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

ISN/Protocol 015K-CL-RAJ2

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STATISTICAL ANALYSIS PLAN

Final Version, dated 12-Nov 2019

Extension Study of ASP015K

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Astellas Pharma Inc. (API)

Table of Contents

I. LIST OF ABBREVIATIONS AND KEY TERMS 5
1 INTRODUCTION 8
2 FLOW CHART AND VISIT SCHEDULE 9
3 STUDY OBJECTIVE(S) AND DESIGN 14
3.1 Study Objective(s) 14
3.2 Study Design 14
3.3 Randomization 14
4 SAMPLE SIZE 15
5 ANALYSIS SETS 15
5.1 Full Analysis Set (FAS) 15
5.2 Safety Analysis Set (SAF) 15
5.3 Pharmacodynamic Analysis Set (PDAS) 15
6 ANALYSIS VARIABLES 16
6.1 Efficacy Endpoints 16
6.1.1 Categorical Variables 16
6.1.2 Continuous Variables 19
6.2 Safety Variables 19
6.3 Pharmacokinetic Variables 19
6.4 Pharmacodynamic Variables 19
6.5 Other Variables 21
7 STATISTICAL METHODOLOGY 22
7.1 General Considerations 22
7.2 Study Population 25
7.2.1 Disposition of Subjects 25
7.2.2 Demographic and Other Baseline Characteristics 26
7.2.3 Concomitant Medications 28
7.3 Study Drugs 29
7.3.1 Exposure 29
7.3.2 Treatment Compliance 30
7.4 Analysis of Efficacy 30
7.4.1 Analysis of Efficacy Endpoint(s) 31

7.4.2 Analysis by Treatment Sequence Set of preceding study ····· 31
7.4.3 Analysis of Efficacy in Initial/Maximum Dose Level ····· 32
7.4.4 Influence of Dose Escalation ····· 32
7.4.5 Subgroup Analysis ····· 32
7.5 Analysis of Safety ····· 33
7.5.1 Adverse Events ····· 33
7.5.2 Clinical Laboratory Evaluation ····· 37
7.5.3 Vital Signs ····· 42
7.5.4 Electrocardiograms (ECGs) ····· 42
7.5.5 Chest radiography ····· 43
7.5.6 Pregnancies ····· 43
7.6 Analysis of PK ····· 43
7.7 Analysis of PD ····· 43
7.8 Subgroups of Interest ····· 44
7.8.1 Subgroup analysis of the selected efficacy endpoint (ACR20-CRP) and treatment emergent adverse events ····· 44
7.8.2 Subgroup analysis by Study Region (Japan, Korea, Taiwan) ····· 45
7.9 Other Analyses ····· 46
7.10 Interim Analysis (and Early Discontinuation of the Clinical Study) ····· 46
7.11 Handling of LLOQ, Missing Data, Outliers, Visit Windows, and Other Information ····· 46
7.11.1 LLOQ ····· 46
7.11.2 Missing Data ····· 46
7.11.3 Outliers ····· 48
7.11.4 Visit Windows ····· 48
7.11.5 Handling of Schedule of Assessments of Efficacy Variables ····· 49
7.11.6 Handling of Schedule of Assessments of Safety Variables ····· 52
7.11.7 Handling of Schedule of Assessments of Pharmacodynamic Variables ····· 55
8 DOCUMENT REVISION HISTORY ····· 56
9 REFERENCES ····· 56
10 APPENDICES ····· 57
10.1 Appendix 1: Overview of Efficacy Endpoints ····· 57
10.2 Appendix 2: Overview of AE analysis ····· 66

10.3 Appendix 3: Overview of Clinical Laboratory Evaluation, Vital Signs, and Electrocardiograms (ECGs) analyses ····· 69

10.4 Appendix 4: Computation of HAQ-DI Score ····· 71

10.5 Appendix 5: Computation of SF-36v2® Score ····· 74

10.6 Appendix 6: Computation of FACIT-Fatigue Scale Score ····· 85

10.7 Appendix 7: Computation of WPAI Scale Score ····· 87

10.8 Appendix 8: AE of Special Interest ····· 88

10.9 Appendix 9: Standard Toxicity Grading for Laboratory Tests According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 ····· 89

10.10 Appendix 10: Key Contributors and Approvers ····· 93

I. LIST OF ABBREVIATIONS AND KEY TERMS

List of Abbreviations

Abbreviations	Description of abbreviations
ACR	American College of Rheumatology
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (GPT)
AST	Aspartate aminotransferase (GOT)
ASP015K	Astellas Pharmaceuticals compound 015K
BUN	Blood urea nitrogen
CDAI	Clinical Disease Activity Index
CI	Confidence Intervals
CK/CPK	Creatine kinase/creatine phosphokinase
CK-MB	Creatine kinase MB isozyme
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSR	Clinical Study Report
DAS	Disease activity score
DMARD	Disease-modifying antirheumatic drug
DSMB	Data and Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic case report form
ESR	Erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
γ-GTP	γ-glutamyl transpeptidase (GGT)
H	High
HAQ-DI	Health Assessment Questionnaire – Disability Index
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International normalized ratio
ISN	International study number
L	Low
LDL	Low-density lipoprotein
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MTX	Methotrexate
N	Normal

Abbreviations	Description of abbreviations
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PD	Pharmacodynamic
PDAS	Pharmacodynamic Analysis Set
PGA	Physician's Global Assessment of Arthritis
PK	Pharmacokinetic
PT	Preferred Term
PY	Patient-years
QD	Once a day
RA	Rheumatoid arthritis
RBC	Red blood cell
RCS	Role/social component score of the SF-36v2®
RF	Rheumatoid Factor
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDAI	Simplified Disease Activity Index
SF-36v2®	Short form health survey – 36 questions, version 2: SF-36 v2®
SFL	Screening Failure Log
SGA	Subject's Global Assessment of Arthritis
SGAP	Subject's Global Assessment of Arthritis Pain
SI	International System of Units
SJC	Swollen joint count
SOC	System Organ Class
SOP	Standard operating procedure
TBL	Total bilirubin
TEAE	Treatment emergent adverse event
TJC	Tender joint count
TLF	Tables, Listings and Figures
TNF	Tumor necrosis factor
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	White blood cell
WHO-DD	World Health Organization Drug Dictionary
WPAI	Work Productivity and Activity Impairment Questionnaire

List of Key Terms

Terms	Definition of terms
Adverse event	An adverse event is as any untoward medical occurrence in a subject administered a study drug and which does not necessarily have a causal relationship with this treatment.
Baseline	The last measured values/findings prior to dosing. There are 2 types of baseline as follow. baseline of preceding study: baseline of RAJ1, RAJ3 or RAJ4 study. Week 0: baseline of RAJ2
Study discontinuation	The act of concluding participation, prior to completion of all protocol-required elements, in a study by an enrolled subject. Four categories of discontinuation are distinguished: a) dropout: Active discontinuation by a subject (also a noun referring to such a discontinued subject); b) discontinuation initiated by the investigator or other responsible personnel (e.g., for cause); c) loss to follow-up: cessation of participation without notice or action by the subject; d) sponsor-initiated discontinuation. Note that subject discontinuation does not necessarily imply exclusion of subject data from analysis.
Enroll	To register or enter into a clinical study; transitively and intransitively. Informed consent precedes enrollment.
Follow-up period	The follow-up period begins at the completion of all assessments/measurements at end of treatment/early termination and ends upon completion of all assessments/measurements at end of study (at time of follow-up).
Serious adverse event	Any adverse event that is judged “serious” by the investigator/sub-investigator or the sponsor and results in any of the following outcomes: death, a life-threatening condition, persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect, hospitalization or prolongation of hospitalization, and other medically significant occurrences.
Screening failure	A subject from whom informed consent was obtained but who did not fulfill protocol inclusion and/or exclusion criteria and did not receive the study drug
Study period	Period of time from obtaining informed consent from subjects to the end of the final evaluation/observation specified in the protocol
Subject	An individual who participates in a clinical study, as a recipient of either the test drug(s) or comparative drug(s)
Suspension	Suspension is defined as a temporary discontinuation of study drug administration for 7 days or less. If administration of the study drug is suspended repeatedly, the discontinuation of the clinical study for the particular subject should be considered in consultation with the sponsor.
Interruption	Interruption is defined as a temporary discontinuation of study drug administration for a period exceeding 7 days.
Variable	Any quantity that varies; any attribute, phenomenon or event that can have different qualitative or quantitative values

1 INTRODUCTION

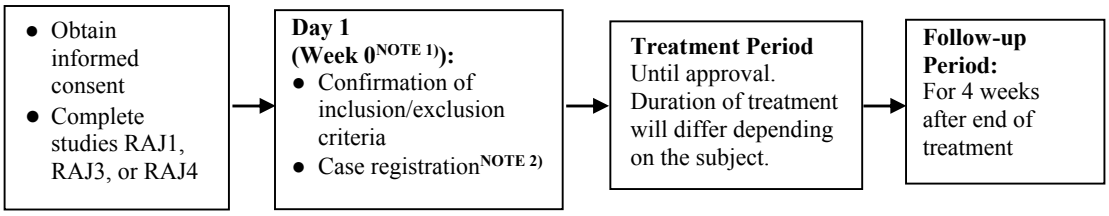
This Statistical Analysis Plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and includes detailed procedures for executing the statistical analysis of the primary and secondary endpoints and other data.

The SAP is finalized and signed prior to data lock.

This statistical analysis is coordinated by the responsible biostatistician of GD, API. Any changes from the analyses planned in the SAP will be justified in the Clinical Study Report (CSR).

2 FLOW CHART AND VISIT SCHEDULE

Flow Chart



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

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

NOTE 2:

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

Start and End of Study

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

End of Study: Point in time where final assessment specified in protocol has been performed in the last subject

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

Schedule of Assessments

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

study visit at the end of treatment will be the date of the previous visit + 84 days (allowable range, ± 14 days).
[Subjects who transferred from studies RAJ3 or RAJ4] The specified date for the study visit at the end of treatment will be the date of previous study visit + 84 days (allowable range, ± 14 days).

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

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

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

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

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

3 STUDY OBJECTIVE(S) AND DESIGN

3.1 Study Objective(s)

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

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

3.2 Study Design

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

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

Because this study will end at the point in time when ASP015K is approved, the duration of treatment with the study drug will differ depending on the subject. To prevent purposeless continuation of dosing without effect, the investigator or sub-investigator will assess each subject for efficacy and safety at each visit, confirm the appropriateness of continued administration for each individual, and decide whether or not to continue dosing.

