/day as ASP015K<br>(ASP015K tablet 100 mg and ASP015K tablet 150 mg placebo)</td></tr>
<tr><td>ASP015K 150 mg group</td><td colspan="3">150 mg/day as ASP015K<br>(ASP015K tablet 100 mg placebo and ASP015K tablet 150 mg)</td></tr>
</table>

1) Subjects in the placebo group whose rate of improvement in tender and swollen joint counts is less than 20% at Week 12 will be assigned to receiving either ASP015K 100 mg or ASP015K 150 mg. Subjects will continue receiving the assigned dose thereafter.

2) Subjects in the placebo group who continued receiving placebo until the visit at Week 28 will be assigned to receiving either ASP015K 100 mg or ASP015K 150 mg. Subjects will continue receiving the assigned dose thereafter.

(2) Mode of administration

The assigned study drug will be orally administered to subjects under double-blind conditions QD after breakfast. The baseline dose should be given at each study center on the day of the baseline visit after all assessments and tests are completed.

Doses on the day of scheduled visits during the treatment period should be given on the day of the visit after all assessments and tests are completed, except for blood sampling for the assessment of post-dose concentrations.

### 5.1.2 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.

(1) Previous medications

Pharmaceutical name, daily dose, route of administration, period of administration, and reason for administration of drugs used within the past 90 days, counting back from before administration on the day of the baseline visit

- DMARD, prohibited concomitant medications, restricted concomitant medications (taken within 28 days prior to baseline), rescue medications (taken within 28 days prior to baseline)

Medications for the treatment of RA (biologic DMARD, non-biologic DMARD) should be entered separately in the eCRF as the treatment history of the target disease described in Section 5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease.

(2) Previous therapies

None

(3) Concomitant medications

The survey period will be from the initiation of study treatment on the day of the baseline visit.

Information on pharmaceutical name, daily dose, route of administration, period of administration, and reason for administration of DMARD, prohibited concomitant medication, restricted concomitant medication, and rescue medication will be collected.

In addition, pharmaceutical name, route of administration, period of administration, and reason for administration of medications other than DMARD, prohibited concomitant medication, restricted concomitant medication, rescue medication, and the following will be obtained.

- Solution for dissolving or diluting (water for injection, saline), disinfectant, rinsing fluid, surface anesthetic for tests and procedures (such as Xylocaine jelly), contrast media for tests (such as barium, noniodinated contrast media), anticoagulants for use by the IV placement route, foaming agents and laxatives for use during tests, and topical drugs for local effect and for purposes other than RA.

  *However, if such medications are used for the purpose of treating an adverse event, they should be entered in the eCRF.

Medications for the treatment of RA (biologic DMARD, non-biologic DMARD) should be entered separately in the eCRF as the treatment history of the target disease described in Section 5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease.

(4) Concomitant therapies

The survey period will be from the initiation of study treatment on the day of the baseline visit.

The name, purpose, and duration of therapies performed for RA, and adverse events will be obtained. Procedures (such as gauze replacement) and therapies (such as rehabilitation) performed for surgery will not be considered as concomitant therapies.

#### 5.1.2.1 Previous Medication (Drugs and Therapies)

A period during which a drug cannot be used or a therapy is prohibited will be established as follows before the initiation of administration of the study drug for any previous medication (drugs and therapies) that could affect the evaluation of ASP015K:

1) Necessary concomitant medications

- MTX

The use of MTX will be continued from 90 or more days before the initiation of screening and under the same dosage and administration schedule (≤ 16 mg/week) from 28 or more days before the initiation of screening until the day of the baseline visit. If MTX is temporarily interrupted or its dose is reduced within 28 days prior to the baseline visit in a subject eligible at screening for the study based on inclusion and exclusion criteria, the screening period will be extended to allow for the same dosage and administration schedule to be observed for 28 days prior to the baseline visit.

- Folic acid

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 ALT/AST becomes ≥ 3 × ULN, MTX must be interrupted, or the dose must be reduced, and daily administration of folic acid should be considered.

2) Prohibited concomitant medications and therapies:

- Biologic DMARD

The following biologic DMARDs will be prohibited during the period shown below:

- Etanercept: within 28 days prior to baseline
- Adalimumab, infliximab: within 56 days prior to baseline
- Golimumab, certolizumab pegol: within 70 days prior to baseline
- Abatacept, tocilizumab: within 84 days prior to baseline
- Denosumab: within 150 days prior to baseline
- Rituximab: within 180 days prior to baseline

- Non-biologic DMARD

Non-biologic DMARDs, excluding MTX, will be prohibited within 28 days prior to baseline. In addition, the use of leflunomide will be prohibited within 180 days prior to baseline. However, if washout with cholestyramine for at least 17 days is completed before 28 days prior to baseline, the use of leflunomide is prohibited within 28 days prior to baseline. 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, minocycline, and other drugs indicated for the treatment of RA will be prohibited within 28 days prior to baseline.

- Corticosteroids

Oral corticosteroids at doses exceeding 10 mg per day in the prednisolone equivalent will be prohibited within 28 days prior to baseline.

The intra-articular, intravenous, intramuscular, and endorectal corticosteroid administration will also be prohibited within 28 days prior to baseline. However, suppositories for anal diseases may be used concomitantly.

- Oral morphine

Oral morphine at doses exceeding 30 mg per day (or equivalent doses of other opioid analgesics) will be prohibited within 28 days prior to baseline.

- Other study drugs

Other study drugs will be prohibited within 90 days or 5 half-lives, whichever is longer, prior to baseline.

- CYP3A substrates

The following CYP3A substrates with a narrow therapeutic range will be prohibited within 14 days prior to baseline: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide, etc.

- Vaccines

Live or live attenuated virus vaccinations will be prohibited within 56 days prior to baseline. Inactivated vaccines may be administered (influenza, pneumococcal vaccines, etc.).

- Plasma exchange therapy

Plasma exchange therapy will be prohibited within 60 days prior to baseline.

- Surgical treatment methods

After obtaining informed consent, surgery involving the target joint will be prohibited.

- Effusion drainage, local anesthesia, and nerve block of the target joint

Effusion drainage, local anesthesia, and nerve block of the target joint will be prohibited within 28 days prior to baseline.

- Articular cartilage protective agents

The use of articular cartilage protective agents in the target joint will be prohibited within 28 days prior to baseline.

3) Restricted concomitant medications

- If administration of concomitant medication is to be continued during the treatment period, changes to the dosage, administration schedule, or route of administration of the drugs below will not be allowed within 28 days prior to baseline.
- If administration of concomitant medication is discontinued before the initiation of study treatment, administration of the drugs below is prohibited within 28 days prior to

baseline [except in cases where NSAIDs and analgesics other than NSAIDs (acetaminophen, opioid analgesics, all-in-one cold and flu medications, etc.) are used as rescue medication].

- In the case of a medically unfavourable event during the screening period, administration may be temporarily interrupted, or the dose may be temporarily reduced. The period of interruption is up to 28 days. When resuming administration, the dose prior to interruption/reduction is the upper limit.
  - NSAIDs (excluding topical drugs with a local action)
  - Oral morphine
    (Not more than 30 mg per day, or equivalent doses of other opioid analgesics)
  - Acetaminophen
  - Oral corticosteroids
    (However, at 10 mg per day or less in the prednisolone equivalent and from the visit at Week 28, the dose may be reduced or increased within the range not exceeding the baseline dose.)

4) Rescue medications

The drugs listed below may be used within 28 days prior to baseline only if they are necessary for treating a medically unfavourable event or acute worsening of the primary disease. However, these medications may not be taken within 24 hours before joint assessment at baseline.

- NSAIDs: For 3 days or less
- Analgesics other than NSAIDs (acetaminophen, opioid analgesics, all-in-one cold and flu medications, etc.): For 7 consecutive days or less.

#### 5.1.2.2 Concomitant Medication (Drugs and Therapies)

1) Necessary concomitant medications

- MTX

MTX will be used from 28 or more days before the initiation of screening under the same dosage and administration schedule (≤ 16 mg/week) and continued during the treatment period under the same dosage.

In the case of AEs, administration may be temporarily interrupted, or the dose may be temporarily reduced. The period of interruption is up to 28 days. When resuming administration, the dose may be increased with the baseline dose as the upper limit. Administration may only be interrupted once.

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 ALT/AST becomes ≥ 3 × ULN, MTX must be interrupted, or the dose must be reduced, and daily administration of folic acid should be considered.

2) Prohibited concomitant medications and therapies:

- Biologic DMARDs

The following biologic DMARDs will be prohibited during the treatment period:

Adalimumab, infliximab, golimumab, certolizumab pegol, abatacept, tocilizumab, rituximab, etanercept, and denosumab

- Non-biologic DMARDs

Non-biologic DMARDs, excluding MTX, will be prohibited during the treatment period. However, topial 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, and other drugs indicated for the treatment of RA will be prohibited during the treatment period.

- Corticosteroids

Oral corticosteroids at doses exceeding 10 mg per day in the prednisolone equivalent will be prohibited during the treatment period.

The intra-articular, intravenous, intramuscular, and endorectal corticosteroid administration will also be prohibited during the treatment period. However, suppositories for anal disease may be used concomitantly.

- Oral morphine

Oral morphine at doses exceeding 30 mg per day (or equivalent doses of other opioid analgesics) will be prohibited during the treatment period.

- Other study drugs

Other study drugs will be prohibited during the treatment period and follow-up period.

- CYP3A substrates

The following CYP3A substrates with a narrow therapeutic range will be prohibited during the treatment period and follow-up period: dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, temsirolimus, disopyramide, etc.

- Vaccines

Live or live attenuated virus vaccinations will be prohibited during the treatment period and the follow-up period. Inactivated vaccines may be administered (influenza, pneumococcal vaccines, etc.)

- Plasma exchange therapy

Plasma exchange therapy will be prohibited during the treatment period.

- Surgical treatment methods

Surgery involving the target joint will be prohibited during the treatment period.

- Effusion drainage, local anesthesia, and nerve block of the target joint

Effusion drainage, local anesthesia, and nerve block of the target joint will be prohibited during the treatment period.

- Articular cartilage protective agents

The use of articular cartilage protective agents in the target joint will be prohibited during the treatment period.

3) Restricted concomitant medications

If the drugs below are to be continued during the treatment period, changes to the dosage, administration schedule, or route of administration of the drugs below will not be allowed from 28 days prior to baseline to the end of treatment, unless the specific conditions for the change are met.

- If the drugs below are discontinued before the initiation of study treatment, administration of the drugs below is prohibited from 28 days prior to baseline to the end of treatment [except in cases where NSAIDs and analgesics other than NSAIDs (acetaminophen, opioid analgesics, all-in-one cold and flu medications, etc.) are used as rescue medication].
- In the case of AEs, administration may be temporarily interrupted, or the dose may be temporarily reduced. The period of interruption is up to 28 days. When resuming administration, the baseline dose is the upper limit.
- From the visit at Week 28, the drugs below may be discontinued, new drugs may be used, and the dosage, administration schedule, or route of administration of the concomitant drugs may be changed. However, with the exception of oral corticosteroids, after changing the conditions, administration must be continued under the same conditions for 12 weeks or longer.
  - NSAIDs (excluding topical drugs with a local action)
  - Oral morphine
    (Not more than 30 mg per day, or equivalent doses of other opioid analgesics)
  - Acetaminophen
  - Oral corticosteroids
    (However, at 10 mg per day or less in the prednisolone equivalent and from the visit at Week 28, the dose may be reduced or increased within the range not exceeding the baseline dose.)

4) Rescue medications

During the treatment period, the drugs listed below may be used if they are necessary for treating AEs, comorbid conditions, or acute aggravation of the primary disease. However, these medications may not be taken within 24 hours before joint assessment at each visit.

- NSAIDs: For 3 days or less
- Analgesics other than NSAIDs (acetaminophen, opioid analgesics, all-in-one flu and cold medications, etc.): For 7 consecutive days or less

### 5.1.3 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.

- Do not take multiple doses all at once if doses of the study drug have been missed.
- Bring any remaining study drug with you to the next scheduled examination.
- Immediately contact the investigator, sub-investigator, or collaborator if there is a shortage of the study drug before the next visit due to the loss of study drugs, etc.

The investigator/sub-investigator will confirm each subject's compliance status during the treatment period with the study drug on the basis of information given by the subject and the number of tablets of the study drug collected from the subject, and the investigator/sub-investigator will record the number of tablets prescribed and the number of unused tablets in the eCRF. 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, each subject should be asked regarding the most recent day on which the study drug was taken and the time at which it was taken, at each scheduled visit at Weeks 4, 8, 12, 20, 28, 40, and 52, and at discontinuation, and information should be recorded in the eCRF.

### 5.1.4 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 under full monitoring to ensure the safety of the subject.

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

### 5.1.5 Criteria for Continuation of Treatment

Subjects in the ASP015K 100 mg, ASP015K 150 mg, or placebo groups who completed the assessment at study visit at Week 52 may participate in an extension study (015K-CL-RAJ2) if they wish to do so. Each subject must provide informed consent for the extension study before completing the assessment at study visit at Week 52.

### 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.

- In principle, subjects should visit the study center for the study visit on the specified date. The visits may be adjusted within an allowable range, but the visit dates must be adjusted so that the intervals between the specified visits are 5 weeks at most.

- The subject should come to the study center on the day of each study visit without taking the 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 a subject must make an unscheduled visit due to adverse events, etc., on the day of taking the study drug, the unscheduled visit will be prioritized regardless of whether the study drug was taken and the timing of meals.
- 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/sub-investigator in advance, the subject should contact one of them, or the collaborator, as soon as possible.
- Any subject who wishes to take prescription medication or over-the-counter drugs unconfirmed by the investigator/sub-investigator should confirm with the investigator, sub-investigator, or collaborator in advance whether to take the drug. If it is not possible to contact the investigator/sub-investigator in advance, the subject should contact one of them, or the collaborator, as soon as possible.
- Subjects must practice contraception through 2 or more appropriate contraceptive methods throughout the study period, and for 90 days after the end of treatment in the case of male subjects and for 60 days after the end of treatment in the case of female subjects of childbearing potential.
- Female subjects must not breastfeed throughout the study period and for 60 days after the end of treatment.
- If another visit is instructed by the investigator/sub-investigator due, for example, to a laboratory finding subject to CPK monitoring and liver function monitoring, the subject must promptly visit the study center.

## 5.2 Demographics and Baseline Characteristics

### 5.2.1 Demographics

The date of obtaining informed consent, date of birth, and sex will be recorded in the eCRF. In addition, height, history of smoking, and alcohol consumption habits will be confirmed during the screening test period and recorded in the eCRF.

### 5.2.2 Medical History

Diseases cured before the initiation of study treatment will be regarded as previous diseases, and diseases that remain uncured at the initiation of study treatment will be regarded as concurrent diseases. All concurrent diseases will be investigated, and the name of the diagnosis will be recorded in the medical record or other source documents, as well as in the eCRF. Serious infectious diseases (in the past 365 days from baseline) and herpes zoster are

subjects to investigation, and the history, name of diagnosis, date of onset, and date of recovery will be entered in the eCRF.

#### 5.2.3 Diagnosis of the Target Disease, Severity, and Duration of Disease

Information on following items will be obtained and entered in the eCRF:

- Name of diagnosis, onset date of RA, and criteria for the classification of RA used for the diagnosis (Appendix 5, Appendix 6)
- ACR 1991 revised criteria for the classification of global functional status in RA (Appendix 7) at screening
- Classification of disease stage/progression of RA (Appendix 8) at screening
- History of surgery for RA (name of surgery, joint operated, possibility of joint assessment)
- Names of RA treatment drugs used in the past (DMARD), treatment response, and tolerability
- Timing for the initiation of MTX for the treatment of RA, dose of MTX from 90 days before the initiation of screening, treatment response at the initiation of screening, tolerability at the initiation of screening, and reason for the assessed tolerability (reason why the dose of MTX cannot be increased)
- Measurements of anti-CCP antibody and RF at the time of the screening test (obtained as laboratory results)
- Date of performing hand and foot radiography during the screening period (radiography results from within 90 days prior to baseline may be used), and presence or absence of bone erosion

## 5.3 Efficacy, Pharmacodynamics, and Pharmacokinetics Assessments

### 5.3.1 Efficacy Assessments

#### 5.3.1.1 Tender and Swollen Joint Counts

The following assessments will be performed on the scheduled assessment days from the screening visit onward:

(1) Tender joint count
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. The 28 joints subject to assessment will also be examined for tender joints and the location will be confirmed. The number of respective confirmed joints and the date of assessment will be entered in the eCRF.

(2) Swollen joint count
The investigator/sub-investigator will examine the subject for swollen joints, assessing the 66 joints listed below, with the exception of the hip joints, and confirm the location of the swollen joints. The 28 joints subject to assessment will also be examined for

swollen joints and the location will be confirmed. The number of respective confirmed joints and the date of assessment will be entered in the eCRF.

Table Joints Subject to Assessment

| |
|---|
| Temporomandibular joints (2), sternoclavicular joints (2), acromioclavicular joints (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

#### 5.3.1.2 Assessment of Pain and Overall Assessment of Disease Activity

The following assessments will be performed on the scheduled assessment days from the baseline onward:

(1) Subject's assessment of pain: The subject assesses his/her own pain severity on a VAS of 0–100 mm on the questionnaire form. The measured value and the date of assessment will be entered in the eCRF.

(2) SGA: The subject assesses his/her own disease activity on a VAS of 0–100 mm on the questionnaire form. The measured value and the date of assessment will be entered in the eCRF.

(3) PGA: The investigator/sub-investigator assesses the subject's disease activity on a VAS of 0–100 mm on the physician assessment table. The measured value and the date of assessment will be entered in the eCRF.

#### 5.3.1.3 Acute Phase Reactant (CPR and ESR)

Only CRP is measured during the screening test period. Blood sampling is performed on the scheduled assessment days from baseline to measure CRP and ESR. The measurement of CRP will be performed by the central laboratory ([redacted]), and the measurement of ESR will be performed by each study center. These results will be used to calculate DAS28, SDAI, and ACR response criteria assessment.

One-hour value of ESR will be measured. The measured ESR and the date of measurement will be entered in the eCRF.

#### 5.3.1.4 EULAR Response Criteria

Based on DAS28 scores and changes in DAS28 scores before and after treatment with the study drug, EULAR Response Criteria categorize response to treatment as "No response," "Moderate response," or "Good response" according to the definition given in the table below [van Gestel et al, 1996; van Gestel et al, 1998].

Table Definition of EULAR Response Criteria Assessment

| DAS28 after treatment | DAS28 response (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 the screening visit and at each subsequent assessment days specified in the 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 of > 5.1
- Moderate disease activity: DAS28 score of > 3.2 and ≤ 5.1
- Low disease activity: DAS28 score of ≤ 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 baseline and Week 12 will be calculated using data from the following assessments, together with 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 HAQ-DI, and acute phase reactant (CRP or ESR).

The ACR20 response requires that all criteria from (1) to (3) below be met. The ACR50 response indicates a 50% improvement in all criteria from (1) to (3) below, and the ACR70 response similarly indicates a 70% improvement. In this study, [5] is assessed with CRP.

(1) TJC: ≥ 20% reduction compared with baseline

(2) SJC: ≥ 20% reduction compared with baseline

(3) ≥ 20% improvement in 3 or more of the following 5 parameters compared with baseline

[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 assessments at baseline and on days specified in the Schedule of Assessments. The outcome of the assessments will be recorded in the eCRF. In principle, the copy of assessment forms will be provided to the sponsor.

- HAQ-DI [Fries et al, 1982; Ramey et al, 1992]
- SF-36v2® [Ware, 2004]
- WPAI [Takeuchi T, 2011; Reilly MC, 1993]

#### 5.3.1.9 Hand and Foot Radiography

Radiography of hands and feet (posterioranterior radiograph of both hands and dorsoplantar radiograph of both feet) will be taken at baseline, Week 12 (only for subjects whose improvement in TJC and SJC from baseline is less than 20%), Week 28, Week 52, and at early termination.

The subject information on hand and foot radiography images (film or digital data) taken from baseline will be masked, and the images will be sent to the institution performing the assessment of hand and foot radiography images. If retake of the images is requested by a third party institution due to faults of the location or quality of the sent images, the images must be retaken immediately and sent within 30 days of the request for retake. The date of taking radiography will be entered in the eCRF.

The manual provided by sponsor will be followed for the method of taking radiography and sending the images.

The third party institution will assess the severity of joint destruction in hands and feet (bone erosion and joint fissure narrowing) through the mTSS method by scoring the severity of bone erosion and joint fissure narrowing of the target joints and calculate the total score. The target joints and the scoring method are described in the SOP prepared by the third party institution.

The results of the assessment will be sent to the sponsor by the third party institution.