3.3 Randomization

Not applicable.

4 SAMPLE SIZE

Approximately 800 treated patients

[Rationale for the sample size]

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

5 ANALYSIS SETS

In accordance with International Conference on Harmonization (ICH) recommendations in guidelines E3 and E9, the following analysis sets will be used for the analyses.

5.1 Full Analysis Set (FAS)

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

5.2 Safety Analysis Set (SAF)

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

5.3 Pharmacodynamic Analysis Set (PDAS)

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

6 ANALYSIS VARIABLES

6.1 Efficacy Endpoints

6.1.1 Categorical Variables

- Percentage of subjects achieving ACR 20/50/70-CRP response at each analysis visit
- Percentage of subjects achieving ACR 20/50/70-ESR response at each analysis visit

Definition ACR20 response rate:

It is defined as percentage of subjects achieving ACR 20 response at each study visit, based on C-reactive protein (CRP). ACR20 is a binary variable, with levels responder and non-responder.

Responder :

A subject will be defined as an ACR20-CRP responder at any time point (e.g. Week 12) if the subject meets ALL the following American College of Rheumatology (ACR) response criteria:

- At least 20% reduction from baseline at the time point (e.g. Week 12) in the number of 68 tender joint count (TJC-68)

AND

- At least 20% reduction from baseline at the time point (e.g. Week 12) in the number of 66 swollen joint count (SJC-66)

AND

- At least 20% reduction from baseline at the time point (e.g. Week 12) in ANY 3 or more of the 5 following ACR components
    - Subject's global assessment of arthritis pain (SGAP) (assessed using a 100 mm VAS ; score of 0 indicates no pain, and score of 100 indicates very severe pain)
    - Subject's global assessment of arthritis (SGA) (assessed using a 100 mm VAS; score of 0 indicates no disease activity, and score of 100 mm indicates very severe disease activity)
    - Physician's global assessment of arthritis (PGA) (assessed using a 100 mm VAS; score of 0 indicates no disease activity, and score of 100 mm indicates very severe disease activity)
    - Health Assessment Questionnaire – Disease Index (HAQ-DI; score ranges from 0 to 3 with higher scores indicating greater disability)
    - CRP (Higher values indicate greater inflammation)

Values at the baseline in the preceding studies (RAJ1, RAJ3, and RAJ4) will be used as the baseline values. A negative percent change indicates a reduction from baseline (i.e., a favorable outcome). If the baseline value is 0 in some of ACR components, then that

component is not included in ACR calculation at any visit and ACR response is calculated based on remaining non-missing components.

Non-responder: A subject will be defined as an ACR20-CRP non-responder at the time point (e.g. Week 12), if the subject does not meet the ACR20-CRP responder criteria.

Note: ACR 20/50/70-ESR response is similar to the above by replacing CRP with ESR.

- Percentage of subjects achieving DAS28-CRP score <2.6 at each analysis visit
- Percentage of subjects achieving DAS28-ESR score <2.6 at each analysis visit
- Percentage of subjects achieving DAS28-CRP score <=3.2 at each analysis visit
- Percentage of subjects achieving DAS28-ESR score <=3.2 at each analysis visit

Calculation DAS28-CRP/ESR response:

DAS28-CRP/ESR response is consist of following parameters, and calculated according to below description.

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

Note: CRP values measured in mg/dL will be converted to mg/L for analysis purposes as: value in mg/L = value in mg/dL × 10; SGA is measured on 100 mm VAS. If any component is a missing value, then DAS28-CRP/ESR will be a missing value. If ESR is 0 then DAS28-ESR is missing.

- Percentage of subjects in DAS28-CRP EULAR response criterion of "Good Response" at each analysis visit
- Percentage of subjects in DAS28-ESR EULAR response criterion of "Good Response" at each analysis visit
- Percentage of subjects in DAS28-CRP EULAR response criterion of "Good Response" or "Moderate Response" at each analysis visit
- Percentage of subjects in DAS28-ESR EULAR response criterion of "Good Response" or "Moderate Response" at each analysis visit

Definition EULAR response:

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

- Percentage of subjects achieving ACR/EULAR score for remission at each analysis visit
  If all of the following 4 parameters are fulfilled, it is defined as remission:
  - TJC (68 joints) <= 1
  - SJC (66 joints) <= 1
  - CRP <= 1 mg/dL
  - SGA <= 1 cm (on a VAS of 0-100 mm)

  Note: All 4 conditions must be fulfilled to be in remission. If any component is a missing value, then ACR/EULAR score for remission will be a missing value.

- Percentage of subjects with a simplified disease activity index (SDAI) score of <= 3.3 at each analysis visit
  SDAI score is consist of following parameters, and calculated according to below description.
  - TJC (28 joints)
  - SJC (28 joints)
  - SGA (0-10 cm VAS)
  - PGA (0-10 cm VAS)
  - CRP (mg/dL)

  SDAI = TJC +SJC +SGA +PGA + CRP

  Note: If any component is a missing value, then SDAI score will be a missing value.
- Percentage of subjects with a CDAI score of <= 2.8 at each analysis visit
  CDAI score is consist of following parameters, and calculated according to below description.
  - TJC (28 joints)
  - SJC (28 joints)
  - SGA (0-10 cm VAS)
  - PGA (0-10 cm VAS)

  CDAI = TJC +SJC +SGA +PGA

  Note: If any component is a missing value, then CDAI score will be a missing value.

- Percentage of subjects achieving HAQ-DI (<=0.5) at each analysis visit
- Percentage of subjects achieving decrease of baseline HAQ-DI of at least 0.22 at each analysis visit

- Percentage of subjects achieving SF-36v2 of difference >= 5 at each visit

6.1.2 Continuous Variables

- Raw value and change from baseline in the following assessments:
  - TJC (68 joints)
  - SJC (66 joints)
  - CRP
  - ESR
  - SGAP (VAS) (100 mm VAS)
  - SGA (VAS) (100 mm VAS)
  - PGA (VAS) (100 mm VAS)
  - HAQ-DI (See Section 10.5 Appendix 5: Computation of HAQ-DI Score)
  - DAS28-CRP score
  - DAS28-ESR score
  - SF-36v2®
  - SDAI score
  - CDAI score
  - FACIT-Fatigue Score (only for subjects who transferred from study RAJ1. See Section 10.6 Appendix 6: Computation of FACIT-Fatigue Scale Score)
  - WPAI score (only for subjects who transferred from studies RAJ3 or RAJ4. See Section 10.7 Appendix 7: Computation of WPAI Scale Score)

6.2 Safety Variables

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

6.3 Pharmacokinetic Variables

Refer to PK analysis plan.

6.4 Pharmacodynamic Variables

- Change from baseline for following variables in lymphocyte subset assays

1. Japan
   - CD3+/Lymphocytes (%), CD3+ (cells/uL)
   - CD8+/Lymphocytes (%), CD8+ (cells/uL)

- CD4+/Lymphocytes (%), CD4+ (cells/uL)
- CD19+/Lymphocytes (%), CD19+ (cells/uL)
- CD4/CD8 Ratio
- (CD16 or CD56)+/Lymphocytes (%), (CD16 or CD56)+ (cells/uL)
- (CD16+ and CD56+)/CD3- (%), CD16+ and CD56+ (cells/uL)
- (CD16- and CD56+)/CD3- (%), CD16- and CD56+ (cells/uL)
- (CD16+ and CD56-)/CD3- (%), CD16+ and CD56- (cells/uL)
- (CD16- and CD56-)/CD3- (%), CD16- and CD56- (cells/uL)
- CD56 bright/CD3- (%), CD56 bright (cells/uL)
- CD56 dim/CD3- (%), CD56 dim (cells/uL)

2. Korea
   - CD3+/Lymphocytes (%), CD3 (cells/uL)
   - (CD3+ and CD8+)/CD3+ (%), CD3+ and CD8+ (cells/uL)
   - (CD3+ and CD4+)/CD3+ (%), CD3+ and CD4+ (cells/uL)
   - (CD16 or CD56)+/CD3- (%), (CD16 or CD56)+ (cells/uL)
   - CD19+/CD3- (%), CD19+ (cells/uL)
   - CD4/CD8 Ratio
   - (CD16+ and CD56+)/CD3- (%), CD16+ and CD56+ (cells/uL)
   - (CD16- and CD56+)/CD3- (%), CD16- and CD56+ (cells/uL)
   - (CD16+ and CD56-)/CD3- (%), CD16+ and CD56- (cells/uL)
   - (CD16- and CD56-)/CD3- (%), CD16- and CD56- (cells/uL)
3. Taiwan
   - CD3+/Lymphocytes (%), CD3 (cells/uL)
   - (CD3+ and CD8+)/Lymphocytes (%), CD3+ and CD8+ (cells/uL)
   - (CD3+ and CD4+)/Lymphocytes (%), CD3+ and CD4+ (cells/uL)
   - (CD16 or CD56)+/Lymphocytes (%), (CD16 or CD56)+ (cells/uL)
   - CD19+/Lymphocytes (%), CD19+ (cells/uL)
   - CD4/CD8 Ratio
   - (CD16+ and CD56+)/Lymphocytes (%), CD16+ and CD56+ (cells/uL)
   - (CD16- and CD56+)/Lymphocytes (%), CD16- and CD56+ (cells/uL)
   - (CD16+ and CD56-)/Lymphocytes (%), CD16+ and CD56- (cells/uL)

- (CD16- and CD56-)/Lymphocytes (%), CD16- and CD56- (cells/uL)

6.5 Other Variables

- Date of Last Dose of Study Drug:
  If date of last dose of study is unknown, the date will be imputed by date of withdrawal.
- Duration of RA at baseline of preceding study (years), calculated as: (Date of Screening visit of preceding study – Onset Date of RA +1) / 365.25, and then rounded to one decimal place. The onset date of RA doesn't have the day (e.g., 2013-03), therefore the first day of the month will be used (2013-03-01).
  Missing onset date of RA will be imputed. For example, if month is missing (e.g., 2013), then the first day of January will be used (2013-01-01).
- Age at Week 0 (years), calculated as: integer part of (Date of Week 0 visit – date of birth +1) / 365.25.
- Duration of exposure during RAJ2 (months)
  Duration of exposure during RAJ2 will be calculated in days, using the following formula:
  (('Date of Last Dose of Study Drug'* - 'Date of First Study Drug Taken at RAJ2'**) + 1)/30.4375
  *: DSLDT [End of Study-page of the CRF].
  **: EXSTDT [Date of First Study Drug Taken -page of the CRF]
- Treatment compliance during RAJ2 (%)
  Treatment compliance will be based on number of tablets and calculated as follows:
  Treatment compliance (%) =
  [Total number of tablets actually received in the treatment period]
  ----------x 100
  [Total number of tablets planned to receive in the treatment period]

  Where total number of tablets planned to receive in the treatment period is calculated as below: ∑{(number of tablets per administration#) x (duration of administration##)} in ASP015K 50,100, 150 mg. It will be summed up to Date of Last Dose of Study Drug.
  #: refer to the table below; differ depending on the protocol version
  ##: summarized by dose level [ASP015K 50,100, 150 mg], by protocol version [Ver. 1.0, On and After Ver. 2.0]

Protocol Version	Ver. 1.0		On and After Ver. 2.0		
Dose per administration	50 mg	100 mg	50 mg	100 mg	150 mg
Number of tablets per administration	3 tablets	4 tablets	1 tablets	1 tablets	1 tablets

And total number of tablets actually received in the treatment period will be calculated as: (total number of tablets dispensed) – (total number of tablets returned) – (total number of tablets lost) up to Date of Last Dose of Study Drug. After study completion and data base is locked, all data will be used to calculate the compliance.