The attending physician will confirm the hand and foot radiography at screening for the presence/absence of bone erosion, and this physician will enter the date of taking the images, date of assessment, and the presence/absence of erosion in the eCRF. However, the presence/absence of bone erosion may be confirmed from hand and foot radiography taken within 90 days prior to baseline.

### 5.3.2 Pharmacodynamic Assessments

Blood samples will be collected at baseline and on days specified in the Schedule of Assessments. At the study visit points where blood sample collection for PK assessment is performed, sample collection for PD assessment will be performed before study drug administration and at the same time as that for the sampling for PK assessment. These measurements will be performed at the central laboratory ([redacted]), and the results will be reported to the sponsor and the study center after the breaking of the treatment code.

#### 5.3.2.1 Lymphocyte Subsets

Lymphocyte subset quantification of CD3, CD4, CD8, CD16, CD19, CD56, and CD56/16 will be performed, and the changes from baseline will be calculated. The date of blood sampling will be entered in the eCRF.

#### 5.3.2.2 Biomarkers for Efficacy and Safety Assessments

To assess the effects of ASP015K on biomarkers, VEGF and MMP-3 will be measured, and the changes from baseline will be calculated. The date of blood sampling will be entered in the eCRF.

Additional analysis may be performed for biomarkers for efficacy and safety assessments based on study results using blood samples that have been collected during the study and biobanked (i.e., residual sample stored for retrospective analysis). These could include biomarkers of inflammation, bone or cartilage metabolism, or inhibitory activity of JAK, but other biomarkers may also be subject to analysis.

### 5.3.3 Pharmacokinetic Assessments

The concentration of ASP015K will be measured. If necessary, the concentrations of ASP015K metabolites will be measured. Blood samples will be collected at baseline and on the days specified in the Schedule of Assessments. Moreover, the date and time on which the

last dose of study drug will be taken just prior to blood sampling will be recorded in the eCRF, together with the date and time of blood sampling.

The sampling for the assessment of post-dose concentrations will be performed as a substudy at study centers approved for the sampling. The sampling for the assessment of post-dose concentrations will be performed at either Week 4 or Week 8, 2 hours after the administration of the study drug (the acceptable time range is from 1 hour to 4 hours post-dose). In addition, the sampling for post-dose concentrations will be performed on the same day as Central ECG at Week 4 or Week 8, promptly after the Central ECG.

## 5.4 Safety Assessment

The following tests and observations will be made for the purpose of safety assessments at baseline and on the days specified in the Schedule of Assessments. The requirements for reporting and analysis of information on drug-induced liver injury (DILI) are in Appendix 4 "Liver Safety Monitoring and Assessment." If marked liver function abnormal in Appendix 4 is observed, the investigator or the responsible personnel should contact the sponsor or CRO by telephone or fax (within 24 hours of awareness).

### 5.4.1 Vital Signs

Blood pressure (in the sitting position), pulse rate, and body temperature at rest will be measured at screening and on the days specified in the Schedule of Assessments. The date of measuring and measurements taken (blood pressure and the measuring position, systolic blood pressure, diastolic blood pressure, pulse rate, and body temperature) will be entered in the eCRF.

### 5.4.2 Body Weight

Body weight will be measured at screening and on the days specified in the Schedule of Assessments. The date of measuring and measurements taken will be entered in the eCRF.

### 5.4.3 Adverse Events

The survey period for AEs will be from the initiation of study treatment to before the initiation of administration in the extension study or until the end of follow-up.

Events that occurred after study drug administration until before the initiation of administration in the extension study or until the end of follow-up will be recorded as AEs. Concurrent diseases that worsened during the study will also be recorded as AEs. AEs that occurred after the subject has completed the study plan or has been discharged from the hospital or the study center will not be recorded.

AEs that have not resolved before the initiation of administration in the extension study or at the end of follow-up must 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 the event resolves during the study period, the date of resolution is to be entered in the eCRF.

See Appendix 4 "Liver Safety Monitoring and Assessment" for the assessment of AEs caused by DILI.

Herpes zoster should be entered as an AE information in the eCRF, and also, a separate Herpes Zoster (shingles) Worksheet should be prepared, and a copy should be submitted to the sponsor. If the sponsor considers necessary and requests for submission of forms for the purpose of providing additional information on other AEs, a form must be prepared to report to the sponsor.

#### 5.4.3.1 Adverse Events of Possible Hepatic Origin

Subjects with liver-derived AEs associated with hepatic function abnormal should be monitored carefully.

### 5.4.4 Laboratory Assessments

The below hematology, biochemistry, fasting lipid profile, and urinalysis will be performed at screening and on each of the days specified in the Schedule of Assessments. These measurements will be performed at the central laboratory ([redacted]). For the period of performing additional laboratory tests for DILI, see Appendix 4 "Liver Safety Monitoring and Assessment."

Additional sampling and tests may be performed if it is considered necessary by the investigator/sub-investigator or if retesting is considered necessary by the investigator/sub-investigator because the results could not be obtained due to defects in the sample. Additional tests and analysis may be performed based on the study results using blood samples for laboratory assessments that have been collected during the study and have been biobanked (i.e., residual samples stored for retrospective analyses).

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

   The following hematology, biochemistry, fasting lipid profile tests, and urinalysis will be performed:

- Hematology

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

  Each blood cell count will be calculated from the differential WBC.

- Biochemistry

  Na, K, Ca, Cl, Mg, $HCO_3$, BUN, phosphorus, glucose, creatinine, ALP, AST (GOT), ALT (GPT), γ-GTP, total bilirubin, total protein, albumin, uric acid, CPK, LDH, serum amylase, eGFR, β-D-glucan

- Fasting lipid profile

  Total cholesterol, LDL, HDL, triglycerides

  The date of sample collection will be entered in the eCRF.

- Blood specimens for scheduled fasting lipid profile tests should be drawn after the subject has fasted for at least 8 hours, unless it is at termination or at an unscheduled visit when the subject could not fast.

- Urinalysis

  pH, specific gravity, protein (qualitative), glucose (qualitative), keton bodies (qualitative), bilirubin (qualitative), occult blood, sediment

2) Pregnancy test (for females only)

   Pregnancy testing will be performed from screening according to the Schedule of Assessments. Serum pregnancy testing is required only at screening, and urine pregnancy testing will be performed after baseline. The serum pregnancy testing will be performed by the central laboratory and the urine pregnancy testing will be performed by the study centers using the kits provided by the central laboratory. If, in the serum pregnancy test, hCG level exceeds ULN, but the possibility of pregnancy can be completely ruled out by another test, the subject is eligible for enrollment. Pregnancy testing is not subject to the safety assessment.

   - If a urine pregnancy test is positive at any time, a negative serum pregnancy is required for the subject to continue participation in the study. If the possibility of pregnancy can be completely ruled out by another test, the subject may continue to participate 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.

3) Tuberculosis test

   The tuberculosis test will be performed at screening to confirm the eligibility of the subject in accordance with Exclusion Criterion 13. T-SPOT or QuantiFERON Gold test is the preferential test for tuberculosis infection. If T-SPOT or QuantiFERON Gold test cannot be performed, tuberculin skin test may be performed instead. Tuberculin test and QuantiFERON Gold test cannot be performed at the central laboratory.

   Tuberculosis test is not required at screening provided that there is documentation of a negative tuberculosis test within 90 days prior to baseline.

4) Hepatitis test

   Tests for HBs antigens, HBs antibodies, the HBV-DNA assay, HBc antibodies, and HCV antibodies will be performed at the screening visit to confirm the eligibility of the subject. If a subject is positive for either or both HBc antibodies and HBs antibodies, the subject will be monitored during the treatment period by performing an HBV-DNA assay at scheduled visits and early termination. Safety analysis will not be performed for the results of HBV-DNA assays from baseline.

5) CPK monitoring

If an increase in CPK is observed, in accordance with Section 5.4.4.1 CPK Monitoring, when CPK is retested, CPK, CK-MB, troponin T, and aldolase should also be tested. Urinalysis (blood and microscopy) will be performed as part of the targeted physical examination.

#### 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 laboratory testing reveals CPK > 3 × ULN, and the subject is asymptomatic, retest CPK preferably within 1 week of previous blood sampling to confirm it. Subsequently, retest CPK weekly (from the date of the initial CPK elevation) until CPK is ≤ 3 × ULN or is stable according to the judgment of the investigator/sub-investigator. If the retest cannot be performed within 1 week of blood sampling, which marks the starting point of CPK monitoring, suspension or interruption of the study drug should be considered until the retest results are obtained.
- In subjects whose baseline CPK is already > 3 × ULN, if laboratory testing reveals CPK > 2 × baseline, and the subject is asymptomatic, retest CPK preferably within 1 week of previous blood sampling to confirm it. Subsequently, retest CPK weekly (from the date of CPK elevation to > 2 × baseline) until CPK is ≤ 2 × baseline, or is stable in the judgment of the investigator/sub-investigator. If the retest cannot be performed within 1 week of blood sampling, which marks the starting point of CPK monitoring, suspension or interruption of the study drug should be considered until the retest results are obtained.
- If CPK is > 10 × ULN at any time, treatment will be immediately suspended or interrupted (see Section 3.4 Discontinuation Criteria for Individual Subjects), and retest CPK.
- If there is a symptomatic CPK elevation (CPK elevation > 1.5 × ULN accompanied by severe and unusual episodes of myalgia, muscular weakness, or muscle twitching), as reported by the investigator/sub-investigator, treatment will be immediately discontinued (see Section 3.4 Discontinuation Criteria for Individual Subjects).

In the retest for CPK monitoring, the following tests will be performed in addition to CPK measurements. The content of the subject questionnaire will be entered in the eCRF.

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

#### 5.4.4.2 Hepatic Function Abnormal

If laboratory testing for a subject enrolled in the study and receiving the study drug reveals an increase in serum aminotransferase (ALT, AST) > 3 × ULN or TBL > 2 × ULN, at least 4 parameters (ALT, AST, ALP, and TBL) of the usual hepatic function test parameters should be retested. The retest should be performed between 48 hours and 72 hours after notification of the test results.

For additional information on monitoring and the assessment of the hepatic function test, see Appendix 4 “Liver Safety Monitoring and Assessment.”

If laboratory testing for a subject enrolled in the study receiving the study drug reveals an increase in serum aminotransferase (ALT, AST) > 3 × ULN and TBL > 2 × ULN, the investigator will determine whether it is an SAE. Even if the abnormality is not considered an SAE by the investigator/sub-investigator, it will be reported to the sponsor or CRO in writing as in the case of SAEs.

### 5.4.5 Physical Examination

A physical examination will be performed at scheduled visits and early termination to confirm physical findings.

Physical findings and RA symptoms will be confirmed at unscheduled visits whenever possible.

### 5.4.6 12-lead Electrocardiogram (ECG)

A 12-lead ECG will be obtained at screening and on the assessment dates specified in the Schedule of Assessments. The investigator/sub-investigator will confirm the ECG chart, assess the results as “normal,” “abnormal but not to a clinically important degree,” or “clinically important abnormality,” and record the results of the assessment in the CRF. If the finding is “abnormal but not to a clinically important degree” or “clinically important abnormality,” the finding will be recorded in the CRF.

The screening 12-lead ECG must be performed within 4 weeks prior to the first dose of study drug. In addition, the clinical interpretation of the results of this examination must be completed prior to the first dose of study drug.

### 5.4.7 Radiography

Chest radiography will be performed at screening and on the assessment dates specified in the Schedule of Assessments. Chest radiography examination will be performed at early termination if it is determined necessary by the investigator/sub-investigator. However, chest radiography at screening is not required provided that there is documentation of a normal chest radiograph within 90 days of baseline. The investigator/sub-investigator will confirm the chest radiographic images, assess the results as “normal,” “abnormal but not to a clinically important degree,” or “clinically important abnormality,” and the investigator/sub-investigator record the results of the assessment in the eCRF.

If the results of chest radiography at screening reveal findings of tuberculosis, the subject's eligibility will be decided in accordance with Exclusion Criterion 13.

### 5.4.8 Central ECG

Central ECG is conducted as sub-study at the sites which approved blood sampling for post-dose drug concentration. Subjects in the reference group will be excluded from Central ECG. Central ECG is performed at baseline before study drug administration, as well as before study drug administration and 2 hours after study drug administration at Week 4 or Week 8 on the same day as blood sampling for post-dose drug concentration at Week 4 or Week 8. 12-lead ECG is performed as Central ECG. The measurement date and time of central ECG is recorded in the eCRF.

The measuring and transmittal method of Central ECG in the handling manual provided by sponsor is followed. The QT interval, QTcF, and QTcB will be calculated by the third party using the Central ECG data transmitted and the method of ECG analysis is described in the handling manual prepared by the third party.

## 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 or has undergone study procedures and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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 the study drug
- 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. The rationale for the assessment of the causal relationship does not need to be recorded for all AEs but only at the request of the sponsor. The severity of each event should be recorded on a scale of Grade 1 to Grade 5 in the eCRF, and the causal relationship to the study drug should be recorded as "Probable," "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 documents and in the eCRF. The outcome should be recorded in the medical record or other source documents and in the eCRF as "resolved," "alleviated," "unresolved," "resolved but with late effects," "death," or "unknown."

### 5.5.2 Definition of Serious Adverse Events (SAEs)

An adverse event 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 adverse event 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 adverse event that, had it occurred in a more severe form, might have caused death)
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- 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 to be considered as 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 one 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 intensive treatment in an emergency room or at home for allergic bronchospasm; 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 the medical events described in Appendix 3 "Events Always considered to be Serious" and Appendix 4 "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 drug 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 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:<br>• Could also be explained by concurrent/underlying disease or other drugs<br>• 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:<br>• Recurs upon re-administration of the drug, or disappears or is alleviated when the drug is withdrawn.<br>• 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 a serious adverse event (SAE), the investigator must contact the Sponsor/delegated CRO by telephone or fax immediately (within 24 hours of awareness).

The investigator should complete and submit an SAE Worksheet containing all information that is required by the Regulatory Authorities to the Sponsor/delegated CRO by fax immediately (within 24 hours of awareness). If the faxing of an SAE Worksheet is not possible or is not possible within 24 hours, the local drug safety contact should be informed by phone.

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

Please fax the SAE Worksheet to:

Contact Information of the Sponsor

[redacted]

TEL: [redacted], FAX: [redacted]

Contact Information of CRO

[redacted]

TEL: [redacted], FAX: [redacted]

### 5.5.6 Follow-up of 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 adverse event progresses to an "SAE", or if a subject experiences a new SAE, the investigator must immediately report the information to the Sponsor.

Even if the subject does not return to normal or to his/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 on the case report form for the follow-up, and
3. The Sponsor judges that the reason is acceptable with regard to the safety of the subject concerned.

For details of follow-up of DILI (medical history, concomitant medications, history of alcohol intake and narcotic use), see Appendix 4 “Liver Safety Monitoring and Assessment.”

### 5.5.7 Procedure in Case of Pregnancy

If a woman is proven to be pregnant during the treatment period or within 28 days from the end of treatment or at early termination, the investigator should report this information to the sponsor/CRO in the same manner as that for an SAE. The expected date of delivery, last menstruation, 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 anomalies), 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 the miscarried fetus is evaluated by visual examination unless test results which 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, and the investigator must report the pregnancy to the sponsor/CRO.

### 5.5.8 Supply of New Information Affecting the Conduct of the Study

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, the Sponsor should inform all the investigators involved in the clinical study, the head of the study site, and the regulatory authorities of such information. The head of the study site who receives such information 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 8.2.3.3 Supply of New and Important Information Influencing the Subject's Consent and Revision of the Written Information.
2. In addition to the above item 1, when the head of the study site receives the revisions of the Investigator's Brochure, protocol, or written information, information on the matters covering the quality of the study drug, efficacy and safety, information necessary for conducting the clinical study properly, or documents to be examined by the IRB should be sent to the IRB.

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

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the subjects. When the investigator does not follow the protocol in order to avoid urgent risks for subjects, the investigator should take the following actions.

1. Describe the contents of the deviation or amendment and the reasons 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 site. 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. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the Sponsor.

## 5.6 Test Drug Concentration

The plasma concentrations of ASP015K will be measured in the samples collected at the time points in Table 1 Schedule of Assessments. The concentrations of ASP015K metabolites H1, H2, and H4 will be measured if necessary.

In the placebo group, the concentrations of samples collected during the period of the administration of placebo will not be measured, but the concentration of samples collected after switching to ASP015K 100 mg or ASP015K 150 mg will be measured. The concentration of the sample collected on the day of the visit for switching will be measured as baseline.

The subject registration center will provide information on study drug assignment to the institution performing measurements of drug concentrations.

Whether to measure the concentrations of samples from the placebo group depends on switching to ASP015K 100 mg or ASP015K 150 mg; thus, the subject registration center will provide the institution performing measurements of drug concentrations with information on whether subjects switched to ASP015K 100 mg or ASP015K 150 mg at Week 12. After obtaining information on switching, the institution performing measurements of drug concentrations will measure the drug concentrations of samples of subjects in the placebo group who switched to ASP015K 100 mg or ASP015K 150 mg.

Concentration measurements will be performed by [redacted] using a validated, established LC-MS/MS method [Test No.: [redacted] (ASP015K, H2), [redacted] (H4), [redacted] (H1)]. The lower limit of quantification is 0.25 ng/mL. Blood samples for drug concentration (2 mL/sample) will be collected into a 2 mL vacutainer tube containing ethylenediamine-tetra-acetic acid ($K_3$EDTA-3K). See the written explanation of testing procedure enclosed in the clinical laboratory testing kit for descriptions of the procedure for sampling blood and storing and shipping the blood samples. The central laboratory ([redacted]) will not report the results of determinations to the investigator, sub-investigator, sponsor, or other third parties until the breaking of the treatment code.

## 5.7 Other Measurements, Assessments, or Methods

### 5.7.1 Pharmacodynamic Measurements

In this study, the following will be measured as part of the pharmacodynamic evaluation: biomarkers of bone or cartilage metabolism and lymphocyte subsets (see Section 5.3.2.2 Biomarkers for Efficacy and Safety Assessments).

Blood samples for biomarkers of bone or cartilage metabolism will be collected in a 2 mL sampling tube containing EDTA-2Na, and samples for lymphocyte subsets will be collected in a 2 mL vacutainer tube containing EDTA-2K. See the written explanation of testing procedure enclosed in the clinical laboratory testing kit for descriptions of the procedure for sampling blood and storing and shipping the blood samples.

The central laboratory ([redacted]) will not report the results to the investigator, sub-investigator, sponsor, or other third parties until the breaking of the treatment code.

### 5.7.2 Purposes of Pharmacogenomics

- Pharmacogenomics will only be performed at study centers that have approved to the content of the research, and only those study centers will follow the procedures described in Sections 5.7, 8.2, and 8.3.
- To prepare for future research that will analyze the relationship between genes and the efficacy, safety, or pharmacokinetics of the test drug, blood samples will be collected and stored.
- To prepare for future research that will analyze the relationship between genome and the efficacy or safety of the test drug, biological samples will be stored over long-term. Details will be described in the “Bio-Banking Procedures” prepared separately.
- To prepare for future exploratory research on biomarkers that can predict the pharmacologic response [efficacy and toxicity (adverse drug reactions)] through the analysis of genetic information from this study or from integration of other studies using this test drug, biological samples will be collected and stored.
- If a serious adverse drug reaction is observed, samples for genomic/genetic analysis will be collected to explore the markers related to the adverse drug reaction.

### 5.7.3 Handling and Storage for Samples Used for Pharmacogenomics

To prepare for future research that will analyze the relationship between genes and the efficacy, safety, or pharmacokinetics of the study drug, blood samples will be collected and stored after obtaining consent from the subject to participate in PGx research and after randomization of blood samples and, whenever possible, before the first dose of the study drug. If it is not possible to take the sample before the first dose, it should be taken by the end of the study. The subject’s consent to participate in the PGx research must be obtained after the subject has given consent to participate in the main study and by the time the blood sample for bio-banking is taken.

At study centers approved to conduct PGx research, blood samples will be taken from those subjects participating in the main study who have given written consent for the collection and storage of blood samples for use in PGx research. On one occasion during the study period, the investigator, sub-investigator, or collaborator will collect 5 mL of peripheral blood from a forearm vein(s) in a storage tube and store it at the study center at 4ºC until the time of specimen collection. The date on which informed consent was obtained and the sampling date should be recorded for each subject and entered into the eCRF. The sample collection and shipping agency should then temporarily store the blood sample for PGx research (at −20ºC or −80ºC) and send it to the prolonged storage laboratory for samples used in PGx research. The prolonged storage laboratory for samples used in PGx research will collect the blood samples and store them at −80ºC until it is time to analyze them. All collected PGx samples will be maintained for a period of up to 15 years after database hard lock.