- Number of prior DMARD biologics, According to the preceding study
- Prior Biologic DMARD-IR, According to the preceding study

7 STATISTICAL METHODOLOGY

7.1 General Considerations

- For continuous variables, descriptive statistics will include the number of subjects (n), mean, standard deviation (SD), median, minimum, and maximum.
- For categorical variables: number and percentages of subjects will be described.
- For time-to-event variables: number and percentage of subjects with the event using Kaplan-Meier method, the cumulative event rate will be estimated and a plot will be constructed.
- All data processing, summarization, and analyses will be performed using SAS Drug Development (ver. 4.5), and PC-SAS (ver. 9.4) or higher versions.
- Specifications for table, figures, and data listing formats can be found in the TLF specifications for this study.
- For the definition of subgroups of interest can be referred to Section 7.8.
- Summaries based on FAS and SAF (e.g. disposition, baseline, efficacy data and safety data) will be presented by preceding studies and overall, unless specifically stated otherwise.
- Medical Dictionary for Regulatory Activities (MedDRA) 11.1 will be used as the coding dictionary for adverse event and medical history.
- Confidence interval for binary outcome is continuity corrected in all analysis.
- For the analyses of efficacy and pharmacodynamics variables in this extension study, values at the baseline in the preceding studies (RAJ1, RAJ3, and RAJ4) will be used as the baseline values. However, changes from baseline values of this extension study will also be examined where appropriate. For the analyses of safety, Week 0 of this extension study will be referred to as the baseline; however, changes from baseline values of the preceding studies (RAJ1, RAJ3, and RAJ4) will also be examined where appropriate.
- Change from baseline to post-baseline will be calculated as: post-baseline value - baseline value. If the baseline value is missing, then that subject is not included in the calculation at any visit.
- Percent change from baseline to post-baseline will be calculated as: 100 × (change /baseline). If the baseline value is 0 or missing, or post-baseline value is missing, then percent change from baseline to post-baseline is missing.
- The values below the lower limit of quantitation (BQL) for β-D-glucan, hCG, Troponin, CK-MB will be treated as it is and these variables are not used for descriptive statistics

and displayed in the listings. As for β-D-glucan, it is used for shift-from baseline analysis.

- If CRP value (mg/dL) is the lower or equal limit of quantitation (i.e. <0.01 mg/dL or =<0.01 mg/dL) then CRP is regarded as 0.01 mg/dL, and used for the calculation of DAS28-CRP, etc. and categorized in <0.01 mg/dL.
- If ESR value (mm/hr) is the upper limit of quantitation (i.e. >=100 mm/hr) then ESR is regarded as 100 mm/hr, and used for the calculation of DAS28-ESR.
- **Treatment Sequence Set of preceding study** will be used for the analysis by preceding study. This set takes into consideration the initial treatment groups (in RAJ1), a switch from placebo to active treatment at Week 12 (in RAJ3), and a switch from placebo to active treatment at Week 12 or Week 28 (in RAJ4). For subjects in each preceding study, following groups are defined:

Treatment Sequence Set for RAJ1

Treatment Sequence Code	Treatment Sequence Label	initial treatment group
SEQ J1-1	25mg	ASP015K 25mg
SEQ J1-2	50mg	ASP015K 50mg
SEQ J1-3	100mg	ASP015K 100mg
SEQ J1-4	150mg	ASP015K 150mg
SEQ J1-5	Placebo	Placebo

  - 25 mg: subjects who initially treated as ASP015K 25 mg Group
  - 50 mg: subjects who initially treated as ASP015K 50 mg Group
  - 100 mg: subjects who initially treated as ASP015K 100 mg Group
  - 150 mg: subjects who initially treated as ASP015K 150 mg Group
  - Placebo: subjects who initially treated as Placebo Group

Treatment Sequence Set for RAJ3

Treatment Sequence Code	Treatment Sequence Label	Week 0- Week 12	Week 12- Week 52
SEQ J3-1	100mg	ASP015K 100 mg	ASP015K 100 mg
SEQ J3-2	150mg	ASP015K 150 mg	ASP015K 150 mg
SEQ J3-3	Placebo to 100mg at Week 12	Placebo	ASP015K 100 mg
SEQ J3-4	Placebo to 150mg at Week 12	Placebo	ASP015K 150 mg
SEQ J3-5	Etanercept	Etanercept	Etanercept

  - 100 mg: subjects who initially treated as ASP015K 100 mg Group
  - 150 mg: subjects who initially treated as ASP015K 150 mg Group
  - Placebo to 100 mg at Week 12: subjects who initially treated as Placebo group and switched ASP015K 100 mg at Week 12 and at least one dose of ASP015K 100 mg drug after switched

- Placebo to 150 mg at Week 12: subjects who initially treated as Placebo group and switched ASP015K 150 mg at Week 12 and at least one dose of ASP015K 150 mg drug after switched
- Etanercept: subjects who initially treated as Etanercept Group. Subjects in this group do not shift to this study.

Treatment Sequence Set for RAJ4

Treatment Sequence Code	Treatment Sequence Label	Week 0- Week 12	Week 12- Week 28	Week 28- Week 52
SEQ J4-1	100mg	ASP015K 100 mg	ASP015K 100 mg	ASP015K 100 mg
SEQ J4-2	150mg	ASP015K 150 mg	ASP015K 150 mg	ASP015K 150 mg
SEQ J4-3	Placebo to 100mg at Week 12	Placebo	ASP015K 100 mg	ASP015K 100 mg
SEQ J4-4	Placebo to 150mg at Week 12	Placebo	ASP015K 150 mg	ASP015K 150 mg
SEQ J4-5	Placebo to 100mg at Week 28	Placebo	Placebo	ASP015K 100 mg
SEQ J4-6	Placebo to 150mg at Week 28	Placebo	Placebo	ASP015K 150 mg

- 100 mg: subjects who initially treated ASP015K 100 mg
- 150 mg: subjects who initially treated ASP015K 150 mg
- Placebo to 100 mg at Week 12: subjects who initially treated Placebo group and switched 100 mg at Week 12 and at least one dose of ASP015K 100 mg drug after switched
- Placebo to 150 mg at Week 12: subjects who initially treated Placebo group and switched ASP015K 150 mg at Week 12 and at least one dose of ASP015K 150 mg drug after switched
- Placebo to 100 mg at Week 28: subjects who initially treated Placebo group and switched ASP015K 100 mg at Week 28 and at least one dose of ASP015K 100 mg drug after switched
- Placebo to 150 mg at Week 28: subjects who initially treated Placebo group and switched ASP015K 150 mg at Week 28 and at least one dose of ASP015K 150 mg drug after switched

- If onset date of AE is Unknown, then missing onset date of AE will be imputed as following steps.
  1. If only the day of the month is missing (e.g., 2013-03), then the first day of the month will be used (2013-03-01),
  2. If both day and month are missing (e.g., 2013), then the first day of January will be used (2013-01-01).
  3. If day, month and year are missing, then the first date of study drug will be used.
  4. If imputed onset date of AE is earlier than the first date of study drug, [Adverse Events(From RAJ2) -page of the CRF]

then the onset date of AE will be re-imputed by the same date as the first date of study drug at RAJ2.
[Adverse Events(From RAJ1)/(From RAJ3 or RAJ4) -page of the CRF]
then the onset date of AE will be re-imputed by the same date as the first date of study drug at the preceding study.

7.2 Study Population

These analyses will be also conducted for overall by Study Region.

7.2.1 Disposition of Subjects

[Analysis Set: All Subjects with Informed Consent]

The following subject data will be summarized and presented:

- Screened
- Screen failed
- Dosed

[Analysis Set: All Dosed Subjects]

The following subject data will be summarized and presented:

- Subjects who prematurely discontinued from the study period during overall period
- In addition, subjects who prematurely discontinued from the study period will be summarized for primary reason for withdrawal during overall period.

- Subjects who prematurely discontinued from the study period up to 84 months, each interval are as follows:
- In addition, subjects who prematurely discontinued from the study period will be summarized for primary reason for withdrawal up to 84 months
  - 0 – 1 month
  - 1 <- 3 months
  - 3 <- 6 months
  - 6 <- 12 months
  - 12 <- 24 months
  - 24 <- 36 months
  - 36 <- 48 months
  - 48 <- 60 months
  - 60 <- 72 months
  - 72 <- 84 months
  - 84 months <

- Subjects who included/excluded of FAS, SAF, and PDAS

- In addition, subjects who were excluded from FAS, SAF, and PDAS will be summarized by reason for exclusion

[Analysis Set: Subject who experienced dose decrease to 50 mg]

The following subject data will be summarized and presented:

- Subjects who prematurely discontinued from the study period during overall period
- In addition, subjects who prematurely discontinued from the study period will be summarized for primary reason for withdrawal during overall period.

7.2.2 Demographic and Other Baseline Characteristics

7.2.2.1 Demographics

[Analysis Set: FAS, SAF, PDAS]

The following demographic variables will be summarized.

Demographic Variables

Item	Classification
Age (years) at Week 0	Measurement value
	<65, >= 65
Sex	Male, Female
Body Weight (kg) at Week 0	Measurement value
	<- 40 kg, 40 kg <- 60 kg, 60 kg <- 80 kg, > 80 kg
Complications at Week 0	No, Yes
Concomitant Medications at Week 0	No, Yes
Concomitant DMARD at Week 0	No, Yes
Concomitant MTX at Week 0	No, Yes
Concomitant DMARD category at Week 0	MTX, DMARD except for MTX only, None
Concomitant Steroid at Week 0	No, Yes
Prednisone dose (mg/day) at Week 0	Measurement value
	None, 0 =< 5 mg/day, > 5 mg/day
Study Region	Japan, Korea, Taiwan

7.2.2.2 Baseline Disease Activity

[Analysis Set: FAS, SAF, PDAS]

The following baseline disease activity variables will be summarized by descriptive statistics. The summaries will be presented for values at both “Week 0” and “baseline of preceding study”.

- TJC-68
- TJC-28
- SJC-66
- SJC-28
- SGAP (100 mm VAS)
- SGA (100 mm VAS)
- PGA (100 mm VAS)
- HAQ-DI (scale 0 - 3)
- CRP (mg/dL)
- ESR (mm/hr)
- DAS28-CRP
- DAS28–ESR
- SDAI score
- CDAI score
- WPAI (only for subjects who transferred from studies RAJ3 or RAJ4)
- SF-36V2®

In addition, following baseline efficacy categorical variables will be summarized as well.

- Baseline CRP (< 1.0, >= 1.0)
- Baseline DAS28-CRP/ ESR (<= 3.2, 3.2<-5.1, > 5.1)

7.2.2.3 RA History

[Analysis Set: SAF]

The following RA history variables will be summarized. The summaries will be presented for values at both "Week 0" and "baseline of preceding study", unless specifically stated otherwise.

RA History and Analysis Methods

Item	Classification
ACR 1991 Revised Criteria for Global Functional Status in RA	Class I, Class II, Class III, Class IV
Steinbrocker Classification	Stage I, Stage II, Stage III, Stage IV
Duration of RA (years) [#]	Measurement value
	< 5 years, >- 5 years
	< 1 year, 1 year -<5 years,

		5 years -< 10 years, >- 10 years
Prior MTX #	Use	Non-User, User
	Maximum Dose (mg/week)	Measurement value
	Reactivity	Response, Inadequate Response, Unknown
	Tolerance	Intolerance, Tolerance, Unknown
MTX Dose (mg/week) at Week 0		Measurement value
		None, 0 <- 8 mg/week, 8 <- 12 mg/week, > 12 mg/week
Prior Non-Biologic DMARD Except for MTX #	Use	Non-User, User
Prior Anti-TNF DMARD Use #	Use	Non-User, User
Prior Biologic DMARD #	Use	Non-User, User
	Reactivity	Response, Inadequate Response, Unknown
Prior Biologic DMARD-IR #		No, Yes
Number of Prior Biologic DMARDs #		0, 1, 2, >= 3
Number of Prior DMARDs (including biologics) #		0, 1, 2, >= 3

#: only for baseline of preceding study

7.2.2.4 Medical Condition

[Analysis Set: SAF]

Medical Conditions at "baseline of preceding study" will be coded using MedDRA (Version 11.1) and summarized.

7.2.3 Concomitant Medications

[Analysis Set: SAF]

Previous DMARD medications up to Screening of preceding study will be summarized as described in 7.2.2.3.

For subjects who shift from RAJ3/4, concomitant medications (Non-Biologic DMARD/ Medications except for Non-Biologic DMARD) will be coded using WHODDE (B2) (V2011SEP) and summarized with preferred WHO name, respectively from following CRF page. Concomitant medications are defined as any drug medications after the first dose of study drug at RAJ2 up to the end of study.

- Concomitant Medication 2B -page of the CRF
- Concomitant Medication (Non-Biologic DMARD) -page of the CRF

Subjects taking the same medication multiple times will be counted once per medication.

In addition to this, the maximum/ minimum MTX Dose (mg/week) during the study period will be summarized by descriptive statistics.

7.3 Study Drugs

These analyses will be also conducted for overall by Study Region.

7.3.1 Exposure

[Analysis Set: SAF]

Duration of exposure during RAJ2 will be summarized in two ways.

- Descriptive statistics will be presented
- Exposure time for overall period will be categorized according to the following categories:
  - 0 – 1 month
  - 1 <- 3 months
  - 3 <- 6 months
  - 6 <- 12 months
  - 12 <- 24 months
  - 24 <- 36 months
  - 36 <- 48 months
  - 48 <- 60 months
  - 60 <- 72 months
  - 72 <- 84 months
  - 84 months <

Counts and percentages of subjects in each category will be summarized.

In addition to this, the following information on drug exposure will be presented:

- Number and percent of subject with dose increase/ dose decrease/ drug suspension/ drug interruption
- Number of experience for dose increase/ dose decrease/ drug suspension/ drug interruption per subject
- Duration from First Study Drug Taken up to First Dose Change to ASP015K 100 mg (from RAJ1) or 150 mg (from RAJ3/RAJ4)
- Maximum Dose of Study Drug (ASP015K 50 mg/ 100 mg/ 150 mg)

The following Kaplan-Meier plot of time-to-event from initial dose will be constructed.

		Event	Censor
Time to changing initial 50mg	RAJ1	Dose increase Discontinuation	Study Completion
Time to changing initial 100mg	RAJ3/4	Dose increase Dose decrease Discontinuation	Study Completion
Time to dose increasing initial 100mg	RAJ3/4	Dose increase	Study Completion Discontinuation Dose decrease
Time to dose decrease initial 100mg	RAJ3/4	Dose decrease	Study Completion Discontinuation Dose increase

7.3.2 Treatment Compliance

[Analysis Set: SAF]

Treatment compliance during RAJ2 will be examined for subjects in the SAF whose total study drug count and first and last days of treatment are known. These data will be summarized as below.

- Descriptive statistics for treatment compliance during RAJ2 will be presented.
- Treatment compliance during RAJ2 will be categorized according to the following categories:
  - <50%
  - 50% - <75%
  - 75% - <90%
  - 90% - 100%

7.4 Analysis of Efficacy

[Analysis Set: FAS]

Details for analysis of efficacy will be described in 10.1 Appendix 1: Overview of Efficacy Endpoints. They include categorical, and continuous variables, with "X" indicating that the

variable will be analyzed. Basically, analysis of efficacy will be performed by preceding studies only, not performed by overall.

7.4.1 Analysis of Efficacy Endpoint(s)

The efficacy variables and analyses are as follows.

- Categorical variables at each visit will be summarized.
- For continuous variables, raw value and change from baseline of preceding study at each visit will be summarized by descriptive statistics. In addition, for the selected efficacy variables (DAS28-CRP), change from Week 0 at each visit will be summarized similarly.
- Graphical analysis:
  - ACR20/50/70-CRP/ESR will be plotted for over time.
  - The mean-standard deviation plot of actual values and changes from baseline of preceding study will be presented for DAS28-CRP and DAS28-ESR.

7.4.2 Analysis by Treatment Sequence Set of preceding study

The selected efficacy variables (ACR20-CRP and DAS28-CRP) are summarized by Treatment Sequence Set, and by preceding study respectively. In this analysis, time course of each efficacy variable will be presented from baseline of preceding study up to end of RAJ2 study. Following analysis visits of preceding study will be used,

- Subjects shifted from RAJ1
  - RAJ1 – Week 0
  - RAJ1 – Week 12
  - Week 0 (RAJ1 – Week 16)
- Subjects shifted from RAJ3/4
  - RAJ3/4 – Week 0
  - RAJ3/4 – Week 12
  - RAJ3/4 – Week 28
  - RAJ3/4 – Week 40
  - RAJ3/4 – Week 52
  - Week 0

- Categorical variables at each visit will be summarized.
- For continuous variables, raw value and change from baseline of preceding study at each visit will be summarized by descriptive statistics.
- Graphical analysis:
  - ACR20-CRP will be plotted from baseline of preceding study.
  - The mean-standard deviation plot of actual values and changes from baseline of preceding study will be presented for DAS28-CRP from baseline of preceding study.

7.4.3 Analysis of Efficacy in Initial/Maximum Dose Level

The selected efficacy variables (ACR20-CRP and DAS28-CRP) are summarized by preceding study. In Initial dose analysis, data obtained after changing initial dose at RAJ2 (50mg for subjects from RAJ1, 100mg for subjects from RAJ3/4) will not be used for efficacy analyses.

- Categorical variables at each visit will be summarized.
- For continuous variables, raw value and change from baseline of preceding study at each visit will be summarized by descriptive statistics.

7.4.4 Influence of Dose Escalation

In order to evaluate influence of ASP015K dose escalation to 100 mg from 50 mg for subjects who shifted from RAJ1 and dose escalation to 150 mg from 100 mg for subjects who shifted from RAJ3 or RAJ4, the selected efficacy variables (ACR20-CRP and DAS28-CRP) will be analyzed based on the days of first dose increase to 100mg or 150mg until dose decrease. Following intervals will be used.

- < -336
- -336 - < -252
- -252 - < -168
- -168 - < -84
- -84 - < 0
- 0 - < 84
- 84 - < 168
- 168 - < 252
- 252 - < 336
- >= 336

If multiple efficacy values are included in one interval, the last one is used.

- Graphical analysis:
  - ACR20-CRP will be plotted
  - The mean-standard deviation plot of actual values and changes from baseline of preceding study will be presented for DAS28-CRP from baseline of preceding study.

7.4.5 Subgroup Analysis

In order to evaluate homogeneity of treatment effects across subjects with different demographic and baseline characteristics, subgroup analysis of the efficacy variables will be performed, respectively. The subgroups in Section 7.8 will be analyzed.

7.5 Analysis of Safety

[Analysis Set: SAF]

Details for analysis of safety will be described in 10.2 Appendix 2: Overview of AE analysis, and, 10.3 Appendix 3: Overview of Clinical Laboratory Evaluation, Vital Signs, and Electrocardiograms (ECGs) analyses.

7.5.1 Adverse Events

Treatment emergent adverse events (TEAEs) in this study will be defined as below:

- Any adverse event that started or worsened in severity after the first dose of study drug at RAJ2 to the end of the final observation

Any unrecovered adverse event that first occurred during the preceding studies (RAJ1, RAJ3, and RAJ4) will be treated as medical conditions and not treated as TEAEs in this study.

A drug-related TEAE is defined as any TEAE with possible, probable or missing relationship to study drug as assessed by the investigator. Moreover, any TEAE with missing relationship to study drug or reference drug was counted as drug related (probable).

Adverse events will be coded using the MedDRA.

All adverse events reported during the study period will be presented in subject listings.

In this study 2 types of analyses for TEAEs will be performed:

- TEAE occurrence analysis
- TEAE per 100 patient-years analysis

TEAE occurrence analysis will be displayed by whole treatment period, unless specifically stated otherwise. TEAE per 100 patient-years analysis will be displayed the following category, and by overall period.