- Sample anonymization: Because the specific content of the analyses to be performed in the PGx research has not yet been determined, the specimens will be double coded and anonymized. After the first code (subject identification code) has been assigned by the study center, the second code will be assigned by the prolonged storage laboratory for samples used in PGx research.

### 5.7.4 Disposal of Pharmacogenomics Samples

At the conclusion of the retention period, or if the prolonged storage laboratory for samples used in PGx research has been notified by the investigator to the effect that the subject has withdrawn consent for PGx research or that the sponsor has decided to dispose of the stored samples, the prolonged storage laboratory for samples used in PGx research should promptly remove the labels from the tubes holding the subject's samples and dispose of the samples as appropriate. If genome/gene analysis has been performed before the end of the storage period or before consent is withdrawn, the data obtained through that analysis will not be destroyed.

### 5.7.5 Disclosure of Genetic Information

Even if PGx research is conducted in the future, the research will be exploratory, and since any results obtained from the gene analyses (results of gene assays, relationship between genes and drug response) are expected to be lacking in accuracy and definitiveness, the results of the gene analysis will not be disclosed.

## 5.8 Total Amount of Blood

The approximate total volume of blood required for tests performed at the central laboratory ([redacted]) during the study period is as follows:

Additionally, there will be 15 samplings for ESR at the study center, and the amount will differ between the centers (1 mL to 2 mL). The amount of blood required for T-SPOT (tuberculosis test) to be performed at the central laboratory is 10 mL.

Subjects who are positive for hepatitis and continuing the study will require a HBV-DNA assay at each scheduled visit after initiation of study drug administration, and the amount of blood required is 5 mL per assay.

Moreover, if blood samples are required at unscheduled visits or follow-up, the amount will increase. If CK-MB, troponin T, and aldolase are measured as part of CPK monitoring, the amount of blood required is 4 mL per assessment.

| Assessment | Screening | Baseline | Week 4 | Week 8 | Week 12 | Weeks 16, 20, 24, 28, 32, 36, 40, 44, 48 | Week 52 or at early termination | Follow -up | Volume of sample (mL) |
|---|---|---|---|---|---|---|---|---|---|
| Hematology, biochemistry (including CRP, fasting lipid profile test) | 16 | 16 | 16 | 16 | 16 | 144 (16 × 9) | 16 | 16 | 256 |
| Hepatitis test, anti-CCP antibody, RF | 9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 9 |
| Hepatitis DNA testing* | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| Trough concentration | 0 | 2 | 2 | 2 | 2 | 6 (2 × 3) (Weeks 20, 28, 40 only) | 2 | 0 | 16 |
| PD sampling | 0 | 4 | 4 | 4 | 4 | 4 (Week 28 only) | 4 | 4 | 28 |
| PGx | 0 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 5 |
| Post-dose concentration (if performed) | | | 2 | | | | | | 2 |
| Total | 30 | 27 | 24** | 22 | 22 | 154 | 22 | 20 | 321 |

*: HBs antibody, if a subject is HBc antibody-positive and requires hepatitis DNA testing from baseline, 5 mL of the blood sample are required at each scheduled visit.

**: For convenience, the sampling for the assessment of post-dose concentration is summarized at Week 4.

# 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 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 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 and PK analysis plan based on the opinions and advice from a medical expert and/or statistical advisor. After review, it will be finalized prior to unblinding.

## 7.1 Sample Size

A total of 510 treated patients, with 170 in each treatment group

[Rationale for the sample size]

The sample size calculation was based on ASP015K Japanese Phase IIb study (015K-CL-RAJ1) result and other Japanese studies for patients with RA [XELJANZ®, tablet, 5 mg, CTD (2013)] [CIMZIA, sc, 200 mg, Syringe, CTD (2012)]. In the 015K-CL-RAJ1 study, the primary efficacy endpoint, which was Percentage of Subjects achieving ACR20 response at Week 12/ET, was 54.5% in the 100 mg, and 65.5% in the 150 mg. Therefore, in the 015K-CL-RAJ4 study, it can be assumed to achieve same magnitude of ACR20 response at Week 12/ET for both 100 mg and 150 mg. For ACR20 response at Week 12/ET in the placebo group, it was assumed 25% based on other Japanese drugs for RA.

Meanwhile, the change in mTSS at Week 28 was estimated to be 0.5 in ASP015K 150 mg group, considering the results of the Japanese subgroup analysis of the Oral Scan Study of Tofacitinib, a drug of same class and indication (5 mg group: −0.0, 10 mg group: 0.5), Study CDP870-041 of Cimzia (100 mg group: 1.05, 200 mg group: 0.21, 400 mg group: 0.65), and Study RA0006 (200 mg group: 0.44). Similarly, the change in mTSS at Week 28 was estimated to be 2.0 in the placebo group, considering the results of the Japanese subgroup analysis of the Oral Scan Study (placebo group: 1.4), Study CDP870-041 (placebo group: 2.78), and Study RA0006 (placebo group: 2.49). The standard deviation of the change was also estimated and set to 4.0 based on the results reported from the same studies [Japanese subgroup analysis of the Oral Scan Study (placebo group: 3.15, 5 mg group: 1.09, 10 mg group: 1.54), Study CDP870-041 (placebo group: 5.15, 100 mg group: 2.85, 200 mg group: 2.01, 400 mg group: 2.95), and Study RA0006 (placebo group: 5.52, 200 mg group: 1.83)].

On this assumption, the necessary sample size was calculated to enable to analyze ACR20 using the Fisher's exact test and the change in mTSS at Week 28 using the t-test. When a closed testing procedure (in Section 7.4.1.1 Primary Analysis) considering multiplicity is used in the primary analysis, the sample size needed to verify the hypotheses Step 1 through Step 3 at a 2-sided 5% significance level with 90% power is 151 subjects per group. By considering about 10% drop-out, this study will enroll 170 patients in each treatment group. Moreover, from the long term safety point of view, this sample size is also needed to keep 300 subjects for 6 month period, 100 subjects for 1 year period in both ASP015K 100 mg and 150 mg among RAJ2/RAJ3/RAJ4 studies.

## 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 at the Case Review Meeting based on the opinions and advice from a medical expert and/or statistical advisor.

### 7.2.1 Full Analysis Set (FAS)

The FAS will consist of all subjects who are randomized and receive at least one dose of the study drug. This will be the primary data set for efficacy analyses.

### 7.2.2 Per Protocol Set (PPS)

#### 7.2.2.1 PPS for Assessing ACR and DAS at Week 12 (PPS-ACR)

The PPS-ACR includes all subjects of the FAS who meet the following criteria. PPS-ACR is defined based on the data up to Week 12.

- Have no violation of inclusion criteria;
- Do not meet any exclusion criteria possibly interfering with the efficacy evaluation;
- Period of study treatment between the initiation of administration and Week 12 is 8 weeks (56 days) or longer (those who have discontinued study treatment due to the lack of efficacy will be included in PPS);
- Have treatment compliance of 75% or higher during the 12 weeks of study administration (Week 12 or at early termination before Week 12);
- Have evaluable ACR20 at the end of Week 12 (Week 12 or at early termination before Week 12);
- Have no major protocol violations after registration.

Subjects who are considered to have no impact on the efficacy evaluation at the Case Review Meeting will also be included in the PPS-ACR, if they are not satisfying these criteria.

#### 7.2.2.2 PPS for the Assessment of the Inhibition of Joint Destruction at Week 28 (PPS-MTSS)

The PPS-MTSS includes all subjects of the FAS who meet the following criteria. PPS-MTSS is defined based on the data up to Week 28.

- Have no violation of inclusion criteria;
- Do not meet any exclusion criteria possibly interfering with the efficacy evaluation;
- Period of study treatment between the initiation of administration and Week 28 is 8 weeks (56 days) or longer (those who have discontinued study treatment due to the lack of efficacy will be included in PPS);
- Have treatment compliance of 75% or higher during the 28 weeks of study administration (Week 28 or at early termination before Week 28)
- Have evaluable change in mTSS from baseline at the end of Week 28 (Week 28 or at early termination before Week 28)
- Have at least 1 mTSS data at baseline and from Week 12
- Have no major protocol violations after registration

Subjects who are considered to have no impact on the efficacy evaluation at the Case Review Meeting will also be included in the PPS-MTSS, if they are not satisfying these criteria.

#### 7.2.3 Safety Analysis Set (SAF)

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

#### 7.2.4 Pharmacokinetic Analysis Set (PKAS)

The PKAS will consist of all subjects who receive at least one dose of the study drug and who provide samples for drug concentrations for at least one time point.

#### 7.2.5 Pharmacodynamics Analysis Set (PDAS)

All subjects who receive at least one dose of the study drug and who provide samples for the determination of pharmacodynamic parameters at least one time point will be included in the PDAS.

## 7.3 Demographics and Other Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group (ASP015K 100 mg group, ASP015K 150 mg group, placebo group) for SAF. Descriptive statistics will include sample size, mean, standard deviation, minimum, median and maximum for continuous variables, and frequency and percentage for categorical variables. To detect a possible treatment imbalance among treatment groups, chi-squared test will be used to analyze categorical variables and one-way analysis of variance (ANOVA) will be used to analyze continuous variables. The significance level is set at 0.05.

## 7.4 Analysis of Efficacy

Efficacy analysis will be conducted on FAS and PPS. The interpretation of results from statistical tests will be based on the FAS. In the primary analysis of the primary variable, the purpose of using PPS is to assess the robustness of the results from the statistical tests based on FAS. Unless otherwise noted, analysis will performed in the treatment groups at allocation (ASP015K 100 mg group, ASP015K 150 mg group, placebo group) and, if necessary, in the treatment groups taking into consideration a switch from placebo to active treatment (ASP015K 100 mg group, ASP015K 150 mg group, placebo–ASP015K 100 mg group at Week 12, placebo–ASP015K 150 mg group at Week 12, placebo–ASP015K 100 mg group at Week 28, placebo–ASP015K 150 mg group at Week 28).

#### 7.4.1 Analysis of Primary Variable

##### 7.4.1.1 Primary Analysis

Primary analysis will be conducted on FAS. However, the assessment of joint destruction will be performed in subjects with at least 1 data at baseline and from Week 12.

For ACR20 response at Week 12/ET, pairwise comparisons to placebo will be performed at each ASP015K dose level using Fisher's exact test in the primary analysis. For mTSS change from baseline at Week 28/ET, pairwise comparisons to placebo will be performed at each ASP015K dose level using rank analysis of covariance (ANCOVA) with treatment group (Placebo, ASP015K 100 mg, ASP015K 150 mg) as factor and baseline rank mTSS as covariate in the primary analysis.