  - 0 – 6 months
  - 6 <- 12 months
  - 12 <- 24 months
  - 24 <- 36 months
  - 36 <- 48 months
  - 48 <- 60 months
  - 60 <- 72 months
  - 72 <- 84 months
  - 84 months <

7.5.1.1 Adverse events

The coding dictionary for this study will be MedDRA 11.1. It will be used to summarize AEs by SOC and PT. Subjects reporting more than one AE for a given MedDRA PT will be counted only once for that term. Subjects reporting more than one AE within a SOC will be counted only once for the SOC total. Subjects reporting more than one AE will be counted only once in the overall AE total.

SOCs will be presented by descending frequency for "Total" (RAJ1 + RAJ3 + RAJ4) column, and PTs within SOC will be presented by decreasing frequency in "Total".

Number and percentage of subjects with TEAE in the following AE categories will be summarized by SOC and PT:

An overview table will include the following details:

- Number and percentage of subjects with TEAE
- Number and percentage of subjects with drug related TEAE
- Number and percentage of subjects with death
- Number and percentage of subjects with serious TEAE
- Number and percentage of subjects with drug related serious TEAE
- Number and percentage of subjects with Grade 3 or Higher in Severity TEAE
- Number and percentage of subjects with TEAE leading to permanent discontinuation of study drug
- Number and percentage of subjects with drug related TEAE leading to permanent discontinuation of study drug
- Number and percentage of subjects with serious TEAE leading to permanent discontinuation of study drug
- Number and percentage of subjects with drug related serious TEAE leading to permanent discontinuation of study drug
- Number and percentage of subjects with TEAE leading to dose decrease of study drug
- Number and percentage of subjects with drug related TEAE leading to dose decrease of study drug
- Number and percentage of subjects with TEAE leading to temporary discontinuation of study drug
- Number and percentage of subjects with drug related TEAE leading to temporary discontinuation of study drug

The number and percentage of subjects with TEAEs, as classified by SOC and PT will be summarized by preceding studies and overall. Summaries will be provided for:

- TEAEs
- Drug related TEAEs, defined as any TEAE with possible, probable or missing relationship to study drug as assessed by the investigator.
  Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most related category reported.

In addition, the number and percentage of subjects with TEAEs and Drug related TEAEs, as classified by SOC and PT will be presented by preceding studies and overall, by Maximum Dose of Study Drug.

- Serious TEAEs
- Drug related serious TEAEs
- TEAEs by severity based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Grade (Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe or medically significant, Grade 4 = life threatening, Grade 5 = death related to AE)
  Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most severe category reported.
  If a subject has an AE which has a missing severity, then the subject will be counted in the severity category of "Missing" (i.e., missing severity will not be imputed).
- Drug related TEAEs by severity
- Grade 3 or higher TEAEs by severity
- TEAEs by relationship to study drug
  Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most related category reported.
  TEAE with missing relationship to study drug missing will be counted as drug related. Moreover, any TEAE with missing relationship to study drug or reference drug was counted as drug related (probable).
- TEAEs leading to death
- TEAEs leading to permanent discontinuation of study drug
- Drug related TEAEs leading to permanent discontinuation of study drug
- Serious TEAEs leading to permanent discontinuation of study drug
- Drug related serious TEAEs leading to permanent discontinuation of study drug
- TEAE leading to dose decrease of study drug
- Drug related TEAE leading to dose decrease of study drug
- TEAE leading to temporary discontinuation of study drug
- Drug related TEAE leading to temporary discontinuation of study drug
- Most common TEAEs (> 5% in any preceding study)
- Most common serious TEAEs (> 5% in any preceding study)
- TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any preceding study
- The number and percentage of subjects with TEAEs of special interest.

  Following adverse events of special interest are defined:

  - Serious Infections
  - Malignancies
  - Herpes Zoster Related Disease (Herpes Zoster and Varicella)
  - Herpes Zoster
  - Varicella

- Infections That Require Intravenous Anti-infectious Therapy

Note: Definition will be provided in 10.8 Appendix 8: AE of Special Interest.

In addition, the subgroup analysis of Sex, Age Group, Concomitant Steroid at Baseline, Prednisone Dose at Baseline, Body Weight (kg) at Week 0, Concomitant DMARD category at Week 0, Maximum Dose of Study Drug and Study Region will be conducted.

7.5.1.2 Adverse Events Per 100 Patient-Years

In order to adjust for differences in subjects' durations in the study and the potential differential dropout rates between the preceding studies, TEAEs per 100 patient-years (PYs) will be calculated as follows:

Definition 1:

TEAEs per 100 PYs = 100 × (Number of subjects who had at least 1 incidence / Total PYs)

Total PYs will be calculated by summing individual subjects' durations.

If subjects had at least 1 predefined AE, then the duration of these subjects are summed as from initial dose up to first incidence of predefined AEs.

If subjects had no predefined AE, then the duration of these subjects are summed as from initial dose through follow-up. Summed duration will be divided by 365.25 to represent per year.

Definition 2:

TEAEs per 100 PYs = 100 × (Number of TEAEs for all subjects/ Total PYs)

For number of TEAEs for all subjects, multiple occurrences of the same TEAE in the same subject will be counted multiple times.

Total PYs will be calculated by summing subjects' durations in this study through the follow-up period. Each subject's duration will be calculated as: (last date of follow-up in the study – date of initial dose of study drug + 1) / 365.25.

The number of TEAEs and TEAEs per 100 PYs will be provided by Definition 2, for all TEAEs (if analyzable) by SOC and PT for each preceding study, and Total.

Patient-Year analysis for following specified AE will also be conducted by Definition 1 with 95% confidence interval.

- Serious Infections
- Malignancies
- Herpes Zoster Related Disease (Herpes Zoster and Varicella)
- Herpes Zoster
- Varicella
- Infections That Require Intravenous Anti-infectious Therapy

Note: Definition will be provided in 10.8 Appendix 8: AE of Special Interest.

Confidence Interval for TEAEs per 100 patient-years will be calculated for AE of special Interest based on following formula (assuming Poisson distribution).

- Upper limit of CI (TEAEs per 100 PYs) : $100 \times \exp(\log(A/T) + Z_{(alpha)} * \sqrt{(1/A)})$
- Lower limit of CI (TEAEs per 100 PYs) : $100 \times \exp(\log(A/T) - Z_{(alpha)} * \sqrt{(1/A)})$

A: Number of subjects who had at least 1 incidence

T: Total PYs

$Z_{(alpha)}$: alpha % point of standard normal distribution

alpha = 0.025

TEAE of special interest per 100 patient-years analysis will be displayed the following category.

- 0 – 6 months
- 6 <- 12 months
- 12 <- 24 months
- 24 <- 36 months
- 36 <- 48 months
- 48 <- 60 months
- 60 <- 72 months
- 72 <- 84 months
- 84 months <

In addition, the subgroup analysis of Sex, Age Group, Concomitant Steroid at Baseline, Prednisone Dose at Baseline, Body Weight (kg) at Week 0, Concomitant DMARD category at Week 0, Maximum Dose of Study Drug and Study Region will be conducted.

7.5.1.3 Subgroup Analyses

In order to assess whether or not AEs vary across specific patient groups, AE occurrence will be summarized by SOC and PT for the subgroups specified in Section 7.8.

7.5.2 Clinical Laboratory Evaluation

7.5.2.1 All Laboratory Tests

For clinical laboratory parameters (hematology, biochemistry, fasting lipid profile, and urinalysis), raw values at each scheduled visit, change from Week 0 at each post-Week 0 visit, shift from Week 0 and shift from reference range will be summarized using descriptive statistics or frequency tabulations. For Fasting Lipids Profile, all analysis will be conducted using the measured values which are confirmed under fasting condition. In addition, all Lipid

Profile values including non-fasting condition will also be summarized for descriptive statistics.

For subjects who shift from RAJ3, clinical laboratory test is conducted at central institution at each region (Japan, Korea, and Taiwan) in accordance with each procedure and each reagent for clinical test. The possibility of harmonization among each region was conducted before clinical laboratory test was initiated in Korea and Taiwan. If clinical laboratory evaluation could be harmonized, then these measurement data among each region could be regarded as the same scale. If harmonization was reported to be difficult, then clinical test would be summarized by Study Region (Japan, Korea, and Taiwan). However, among clinical laboratory tests not-harmonized, for exploratory analysis, Beta-D-glucan, Glucose, HCO3, urine pH, urine gravity will be summarized by whole population. Qualitative Urinalysis test will be summarized by Study Region, only (see 7.8.2 Subgroup analysis for Study Region (Japan, Korea, and Taiwan).

- Clinical laboratory tests harmonized
  - All of the hematology test
  - Biochemistry test except for Beta-D-glucan, Glucose, HCO3
  - All of the fasting lipid profile
  - CRP
- Clinical laboratory tests not-harmonized
  - Beta-D-glucan, Glucose, HCO3
  - All of the urinalysis test

  * Pregnancy test, CPK monitoring, and Hepatitis test are not applicable to harmonization and it will be displayed in listing only.

- For continuous variables, descriptive statistics of raw values at each scheduled visit will be summarized at each time point using SI unit. For the ratio T-Chol to HDL and the ratio LDL to HDL, descriptive statistics will be summarized at each post-baseline visit.
- For continuous variables, descriptive statistics of change from Week 0 value will be summarized at each visit using SI unit.
- In addition, for the selected laboratory tests (hematology, biochemistry, fasting lipid profile), descriptive statistics of raw values and change from baseline of preceding study at each visit will be summarized similarly. In this analysis, time course of each safety variable will be presented from baseline of preceding study up to end of RAJ2 study by Treatment Sequence Set. Following analysis visits of preceding study will be used,

- Subjects shifted from RAJ1
  - RAJ1 – Week 0
  - RAJ1 – Week 12
  - Week 0 (RAJ1 – Week 16)

- Subjects shifted from RAJ3/4
  - RAJ3/4 – Week 0
  - RAJ3/4 – Week 12
  - RAJ3/4 – Week 28
  - RAJ3/4 – Week 40
  - RAJ3/4 – Week 52
  - Week 0

- Shift-from-Week 0 table: Shift from Week 0 to highest value, and Shift from Week 0 to lowest value during entire period, for all laboratory variables. If the laboratory value of same subject is measured lower from normal range at one visit, and higher from normal range at the other visit, that subject will be counted as both low and high from Week 0 during entire period.

- Graphical analysis:
  - The mean-standard deviation plot of actual values and changes from week 0 will be presented for the selected laboratory tests (hematology, biochemistry, fasting lipid profile).

7.5.2.2 Laboratory Tests for NCI-CTC Toxicity Grading

Laboratory test results for the selected laboratory tests will be graded programmatically using the standardized NCI-CTC toxicity grading criteria (Grade 0, 1, 2, 3, 4) specified in the 10.9 Appendix 9: Standard Toxicity Grading for Laboratory Tests According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0. Shift-from-Week 0 to worst value during entire period will be provided. Note: AEs in this study are graded the investigator using NCI-CTAE Grade (1, 2, 3, 4, 5).

7.5.2.3 Laboratory Tests for Reference Range

Test results for the selected laboratory tests in the table below will be summarized against the reference range indicated. Number and percentage for the Highest/Lowest values of each subject included in pre-specified reference range for select laboratory during entire period will be provided.

Select Laboratory Variables and Corresponding Reference Ranges

Select Laboratory Variable	Reference Range	Highest/Lowest	Note
Aspartate Aminotransferase (AST)	>= 1 × ULN to < 2 × ULN >= 2 × ULN to < 3 × ULN >= 3 × ULN	Highest	
Alanine Aminotransferase (ALT)	>= 1 × ULN to < 2 × ULN >= 2 × ULN to < 3 × ULN >= 3 × ULN	Highest	
Alkaline Phosphatase (ALP)	> 2 × ULN to <= 3 × ULN > 3 × ULN to <= 5 × ULN > 5 × ULN	Highest	
Total Bilirubin	>1.5× ULN	Highest	
Total Bilirubin	>= 1 × ULN to < 2 × ULN >= 2 × ULN to < 3 × ULN >= 3 × ULN	Highest	
Low-Density Lipoprotein (LDL)	> 160 mg/dL	Highest	
Low-Density Lipoprotein (LDL) (maximum value)	< 100 mg/dL 100 to < 130 mg/dL 130 to < 160 mg/dL 160 to < 190 mg/dL >= 190 mg/dL	Highest	
Hemoglobin (HGB)	>=8.0 to < 10.0 g/dL < 8.0 g/dL	Lowest	
Hemoglobin (HGB)	>= (Week 0 value -2) to <(Week 0 value -1) g/dL <(Week 0 value -2) g/dL	Lowest	
Hemoglobin (HGB)	· Mild to Moderate: decrease from Week 0 value >=1 to <=2 g/dL, · Severe: decrease from Week 0 value >2 to <3 g/dL or absolute value >7 and <8 g/dL, · Potentially Life Threatening: decrease from Week 0 value >=3 or absolute value <=7 g/dL	Lowest	
Creatine Phosphokinase (CPK)	> 500 to <= 2,000 U/L > 2,000 U/L	Highest	Based on "CPK Monitoring" in protocol
Creatine Phosphokinase (CPK)	> 5 × Week 0 value	Highest	Based on "CPK Monitoring" in protocol

Select Laboratory Variable	Reference Range	Highest/Lowest	Note
Creatine Phosphokinase (CPK)	> 2× ULN to <= 5 × ULN > 5 × ULN to <= 10 × ULN > 10 × ULN	Highest	Based on "CPK Monitoring" in protocol
Creatinine	> 1.5 × Week 0 value to <= 3.0 ×Week 0 value > 3.0 × Week 0 value	Highest	
Absolute Neutrophil Count (ANC)	>= 1,500 to < 2,000 / mm^3 >= 500 to < 1,500 / mm^3 < 500 / mm^3	Lowest	Based on "OMERACT criteria"
Lymphocytes	>= 200 to < 500 /uL < 200 /uL	Lowest	
Lymphocytes	>= 1,500 to < 2,000 / mm^3 >= 500 to < 1,500 / mm^3 < 500 / mm^3	Lowest	Based on "OMERACT criteria"
Platelets	>= 2 × 10^4 to < 5 × 10^4 /uL < 2 × 10^4 /uL	Lowest	
Platelets	> 600,000 /uL	Highest	
ULN = Upper Limit Normal Each categories are mutually exclusive.			

7.5.2.4 Liver Abnormalities

The following potentially clinically significant criteria in liver function tests for Alkaline Phosphatase (ALP), Alanine Transaminase (ALT), total bilirubin, Aspartate Transaminase (AST) and their combination are defined. The subject's highest value during the investigational period will be used.

Parameter	Criteria
ALT	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
AST	> 3xULN
	> 5xULN
	> 10xULN
	> 20xULN
ALT or AST	> 3xULN

	> 8xULN
Total Bilirubin	> 2xULN
ALP	> 1.5xULN
ALT and/or AST OR Total Bilirubin(*)	(ALT and/or AST > 3xULN) or total bilirubin > 2xULN
ALT and/or AST AND Total Bilirubin(*)	(ALT and/or AST > 3xULN) and total bilirubin > 2xULN

(*) Combination of values measured within same sample

The number and percentage of subjects with potentially clinically significant values in liver function tests during the investigational period will be presented.

Additionally, confirmed liver abnormities will be characterized as moderate and marked, as follow:

Moderate: ALT or AST > 3×ULN OR Total Bilirubin > 2×ULN.

Marked: ALT or AST > 3×ULN AND Total Bilirubin > 2×ULN.

Number and percentage of subjects in each category at each scheduled visit will be summarized. These combinations of elevated values are based on measured value within the same sample.

7.5.2.5 Liver Functions Plots

A matrix scatter plot of liver function test will be plotted showing the maximum ALT, AST, ALP and total bilirubin during the study period crossed against each other. Different dots will be used for preceding studies.

7.5.3 Vital Signs

Raw values and changes from Week 0 at each scheduled visit will be summarized using descriptive statistics.

7.5.4 Electrocardiograms (ECGs)

<12-lead ECG>

- Raw values (categorical) and changes from Week 0 (shift from Week 0) will be summarized, and the summaries will include number and percentage of subjects with normal, not clinically significant abnormal and clinically significant abnormal 12 lead ECG findings.

7.5.5 Chest radiography

Chest radiography will be provided as a subject listing only.

7.5.6 Pregnancies

Pregnancies will be provided as a subject listing only.

7.6 Analysis of PK

Refer to PK SAP.

7.7 Analysis of PD

[Analysis Set: PDAS]

For subjects who shift from RAJ3, as described in 7.5.2, harmonization for lymphocytes subset variables among each region (Japan, Korea, Taiwan) was reported to be difficult and therefore, raw values and changes from baseline of preceding study will be summarized by Study Region (Japan, Korea, Taiwan), using descriptive statistics. For CD3, CD8, CD4, CD19, CD4/CD8 ratio, (CD16 or CD56)+, CD16+ and CD56+, CD16- and CD56+, CD16+ and CD56-, CD16- and CD56-, count values (cells/uL) will be summarized by whole population for exploratory analysis.

1. Japan
    - CD3+/Lymphocytes (%), CD3+ (cells/uL)
    - CD8+/Lymphocytes (%), CD8+ (cells/uL)
    - CD4+/Lymphocytes (%), CD4+ (cells/uL)
    - CD19+/Lymphocytes (%), CD19+ (cells/uL)
    - CD4/CD8 Ratio
    - (CD16 or CD56)+/Lymphocytes (%), (CD16 or CD56)+ (cells/uL)
    - (CD16+ and CD56+)/CD3- (%), CD16+ and CD56+ (cells/uL)
    - (CD16- and CD56+)/CD3- (%), CD16- and CD56+ (cells/uL)
    - (CD16+ and CD56-)/CD3- (%), CD16+ and CD56- (cells/uL)
    - (CD16- and CD56-)/CD3- (%), CD16- and CD56- (cells/uL)
    - CD56 bright/CD3- (%), CD56 bright (cells/uL)
    - CD56 dim/CD3- (%), CD56 dim (cells/uL)

2. Korea
    - CD3+/Lymphocytes (%), CD3 (cells/uL)
    - (CD3+ and CD8+)/CD3+ (%), CD3+ and CD8+ (cells/uL)
    - (CD3+ and CD4+)/CD3+ (%), CD3+ and CD4+ (cells/uL)
    - (CD16 or CD56)+/CD3- (%), (CD16 or CD56)+ (cells/uL)
    - CD19+/CD3- (%), CD19+ (cells/uL)
    - CD4/CD8 Ratio
    - (CD16+ and CD56+)/CD3- (%), CD16+ and CD56+ (cells/uL)
    - (CD16- and CD56+)/CD3- (%), CD16- and CD56+ (cells/uL)
    - (CD16+ and CD56-)/CD3- (%), CD16+ and CD56- (cells/uL)
    - (CD16- and CD56-)/CD3- (%), CD16- and CD56- (cells/uL)
3. Taiwan
    - CD3+/Lymphocytes (%), CD3 (cells/uL)
    - (CD3+ and CD8+)/Lymphocytes (%), CD3+ and CD8+ (cells/uL)
    - (CD3+ and CD4+)/Lymphocytes (%), CD3+ and CD4+ (cells/uL)
    - (CD16 or CD56)+/Lymphocytes (%), (CD16 or CD56)+ (cells/uL)
    - CD19+/Lymphocytes (%), CD19+ (cells/uL)
    - CD4/CD8 Ratio
    - (CD16+ and CD56+)/Lymphocytes (%), CD16+ and CD56+ (cells/uL)
    - (CD16- and CD56+)/Lymphocytes (%), CD16- and CD56+ (cells/uL)
    - (CD16+ and CD56-)/Lymphocytes (%), CD16+ and CD56- (cells/uL)
    - (CD16- and CD56-)/Lymphocytes (%), CD16- and CD56- (cells/uL)

7.8 Subgroups of Interest

7.8.1 Subgroup analysis of the selected efficacy endpoint (ACR20-CRP) and treatment emergent adverse events

The selected efficacy variable (ACR20-CRP) and TEAEs will be summarized for the subgroups defined on the basis of the categorized variables listed below:

- Sex (Male, Female,)
- Age Group at Week 0 (< 65 years, >= 65 years)
- Prior Anti-TNF DMARD Use in preceding study (User, Non-user)
- Prior Biologic DMARD-IR in preceding study (No, Yes)

- Duration of RA (years) in preceding study (< 5 years, >= 5 years)
- Number of Prior DMARDs Used in preceding study (0, 1, 2, >= 3)
- Number of Prior Biologic DMARDs Used in preceding study (0, 1, 2, >= 3)
- MTX Dose (mg/week) at Week 0 (None, 0 <- 8 mg/week, 8 <- 12 mg/week, > 12 mg/week)
- Concomitant Steroid at Week 0 (No, Yes)
- Prednisone Dose (mg/day) at Week 0 (None, 0 <- 5 mg/day, > 5 mg/day)
- Concomitant non-Biologic DMARD Use at Week 0 (No, Yes)
- Study Region (Japan, Korea, Taiwan)
- Baseline DAS28-CRP in preceding study (<= 3.2, 3.2<-5.1, > 5.1), efficacy analyses only
- Baseline DAS28-ESR in preceding study (<= 3.2, 3.2<-5.1, > 5.1), efficacy analyses only
- Baseline CRP in preceding study (< 1.0, >= 1.0) , efficacy analyses only
- Concomitant DMARD category at Week 0 (MTX, DMARD except for MTX only, None)
- Body Weight (kg) at Week 0 (<- 40 kg, 40 kg <- 60 kg, 60 kg <- 80 kg, > 80 kg)
- Maximum Dose of Study Drug (50 mg, 100 mg, 150 mg)

7.8.2 Subgroup analysis by Study Region (Japan, Korea, Taiwan)

Following efficacy, safety, and pharmacodynamic variables will be analyzed by Study Region (Japan, Korea, Taiwan) in addition to 7.8.1 Subgroup analysis.