Closed testing procedure shown below will be used for multiplicity adjustment in the primary analysis.

Step 1. ACR20 response at Week 12/ET: ASP015K 150 mg vs. Placebo

Step 2. ACR20 response at Week 12/ET: ASP015K 100 mg vs. Placebo

Step 3. mTSS change from baseline at Week 28/ET: ASP015K 150 mg vs. Placebo

Step 4. mTSS change from baseline at Week 28/ET: ASP015K 100 mg vs. Placebo

The null hypothesis at Step 1 will be tested at a significance level of 0.05. If it is statistically significant, the next step will be initiated. Otherwise, it is completion of the hypothesis test. These hypothesis tests continue up to Step 4 unless it is rejected.

For the missing imputation of ACR20 at Week 12/ET, Last Observation Carried Forward (LOCF) methodology will be used.

For subjects who discontinued at or before Week 28 or switched to receive ASP015K instead of placebo at Week 12 due to the lack of efficacy, mTSS at Week 28 will be extrapolated using linear extrapolation method based on the mTSS at baseline and early termination or Week 12 (before switching).

#### 7.4.1.2 Secondary Analysis

The same analysis of the primary variable as described in Section 7.4.1.1 will be conducted using the PPS. A sensitivity analysis will be conducted to impute the missing data.

#### 7.4.1.3 Subgroup Analysis

Subgroup analyses for sex, age, and other categories may be explored.

### 7.4.2 Analysis of Secondary Variables

For secondary efficacy endpoints, binary variables such as Percentage of subjects achieving ACR50 response at Week 12/ET, Percentage of subjects achieving ACR70 response at Week 12/ET will be analyzed using Fisher’s exact test, and continuous variables, such as Change from baseline/Day 1 to Week 12/ET in DAS28-CRP and DAS28-ESR scores, will be analyzed using ANCOVA with treatment group as factor and baseline as covariate. Each ASP015K group will be compared with placebo group and multiplicity for the secondary efficacy variables will not be adjusted.

## 7.5 Analysis of Safety

The following analyses will be performed in SAF. Unless otherwise noted, analyses will be performed in the treatment groups at allocation (ASP015K 100 mg group, ASP015K 150 mg group, placebo group) and, when necessary, in the treatment groups after placebo was switched to active treatment (ASP015K 100 mg group, ASP015K 150 mg group, placebo–ASP015 100 mg group at Week 12, placebo–ASP015K 150 mg group at Week 12, placebo–ASP015K 100 mg group at Week 28, and placebo–ASP015K 150 mg group at Week 28).

### 7.5.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of AEs, SAEs, AEs leading to discontinuation, and AEs whose relationship to the study drugs could not be ruled out will be summarized by system organ class and preferred term, as well as the treatment group. The incidence of AEs by severity will also be summarized.

### 7.5.2 Laboratory Assessments

Descriptive statistics will be used to summarize clinical laboratory measurements and the change from baseline if quantitative, by time point. The frequency of each discrete value will be summarized by time point.

### 7.5.3 Vital Signs

Descriptive statistics will be used to summarize vital sign measurements and the 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 QT Assessment

- Descriptive statistics will be used to summarize QT assessment (including QTc assessment) measurements and the change from baseline.
- The frequency of each category of QT assessment (including QTc assessment) will be summarized by time point.

In addition, the relationship between quantity of QT change and concentration of ASP015K may be explored.

### 7.5.6 Body Weight

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

## 7.6 Analysis of Pharmacokinetics

A detailed elaboration of the PK analysis will be included in a separate PK analysis plan. The trough plasma concentrations of ASP015K will be summarized by treatment group and visit. Exploratory population PK analysis may be performed by pooling the results obtained so far.

## 7.7 Other Analyses

### 7.7.1 Analysis of Pharmacodynamics

Analysis will be performed in PDAS. Descriptive statistics will be used to summarize PD measurements and the change from baseline by time point.

### 7.7.2 Analysis of Pharmacogenomics

At present, the content of analysis as part of pharmacogenomic research has not been determined yet. The relationship between the results from genetic analyses and study data (clinical information such as pharmacological activity, toxicity and PK) may be explored in the future. The sponsor can initiate such research once a specific methodology is established. Prior to research, the sponsor will prepare a research plan (including procedures and timing of document disposal) and have appropriateness of conduct of the research reviewed and approved by the sponsor's ethics review committee from ethical and scientific viewpoints.

## 7.8 Interim Analysis (and Early Discontinuation of the Clinical Study)

Not applicable. Review of safety data and safety evaluation will be completed by an independent DSMB [see Section 10.1 Independent Data and Safety Monitoring Board (DSMB)] during the study in accordance with separate SOP.

## 7.9 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 and/or statistical advisor prior to treatment code breaking 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 date 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. Subjects who have no evaluable post-dose data on ACR20, ACR50, and ACR70 response rates will be counted as non-responders and included in the analysis at the end of Week 12 (Week 12 or at early termination before Week 12).

### 7.9.1 Handling of Schedule of Assessments of Efficacy Variables

For data after the end of study treatment, data obtained within + 2 days after the last dose is taken will be included in analysis.

(1) TJC (68 joints)/SJC (66 joints), laboratory test (CRP)

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Screening** | Day −28 to Day −1 | Day −28 to Day −1 |
| Baseline | Day 1 | Day 1 |
| Week 4 to Week 48*** | Day 7×x + 1 | Day (7×x − 6) to Day (7×x + 8) and before drug administration on the visit day |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 12 (Week 12 or at early termination before Week 12) | Day 85 | Day 2 to Day 92 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

**: PGA, SGA, subject's assessment of pain, CRP, and ESR are not applicable.

***: Represents the reference date and acceptable time range for Week x.

(2) Hand and foot radiography

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Baseline | Day 1 | Day 1 to Day 30 |
| Week 28 | Day 197 | Day 160 to Day 234 |
| Week 52 | Day 365 | Day 328 to Day 402 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 48 to Day 234 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 48 to Day 402 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

(3) PGA and SGA (VAS), subject's assessment of pain (VAS), HAQ-DI, laboratory test (ESR)

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Baseline | Day 1 | Day 1 |
| Week 4 to Week 48** | Day 7×x + 1 | Day (7×x − 6) to Day (7×x + 8) and before drug administration on the visit day |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 12 (Week 12 or at early termination before Week 12) | Day 85 | Day 2 to Day 92 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

**: Represents the reference date and acceptable time range for Week x.

(4) SF-36 v2®, WPAI

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Baseline | Day 1 | Day 1 |
| Week 4 to Week 28** | Day 7×x + 1 | Day (7×x − 6) to Day (7×x + 8) and before drug administration on the visit day |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 12 (Week 12 or at early termination before Week 12) | Day 85 | Day 2 to Day 92 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

**: Represents the reference date and acceptable time range for Week x.

### 7.9.2 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 is taken will be included in analysis.

(1) Physical examination, vital signs, laboratory test (hematology, biochemistry, urinalysis)

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Screening | Day −28 to Day −1 | Day −28 to Day −1 |
| Baseline | Day 1 | Day 1 |
| Week 4 to Week 48** | Day 7×x + 1 | Day (7×x − 6) to Day (7×x + 8) and before drug administration on the visit day |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 12 (Week 12 or at early termination before Week 12) | Day 85 | Day 2 to Day 92 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

**: Represents the reference date and acceptable time range for Week x.

(2) Laboratory test (fasting lipid profile test)

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Baseline | Day 1 | Before drug administration on Day 1 and 8 hours after the last meal |
| Week 12 | Day 85 | Day 78 to Day 92 |
| Week 28 | Day 197 | Day 190 to Day 204 |
| Week 40 | Day 281 | Day 274 to Day 288 |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 12 (Week 12 or at early termination before Week 12) | Day 85 | Day 2 to Day 92 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

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

**: Represents the reference date and acceptable time range for Week x.

## (3) 12-lead ECG

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Screening | Day −28 to Day −1 | Day −28 to Day −1 |
| Week 28 | Day 197 | Day 190 to Day 204 |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

## (4) Body weight

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Screening | Day −28 to Day −1 | Day −28 to Day −1 |
| Week 12 | Day 85 | Day 78 to Day 92 |
| Week 28 | Day 197 | Day 190 to Day 204 |
| Week 40 | Day 281 | Day 274 to Day 288 |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 12 (Week 12 or at early termination before Week 12) | Day 85 | Day 2 to Day 92 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

## (5) QT assessment

| Time points defined in analysis | Reference date | Acceptable time range |
|---|---|---|
| Baseline | Day 1 | Day 1<br>Before the initiation of treatment with the study drug |
| Week 4 or Week 8 (before study drug administration) | Day 29 or Day 57 | Before the initiation of treatment with the study drug on Reference date ± 7 |
| Week 4 or Week 8 (after study drug administration) | Day 29 or Day 57 | 2 hours post-dose (reference time, but within the range of 1 hour to 4 hours post-dose is acceptable) on Reference date ± 7 |

### 7.9.3 Handling of Schedule of Assessments of Pharmacodynamic Variables

(1) Biomarkers and lymphocyte subsets

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Baseline | Day 1 | Before drug administration on Day 1 |
| Week 4 to Week 28** | Day 7×x + 1 | Day (7×x − 6) to Day (7×x + 8) and before drug administration on the visit day |
| Week 52 | Day 365 | Day 358 to Day 372 |
| End of Week 12 (Week 12 or at early termination before Week 12) | Day 85 | Day 2 to Day 92 |
| End of Week 28 (Week 28 or at early termination before Week 28) | Day 197 | Day 2 to Day 204 |
| End of treatment (Week 52 or at early termination) | Day 365 | Day 2 to Day 372 |

*: Day 1 represents the first day of study treatment. The day before is expressed as Day −1.

**: Represents the reference date and acceptable time range for Week x.

### 7.9.4 Handling of Schedule of Assessments of Pharmacokinetic Variables

(1) Trough concentration

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Baseline | Day 1 | Before drug administration on Day 1 |
| Weeks 4, 8, 12, 20, 28, 40, and 52** | Day 7×x + 1 | Day (7×x − 6) to Day (7×x + 8) and within 19 to 29 hours between the time of treatment with the study drug before blood collection and the time of blood collection |

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

**: Represents the reference date and acceptable time range for Week x.

(2) Post-dose concentration

| Time points defined in analysis | Reference date* | Acceptable time range |
|---|---|---|
| Week 4 or Week 8** | Day 7×x + 1 | Day (7×x − 6) to Day (7×x + 8) and within 1 to 4 hours between the time of treatment with the study drug before blood collection and the time of blood collection |

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

**: Represents the reference date and acceptable time range for Week x.

# 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 Electronic Data Capture (EDC) system. The investigator, sub-investigator, or collaborator will enter the data, in principle within 5 working days from the creation of the data (date of visit by the subject, date of obtaining information, etc.).

In principle, the name of AE must be entered within 5 working days of the date of confirming its occurrence. The name of concomitant drug/therapy must also be entered within 5 working days of the awareness of its use. Other information to be entered in the eCRF must be entered immediately on receipt.

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, birth date, and informed consent date) and, if reason for screening failure is to be obtained, the screening failure log (SFL) will be collected.

Measurements of laboratory tests, pharmacodynamic parameters, and plasma drug concentrations will be performed by [redacted]. The Data Science Department of the sponsor will obtain the laboratory test results, pharmacodynamic measurements, and plasma drug concentration measurements in an electronic format from [redacted] at predefined intervals during the study.

The assessment of hand and foot radiography will be performed by [redacted]. The Data Science Department of the sponsor will obtain the assessment results in an electronic format from [redacted], at predefined intervals during the study.

Analysis of Central ECG will be performed by [redacted]. The Data Science Department of the sponsor will obtain the quality assured analysis data in an electronic format from [redacted] at predefined timing.

The central laboratory and [redacted] will provide the sponsor with a copy of the complete and clean data, together with the quality control report.

### 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, 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
- The results of the relevant examination (e.g., ECG charts, radiographic data, 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®, WPAI)
- Subject questionnaire for 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 of use for previous and concomitant drugs
- Type, treatment dates, and reason of 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 site must accept monitoring and auditing by the Sponsor or delegated CRO as well as inspections from the IRB/IEC and relevant regulatory authorities. In these instances, they must provide all study-related records, such as source documents (refer to 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 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 SOPs for data management. All study specific processes and definitions will be documented by Data Management. eCRF entry 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)

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 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.

Moreover, PGx research should be conducted consistent with “Ethical Guidelines for Human Genome/Gene Analysis Research” (Notification No. 1 issued by Ministry of Education, Culture, Sports, Science and Technology/Ministry of Health, Labour and Welfare [MHLW]/Ministry of Economy, Trade and Industry in 2004) and “Clinical Trials with Pharmacogenomics Analysis” (Notification from the Director of the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated 30 September 2008).

### 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 investigator should submit the written or revised informed consent form and any other written information to the sponsor to be subject to prior approval by IRB/IEC.

- The investigator or other responsible personnel is responsible for explaining the nature and purpose of the study and 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, seal, and date the written information.

- Informed consent must be obtained by the time that the first observations/examinations before the pre-investigational period prior to the initial administration are performed.
- The investigator or other responsible personnel must give a copy of the signed 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 the 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 investigator will retain the signed consent forms, which will be made available (for review only) to the study monitor and auditor on request.

#### 8.2.3.2 Subject Information and Consent for PGx Research

The study centers with approval of the conduct of PGx research should obtain the consent to participate in PGx research in addition to the study entry. Prior to execution of the clinical study, the investigator should prepare the written informed consent form for PGx research in collaboration with the sponsor and revise the information whenever necessary. The written or revised written informed consent form and any other written information should be submitted to the sponsor and be subject to prior approval by the IRB.

Only subjects who have given consent for the study entry are subject to the consent for PGx research. Subjects can withdraw consent for PGx research only, separately from withdrawal of consent for the study entry. Procedures provided in Section 8.2.3.1 Subject Information and Consent should also be applied when obtaining consent for PGx research.

All of the remaining samples for PGx research obtained from the subject who has withdrawn consent for PGx research should be disposed of, except those anonymized.

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

#### 8.2.3.3 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 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

Medical information of individual subjects obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Medical information of individual subjects 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 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 development of the 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 submitting all transcripts, texts of presentations, and abstracts related to the study to the sponsor at least 90 days prior to the intended submission for publication or any other disclosure. Because such disclosure of study results is presupposed, it is important that the information concerning the invention is protected by a patent, through the preparation and submission of a patent application. Moreover, publication of facts and opinions summarized by the investigator is not restricted. 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(s) and sponsor, the manuscript can be submitted for publication.

### 8.3.2 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 Worksheet
- 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 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
- 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:

- Other study documentation
- Unused study drug(s)

The investigator will archive all study data (e.g., subject identification code list, source documents, and investigator's file) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulations (for study centers in the US, 2 years from the approval of NDA or termination of IND). The sponsor will archive and retain all documents pertaining to the study according to local regulations.

The records to be retained at the study sites are the ones listed as essential documents in GCP. These records shall be retained by the head of the study site 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 head of the study site will retain the essential documents that should be stored at the study site in an appropriate manner according to the rules of the study site concerned until the date defined in 1. or 2. below, whichever comes later.

1. Approval date of marketing of the test drug (if development of the drug is stopped, until three years after the decision to discontinue development is notified)
2. Until three years after discontinuation or termination of the study.

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, radiographic 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 [e.g., questionnaires at CPK monitoring, Herpes Zoster (singles) Worksheet] specified by the sponsor, 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 and collaborators, list of signatures and print of seals (copy), and electronic media storing the eCRF data, etc.
3. Documents obtained related to the adequacy of conducting the clinical study by the head of the study centers and the protocol, documents obtained related to the adequacy of conducting the 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), SOP for the investigator, materials and information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE report, etc.), SOP for the IRB, the list of names of the IRB members, material or IRB review (including continuous deliberation), IRB review records (including continuous deliberation), and the review result report of the IRB (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
   The documents of the Independent DSMB (minutes, SOPs, and others) shall be retained by the sponsor.

- Records of PGx research samples

The study centers where the conduct of PGx research has been approved should retain the Subject Identification Code List and written informed consent form (including amendments) for PGx research for up to 15 years after the data lock point in order to comply with the subject's consent withdrawal of PGx research and storage of their samples.

### 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 revision, either IRB/IEC/regulatory authorities' approval or notification is required. The changes and revisions will become effective only after the approval of the sponsor, the investigator, and the IRB/IEC (if applicable), 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 site, the Sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the 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 site should provide medical treatment and other necessary measures. The Sponsor should be notified of the injury.
2. When the subject claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the Sponsor. 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 that forms part of a marketing authorization application be signed by a coordinating or 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 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, eCRF, 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 be organized to review the unblinded safety data, to make a decision on whether to continue or stop the study, or modify the protocol with respect to the safety, and to provide the sponsor with recommendations. The DSMB should follow the procedures separately defined in details, including the frequency of meetings, blind-breaking and data review.

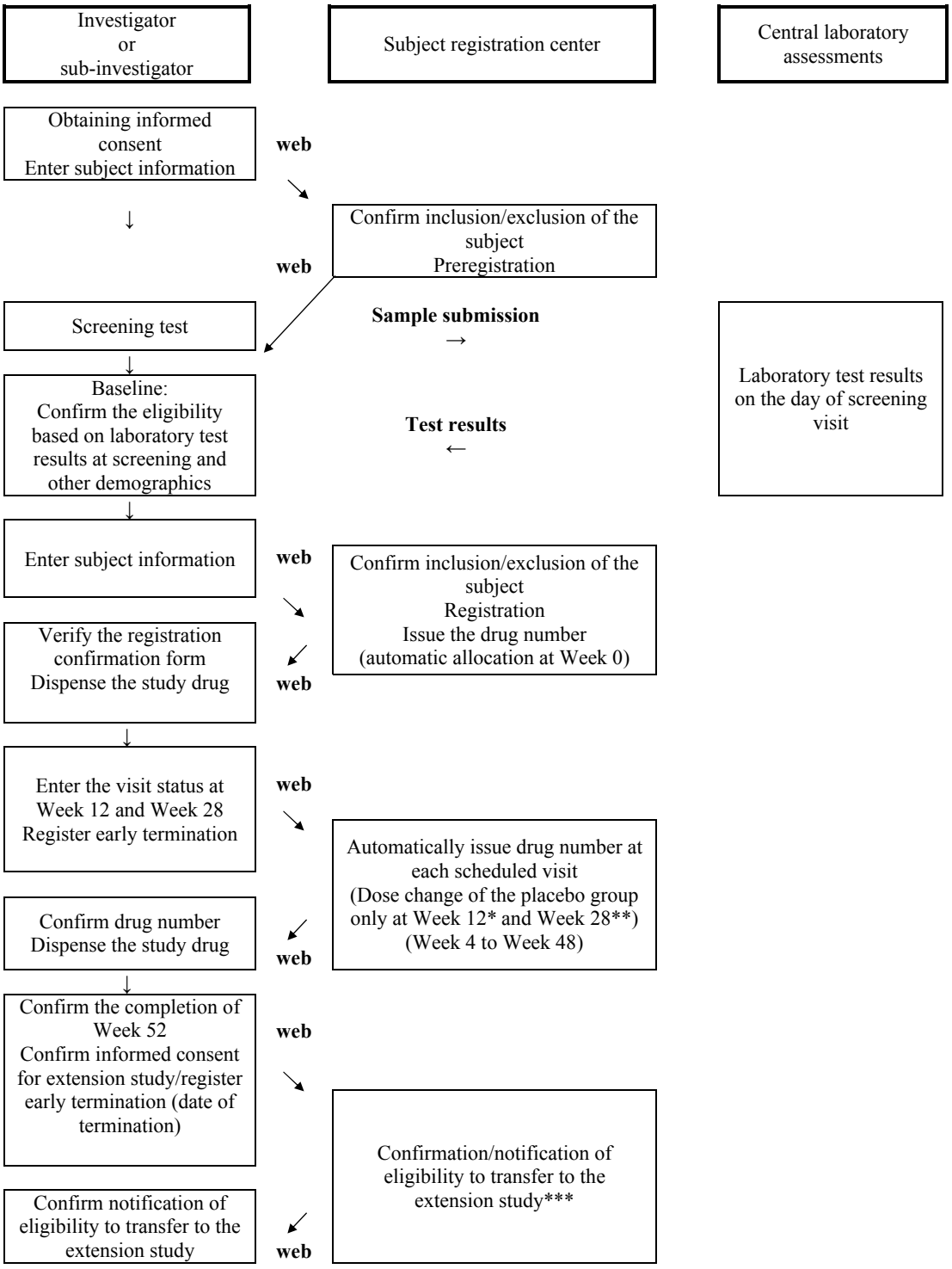
## 10.2 Other Evaluation Committee(s)

Not applicable.