- ACR50
- ACR70
- DAS28-CRP
- DAS28-ESR
- HAQ-DI
- SF-36V2®
- Overview of TEAEs
- Serious TEAEs
- Drug related TEAE
- TEAE leading to permanent discontinuation of study drug
- The number and percentage of subjects with TEAEs of special interest
  - Serious Infections
  - Malignancies
  - Herpes Zoster Related Disease (Herpes Zoster and Varicella)
  - Herpes Zoster
  - Varicella
  - Infections That Require Intravenous Anti-infectious Therapy
- Clinical Laboratory Evaluation

- For continuous variables, descriptive statistics of raw values, change from Week 0 value at each scheduled visit will be summarized at each time point using SI unit
- For categorical variables, frequencies and percentages will be displayed at each scheduled visit.

○ Pharmacodynamic variables
- Described in 7.7

7.9 Other Analyses

Not Applicable.

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

Not applicable for efficacy analysis. Review of safety data and safety evaluation will be conducted by an independent DSMB during the study in accordance with separate SOP.

7.11 Handling of LLOQ, Missing Data, Outliers, Visit Windows, and Other Information

7.11.1 LLOQ

Safety variables

Values below the LLOQ for beta-D-glucan, hCG, Troponin-T, CK-MB will be treated as it is and these variables are not used for descriptive statistics and displayed in the listings. As for beta-D-glucan, it is used for shift-from baseline analysis.

PD variables

Values below the LLOQ will be set to 0 for calculation of descriptive statistics.

7.11.2 Missing Data

Missing Data in ACR20/50/70, DAS28

Table below addresses the handling of missing ACR components and ACR response in analyses of ACR20/50/70, DAS28, and DAS28-related variables at ET. Note that if subject does not have any post-baseline values, then that subject will be defined as a non-responder.

Imputation Methods for ACR and DAS28 for Components and Response at ET

Imputation Method		Explanation/Instruction
For use in all ACR20/50/70 analyses at ET		
1	LOCF components	● LOCF all ACR component value(s) at the last evaluation point and then calculate ACR response as ET.
For use in all DAS28 and DAS28-based analyses at ET		
2	LOCF components	● LOCF all DAS28 CRP component value(s) at the last evaluation point and then calculate the DAS28 score as ET.

Missing Data in HAQ-DI

For HAQ-DI, there are 20 items in 8 categories, with each category having 2 or 3 questions. A subject must have a score in >= 6 of the 8 categories, otherwise the HAQ-DI cannot be computed and will be considered missing for data summarization and analysis purposes. If responses to individual questions within a category are missing, they are not imputed. Therefore, the score in each category is based on non-missing responses. A category score is missing when all responses within a category are missing.

Missing Data in SF-36v2

For SF-36v2, there are 8 scales (domains). Missing values will be imputed if at least half of the items in the domain that included the missing item score(s) are non-missing. In that case, the missing value will be imputed with the average score of the non-missing item scores in this domain.

Missing Data in FACIT-Fatigue

For FACIT-Fatigue, there are 13 items. Missing values of any individual item will be imputed with the average score obtained from the non-missing items if more than 50% of the items are available, i.e., if the number of non-missing items >= 7.

Missing Data in WPAI

For WPAI Scale Score, each score will be computed on condition that the all of the questions for each score will not be non-missing.

Safety Data Imputation Methods

For safety data, LOCF method will be used for the value at ET.

7.11.3 Outliers

All values will be included in the analyses.

7.11.4 Visit Windows

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

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

7.11.5 Handling of Schedule of Assessments of Efficacy Variables

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

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

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

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

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

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

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

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

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

(3) Patient Questionnaires (SF-36v2®)

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

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

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

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

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

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

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

7.11.6 Handling of Schedule of Assessments of Safety Variables

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

(1) Vital Signs

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

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

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

Time points defined in analysis	Reference date*	Acceptable time range
Week 0	Day 1	Day 1
Week 2	Day 15	Day 12 to Day 18
Week 4	Day 29	Day 22 to Day 36
Week 8	Day 57	Day 50 to Day 64
Week 12	Day 85	Day 78 to Day 92
Week 16	Day 113	Day 106 to Day 120
Week 20	Day 141	Day 134 to Day 148
Week 24	Day 169	Day 162 to Day 176
Week 28	Day 197	Day 190 to Day 204
Week 32	Day 225	Day 218 to Day 232
Week 36	Day 253	Day 246 to Day 260
Week 40	Day 281	Day 274 to Day 288
Week 44	Day 309	Day 302 to Day 316
Week 48	Day 337	Day 330 to Day 344
Week 60	Day 421	Day 407 to Day 435
Week 72	Day 505	Day 491 to Day 519
Week 84	Day 589	Day 575 to Day 603
Week 96	Day 673	Day 659 to Day 687
Week 108	Day 757	Day 743 to Day 771
Week 120	Day 841	Day 827 to Day 855
Week 132	Day 925	Day 911 to Day 939
Week 132 + 12 × x	Day 7 × (132 + 12 × x) + 1	Day 7 × (132 + 12 × x) − 13 to Day 7 × (132 + 12 × x) + 15
Minimum on Treatment		Minimum value during Entire Period (No limitation for period)
Maximum on Treatment		Maximum value during Entire Period (No limitation for period)
End/discontinuation of treatment	Day of the last dose	Day 2 to 2 days after the last dose
End of the study (at time of follow-up)	28 days after the last dose	21 to 35 days after the last dose

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

(3) 12-lead ECG, Chest Radiography

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

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

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

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

****: Only Chest radiography is applied for 24 weeks intervals (only for Taiwan).

(4) Body weight

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

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

7.11.7 Handling of Schedule of Assessments of Pharmacodynamic Variables

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

(1) Lymphocyte subsets

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

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

8 DOCUMENT REVISION HISTORY

Version	Date	Changes	Comment/rationale for change
1.00	18-Jan-2018	NA	Document finalized

9 REFERENCES

ICH Harmonized Tripartite Guideline E 3. Structure and Content of Clinical Study Reports, November 1995. (www.ich.org; Guidelines; "Efficacy" Topics)

ICH Harmonized Tripartite Guideline E 9. Statistical Principles for Clinical Trials, February 1998. (www.ich.org; Guidelines; "Efficacy" Topics)

10 APPENDICES

10.1 Appendix 1: Overview of Efficacy Endpoints

Table below summarizes the analyses of the efficacy variables, with "X" indicating that the variable will be analyzed. All analyses will be based on the FAS and presented by preceding studies, unless otherwise specified. No statistical hypothesis testing will be performed.

Overview of Efficacy Endpoints analysis

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
Categorical Variables								
1.1	Percentage of subjects achieving ACR20/50/70 at each visit	X	X		X	X	X	preceding studies
1.2.1	Percentage of subjects achieving ACR20 at each visit Analysis by Treatment Sequence Set of preceding study	X			X			Treatment Sequence Set
1.2.2	Percentage of subjects achieving ACR20 at each visit Analysis by Treatment Sequence Set of preceding study	X				X		Treatment Sequence Set
1.2.3	Percentage of subjects achieving ACR20 at each visit Analysis by Treatment Sequence Set of preceding study	X					X	Treatment Sequence Set
1.3	Percentage of subjects achieving ACR20 at each visit Analysis of Efficacy in Each Dose Level	X			X	X	X	preceding studies

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
1.4.1	Percentage of subjects achieving ACR20 at each interval Influence of Dose Escalation	X			X			Subjects Who Experienced Dose Up to 100 mg
1.4.2	Percentage of subjects achieving ACR20 at each interval Influence of Dose Escalation	X				X		Subjects Who Experienced Dose Up to 150 mg
1.4.3	Percentage of subjects achieving ACR20 at each interval Influence of Dose Escalation	X					X	Subjects Who Experienced Dose Up to 150 mg

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
1.5.1	Percentage of subjects achieving ACR20 at each visit subgroup analysis ● Sex (Male, Female,) ● Age Group at Week 0 (< 65 years, >= 65 years) ● Prior Anti-TNF DMARD Use in preceding study (User, Non-user) ● Prior Biologic DMARD-IR in preceding study (No, Yes) ● Duration of RA (years) in preceding study (< 5 years, >= 5 years) ● Number of Prior DMARDs Used in preceding study (0, 1, 2, >= 3) ● Number of Prior Biologic DMARDs Used in preceding study (0, 1, 2, >= 3) ● MTX Dose (mg/week) at Week 0 (None, 0 <- 8 mg/week, 8 <- 12 mg/week, > 12 mg/week) ● Concomitant Steroid at Week 0 (No, Yes) ● Prednisone Dose (mg/day) at Week 0 (None, 0 <- 5 mg/day, > 5 mg/day) ● Concomitant non-Biologic DMARD Use at Week 0 (No, Yes) ● Study Region (Japan, Korea, Taiwan) ● Baseline DAS28-CRP in preceding study (<= 3.2, 3.2<-5.1, > 5.1), efficacy analyses only ● Baseline DAS28-ESR in preceding study (<= 3.2, 3.2<-5.1, > 5.1), efficacy analyses only ● Baseline CRP in preceding study (< 1.0, >= 1.0) , efficacy analyses only ● Concomitant DMARD category at Week 0 (MTX, DMARD except for MTX only, None)	X			X	X	X	preceding studies
1.5.2	Percentage of subjects achieving ACR50/70 at each visit subgroup analysis ● Study Region (Japan, Korea, Taiwan)	X				X		preceding studies
1.7	Percentage of subjects achieving ACR20 at each visit ACR20 Response plot	X			X	X	X	preceding studies