## 10.3 Other Study Organization

See Attachment.

## 10.4 Registration of Subjects




* At the Week 12 visit, TJC and SJC will be entered, and based on the results, some subjects in the placebo group will be switched to receiving ASP015K 100 mg or ASP015K 150 mg based on the allocation at baseline.

** At the Week 28 visit, only the placebo group will be switched to receiving ASP015K 100 mg or ASP015K 150 mg based on the allocation at baseline.

*** Only subjects who completed Week 52.

<Subject registration center> [redacted]
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)

The investigator/sub-investigator is responsible for conducting a survey on demographics of the candidate subjects and obtaining their written consent. After obtaining written consent, the investigator/sub-investigator should make necessary entries in the case registration form on the web-based registration system. The subject registration center will notify the preregistration results to the study centers via the web-based registration system.

The investigator/sub-investigator will confirm the inclusion/exclusion criteria at baseline, and the investigator/sub-investigator will make the 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/sub-investigator will dispense the study drug to the subject who is considered “eligible” for the study registration.

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# 12 APPENDICES

## APPENDIX <1>: LIST OF PROHIBITED CONCOMITANT MEDICATION

- ✓ **Biologic DMARD (biological drugs for the treatment of RA)**

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

- ✓ **Non-biologic DMARD***

  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.

  **: Administration of corticosteroids at doses exceeding 10 mg/day in prednisolone equivalent is prohibited. Intra-articular, intravenous, intramuscular, or endorectal administration is prohibited. However, suppositories for anal disease may be used concomitantly.

- ✓ **Oral morphine*****

  Morphine hydrochloride, morphine sulfate

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

- ✓ **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, pfreeze-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 | Parameters to be analyzed |
|---|---|---|---|
| Hematology | Screening, Baseline, 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 52, at early termination, follow-up, unscheduled | 2 mL vacutainer tube containing EDTA-2K | Hemoglobin, hematocrit, RBC, WBC, differential WBC, platelet count |
| Biochemistry | Screening, Baseline, 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 52, at early termination, follow-up, unscheduled | 9mL vacutainer tube containing the separating medium<br>For glucose: 2 mL vacutainer tube containing NaF+EDTA-2Na<br>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, eGFR, β-D-glucan |
| Biochemistry (at CPK monitoring) | At CPK monitoring | 4 mL vacutainer tube containing the separating medium | CK-MB, troponin-T, aldolase |
| Fasting lipid profile test | Baseline, Week 12, Week 20, Week 28, Week 40, Week 52, at early termination, follow-up, unscheduled | (Included among biochemistry tests) | Total cholesterol, LDL, HDL, triglycerides |
| Tuberculosis test (When performed at the central laboratory) | Screening | 10 mL vacutainer tube containing heparin Na | Interferon γ titer |
| Anti-CCP antibody, RF, hepatitis test | Screening | 9 mL vacutainer tube containing the separating medium | Anti-CCP antibodies, RF, HBs antigens, HBs antibodies, HBc antibodies, and HCV antibodies |
| Hepatitis DNA test | Screening<br><br>If a subject is positive for HBc antibodies or HBs antibodies, tests should be performed at the following visits: Baseline, 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 52, at early termination, follow-up, unscheduled | 5 mL vacutainer tube containing the separating medium | HBV-DNA assay |

| | | | |
|---|---|---|---|
| Urinalysis | Screening, Baseline, 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 52, at early termination, follow-up, unscheduled | For urinalysis: 10 mL light-blocking urine collection tubes<br>For urine microscopic examination: 10 mL urine collection tubes | pH, specific gravity, protein, glucose, keton bodies, bilirubin, occult blood, sediment |
| Pregnancy testing | Screening, Baseline, 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 52, at early termination, follow-up, unscheduled | Serum pregnancy test (Included among biochemistry tests)<br><br>Urine pregnancy test (In-hospital testing) | Human chorionic gonadotropin (hCG) |
| Acute phase reactants | Screening (CRP only), Baseline, 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 52, at early termination, follow-up, unscheduled | (Included among biochemistry tests) | CRP |
| | | In-hospital testing | ESR |
| PK (Assessment of trough concentration) | Baseline, Week 4, Week 8, Week 12, Week 20, Week 28, Week 40, Week 52, at early termination | 2 mL vacutainer tubes containing EDTA-3K | Concentration of ASP015K (and its metabolites H1, H2, and H4, if necessary) |
| Additional PK (for post-dose concentration) | Week 4 or Week 8 | 2 mL vacutainer tubes containing EDTA-3K | Concentration of ASP015K (and its metabolites H1, H2, and H4, if necessary) |
| PD | Baseline, Week 4, Week 8, Week 12, Week 28, Week 52, at early termination, follow-up, unscheduled | 2 mL vacutainer tubes containing EDTA-2Na (MMP-3 is included among biochemistry tests.) | VEGF<br>MMP-3 |
| | Baseline, Week 4, Week 8, Week 12, Week 28, Week 52, at early termination, follow-up, unscheduled | 2 mL vacutainer tubes containing EDTA-2K | Lymphocyte subset |
| Pharmacogenomics (Only at approved study centers) | After obtaining the subject's consent for PGx | 5 mL vacutainer tubes containing EDTA-2K | PGx analysis |

# APPENDIX <3>: EVENTS ALWAYS CONSIDERED SERIOUS

If any of the following events occurs during the study, it should be regarded as an 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 should be regarded as SAE.

See Appendix 4 "Liver Safety Monitoring and Assessment."

# APPENDIX <4>: LIVER SAFETY MONITORING AND ASSESSMENT

If laboratory testing for a subject enrolled in the study and receiving the study drug reveals an increase in serum aminotransferase (ALT, AST) > 3 × ULN or TBL > 2 × ULN, the investigator/sub-investigator should repeat at least 4 parameters (ALT, AST, ALP, and TBL) of the usual hepatic function test parameters. Retesting should be performed between 48 hours and 72 hours after notification of the test results. For studies for which a central laboratory ([redacted]) is used, alerts will be generated by the central laboratory regarding moderate and marked liver abnormality to inform the investigator or other responsible personnel and the sponsor. Subjects should be asked if they have any symptoms suggestive of hepatobiliary dysfunction by the investigator/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 | | TBL |
|---|---|---|---|
| **Moderate**<br>**Hepatocellular failure type or cholestasis type** | > 3 × ULN | or | > 2 × ULN |
| **Marked**<br>**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/sub-investigator determines that abnormal liver function results, other than as described above, qualify as moderate or marked abnormalities, they 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/sub-investigator. The investigator should complete the liver abnormality case report form (LA-CRF) or an appropriate document. Subjects with confirmed abnormal liver function test results should be followed as described below by the investigator/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 an 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/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/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, direct bilirubin

Consider gastroenterology or hepatology consultations

Enter the 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 for 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 <5>: 1987 ACR CRITERIA FOR THE CLASSIFICATION OF RA

For classification purposes, a patient shall be said to have RA if he/she has satisfied at least 4 of these 7 criteria. Criteria [1] through [4] must have been present for at least 6 weeks.

| Criterion | Definition |
|---|---|
| [1] Morning stiffness | Morning stiffness in and around the joints, lasting at least 1 hour before maximal improvement |
| [2] Arthritis of 3 or more joint areas | At least 3 joint areas simultaneously have had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The 14 possible areas are right or left PIP, MCP, wrist, elbow, knee, ankle, and MTP joints. |
| [3] Arthritis of hand joints | At least 1 area swollen (as defined above) in a wrist, MCP, or PIP joint |
| [4] Symmetric arthritis | Simultaneous involvement of the same joint areas (as defined in [2]) on both sides of the body (bilateral involvement of PIPs, MCPs, or MTPs is acceptable without absolute symmetry) |
| [5] Rheumatoid nodules | Subcutaneous nodules, over bony prominences, or extensor surfaces, or in juxtaarticular regions, observed by a physician |
| [6] Serum rheumatoid factor | Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in ≤ 5% of normal control subjects |
| [7] Radiographic changes | Radiographic changes typical of RA on posteroanterior hand and wrist radiographs, which must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify) |

[Armett FC et al, 1988]

# APPENDIX <6>: 2010 ACR-EULAR CLASSIFICATION CRITERIA FOR RA

1. If a patient has at least 1 joint with synovitis not explained by another disease and scores ≥ 6 in the scoring system of 4 categories, he/she is assessed as having "definite RA."

| | |
|---|---|
| Joint involvement[a)] | |
| 1 large joint[b)] | 0 |
| 2–10 large joints | 1 |
| 1–3 small joints[c)] | 2 |
| 4–10 small joints | 3 |
| ≥ 11 joints (at least 1 small joint) | 5 |
| Serology | |
| RF8 (−) and anti-CCP antibody (−) | 0 |
| Low positive RF or low positive anti-CCP antibody | 2 |
| High positive RF or high positive anti-CCP antibody<br>(High: > 3 × ULN) | 3 |
| Acute phase reactants | |
| Normal CRP and normal ESR | 0 |
| Abnormal CRP or abnormal ESR | 1 |
| Duration of symptoms | |
| < 6 weeks | 0 |
| ≥ 6 weeks | 1 |

a): The distal interphalangeal joints, first CMC joints, and first MTP joints are excluded from assessment.

b): Large joints: Shoulder, elbow, hip, knee, and ankle joints

c): Small joints: PIP joints, MCP joints, 2–5 MTP joints, first IP joints, and wrist joints

[Daniel A et al, 2010]

# APPENDIX <7>: 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 <8>: CLASSIFICATION OF DISEASE STAGE/PROGRESSION OF RA

| | |
|---|---|
| Stage I: Early | 1. X-rays show no evidence of bone destruction.<br>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.<br>2. Joint mobility may be limited, but there is no joint deformation.<br>3. Muscle atrophy surrounding the joint is present.<br>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.<br>2. Joint deformities such as subluxation, ulnar displacement, or hyperextension are present, unaccompanied by fibrous or bony ankylosis.<br>3. Exaggerated muscle atrophy is present.<br>4. Lesions in extra-articular soft tissue, such as nodules and tenosynovitis, may be present. |
| Stage IV: End Stage | 1. Fibrous or bony ankylosis is present.<br>2. Other symptoms meet criteria for Stage III. |

[Steinbrocker O. 1949]

(GPF 3.03)