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
1.8.1	Percentage of subjects achieving ACR20 at each visit ACR20 Response plot Analysis by Treatment Sequence Set of preceding study	X			X			Treatment Sequence Set
1.8.2	Percentage of subjects achieving ACR20 at each visit ACR20 Response plot Analysis by Treatment Sequence Set of preceding study	X				X		Treatment Sequence Set
1.8.3	Percentage of subjects achieving ACR20 at each visit ACR20 Response plot Analysis by Treatment Sequence Set of preceding study	X					X	Treatment Sequence Set
2.1	Percentage of subjects achieving DAS28 score <2.6 at each visit	X	X		X	X	X	preceding studies
2.2	Percentage of subjects achieving DAS28 score <=3.2 at each visit	X	X		X	X	X	preceding studies
3	Percentage of subjects achieving "Good Response" using DAS28 EULAR response criterion at each visit	X	X		X	X	X	preceding studies
4	Percentage of subjects achieving "Good Response" or "Moderate Response" using DAS28 EULAR response criterion at each visit	X	X		X	X	X	preceding studies
5	Percentage of subjects in ACR/EULAR remission at each visit	X			X	X	X	preceding studies
6	Percentage of subjects in SDAI <= 3.3 at each visit	X			X	X	X	preceding studies

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
7	Percentage of subjects in CDAI <= 2.8 at each visit			X	X	X	X	preceding studies
8.1	Percentage of subjects achieving HAQ-DI (<=0.5) at each visit			X	X	X	X	preceding studies
8.2	Percentage of subjects achieving decrease of baseline HAQ-DI in preceding study of at least 0.22 at each visit			X	X	X	X	preceding studies
9	Percentage of subjects achieving SF-36v2 of difference >= 5 at each visit			X	X	X	X	preceding studies
Continuous Variables								
10.1.1	Raw value and change from baseline of preceding study in DAS28 score at each visit	X	X		X	X	X	preceding studies
10.1.2	Raw value and change from Week 0 in DAS28 score at each visit	X			X	X	X	preceding studies
10.2.1	Raw value and change from baseline of preceding study in DAS28 score at each visit Analysis by Treatment Sequence Set of preceding study	X			X			Treatment Sequence Set
10.2.2	Raw value and change from baseline of preceding study in DAS28 score at each visit Analysis by Treatment Sequence Set of preceding study	X				X		Treatment Sequence Set

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
10.2.3	Raw value and change from baseline of preceding study in DAS28 score at each visit Analysis by Treatment Sequence Set of preceding study	X					X	Treatment Sequence Set
10.3	Raw value and change from baseline of preceding study in DAS28 score at each visit Analysis of Efficacy in Each Dose Level	X			X	X	X	preceding studies
10.4.1	Raw value and change from baseline of preceding study in DAS28 score at each interval Influence of Dose Escalation	X			X			Subjects Who Experienced Dose Up to 100 mg
10.4.2	Raw value and change from baseline of preceding study in DAS28 score at each interval Influence of Dose Escalation	X				X		Subjects Who Experienced Dose Up to 150 mg
10.4.3	Raw value and change from baseline of preceding study in DAS28 score at each interval Influence of Dose Escalation	X					X	Subjects Who Experienced Dose Up to 150 mg
10.5	Raw value and change from baseline of preceding study in DAS28 score at each visit subgroup analysis ● Study Region (Japan, Korea, Taiwan)	X	X			X		preceding studies

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
10.6	Raw value and change from baseline of preceding study in DAS28 score at each visit Mean-standard deviation plot	X	X		X	X	X	preceding studies
10.7.1	Raw value and change from baseline of preceding study in DAS28 score at each visit Mean-standard deviation plot Analysis by Treatment Sequence Set of preceding study	X			X			Treatment Sequence Set
10.7.2	Raw value and change from baseline of preceding study in DAS28 score at each visit Mean-standard deviation plot Analysis by Treatment Sequence Set of preceding study	X				X		Treatment Sequence Set
10.7.3	Raw value and change from baseline of preceding study in DAS28 score at each visit Mean-standard deviation plot Analysis by Treatment Sequence Set of preceding study	X					X	Treatment Sequence Set
11	Raw value and change from baseline of preceding study in SDAI score at each visit	X			X	X	X	preceding studies
12	Raw value and change from baseline of preceding study in CDAI score at each visit			X	X	X	X	preceding studies
13	Raw value and change from baseline of preceding study in HAQ-DI at each visit			X	X	X	X	preceding studies

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
14	Raw value and change from baseline of preceding study in FACIT-Fatigue at each visit			X	X			RAJ1
15	Raw value and change from baseline of preceding study in WPAI at each visit			X		X	X	RAJ3 and RAJ4
16	Raw value and change from baseline of preceding study in SF-36v2 at each visit			X	X	X	X	preceding studies
17	Raw value and change from baseline of preceding study in TJC68 at each visit			X	X	X	X	preceding studies
18	Raw value and change from baseline of preceding study in TJC28 at each visit			X	X	X	X	preceding studies
19	Raw value and change from baseline of preceding study in SJC66 at each visit			X	X	X	X	preceding studies
20	Raw value and change from baseline of preceding study in SJC28 at each visit			X	X	X	X	preceding studies
21	Raw value and change from baseline of preceding study in CRP at each visit	X			X	X	X	preceding studies
22	Raw value and change from baseline of preceding study in ESR at each visit		X		X	X	X	preceding studies
23	Raw value and change from baseline of preceding study in SGAP (100 mm VAS) at each visit			X	X	X	X	preceding studies
24	Raw value and change from baseline of preceding study in SGA (100 mm VAS) at each visit			X	X	X	X	preceding studies

Analysis Type/Analysis Variable		Component for use			Study for Analysis			Analysis Group
		CRP	ESR	None	RAJ1	RAJ3	RAJ4	
25	Raw value and change from baseline of preceding study in PGA (100 mm VAS) at each visit			X	X	X	X	preceding studies

10.2 Appendix 2: Overview of AE analysis

Tables below summarize AE occurrence analysis, SOC/PT analysis, and Patient-year analysis with "X" indicating that the variable will be analyzed. All analyses will be based on the SAF and presented by preceding studies and overall, unless otherwise specified.

The overview of AE occurrence analysis

	Study for Analysis			Analysis Group
	RAJ1	RAJ3	RAJ4	
Number and percentage of subjects with TEAE	X			preceding studies and overall
Number and percentage of subjects with drug related TEAE				
Number and percentage of subjects with death				
Number and percentage of subjects with serious TEAE				
Number and percentage of subjects with drug related serious TEAE				
Number and percentage of subjects with Grade 3 or Higher in Severity TEAE				
Number and percentage of subjects with TEAE leading to permanent discontinuation of study drug				
Number and percentage of subjects with drug related TEAE leading to permanent discontinuation of study drug				
Number and percentage of subjects with serious TEAE leading to permanent discontinuation of study drug				
Number and percentage of subjects with drug related serious TEAE leading to permanent discontinuation of study drug				

The overview of the number of SOC/PT analysis

	Study for Analysis			Analysis Group
	RAJ1	RAJ3	RAJ4	
TEAEs	X	X	X	preceding studies and overall
TEAEs by maximum dose of study drug	X	X	X	preceding studies and overall
Drug related TEAEs by maximum dose of study drug	X	X	X	preceding studies and overall
Drug related TEAEs	X	X	X	preceding studies and overall
Serious TEAEs	X	X	X	preceding studies and overall

	Study for Analysis			Analysis Group
	RAJ1	RAJ3	RAJ4	
Drug related serious TEAEs	X	X	X	preceding studies and overall
TEAEs by severity	X	X	X	preceding studies and overall
Drug related TEAEs by severity	X	X	X	preceding studies and overall
TEAEs leading to permanent discontinuation of study drug	X	X	X	preceding studies and overall
Drug related TEAEs leading to permanent discontinuation of study drug	X	X	X	preceding studies and overall
Serious TEAEs leading to permanent discontinuation of study drug	X	X	X	preceding studies and overall
Drug related serious TEAEs leading to permanent discontinuation of study drug	X	X	X	preceding studies and overall
Grade 3 or higher TEAEs by severity	X	X	X	preceding studies and overall
TEAEs by relationship to study drug	X	X	X	preceding studies and overall
TEAEs leading to death	X	X	X	preceding studies and overall
Most common TEAEs (> 5% in any preceding study)	X	X	X	preceding studies and overall
Most common serious TEAEs (> 5% in any preceding study)	X	X	X	preceding studies and overall
TEAEs excluding serious adverse events that equal to or exceed a threshold of 5% in any preceding study	X	X	X	preceding studies and overall
TEAEs of special interest ● Serious Infections ● Malignancies ● Herpes Zoster Related Disease (Herpes Zoster and Varicella) ● Herpes Zoster ● Varicella ● Infections That Require Intravenous Anti-infectious Therapy	X	X	X	preceding studies and overall
TEAEs by subgroups ● Sex (Male, Female,) ● Age Group at Week 0 (< 65 years, >= 65 years) ● Prior Anti-TNF DMARD Use in preceding study (User, Non-user) ● Prior Biologic DMARD-IR in preceding study (No, Yes) ● Duration of RA (years) in preceding study (< 5 years, >= 5 years) ● Number of Prior DMARDs Used in preceding study (0, 1, 2, >= 3) ● Number of Prior Biologic DMARDs Used in preceding study (0, 1, 2, >= 3) ● MTX Dose (mg/week) at Week 0 (None, 0 <- 8 mg/week, 8 <- 12	X	X	X	preceding studies and overall

	Study for Analysis			Analysis Group
	RAJ1	**RAJ3**	**RAJ4**	
mg/week, > 12 mg/week) ● Concomitant Steroid at Week 0 (No, Yes) ● Prednisone Dose (mg/day) at Week 0 (None, 0 <- 5 mg/day, > 5 mg/day) ● Concomitant non-Biologic DMARD Use at Week 0 (No, Yes) ● Study Region (Japan, Korea, Taiwan) ● Concomitant DMARD category at Week 0 (MTX, DMARD except for MTX only, None)				
TEAEs of special interest by subgroups ● Sex (Male, Female,) ● Age Group at Week 0 (< 65 years, >= 65 years) ● Concomitant Steroid at Week 0 (No, Yes) ● Prednisone Dose (mg/day) at Week 0 (None, 0 <- 5 mg/day, > 5 mg/day)	X	X	X	preceding studies and overall

Patient-year analysis

	Study for Analysis			Analysis Group
	RAJ1	**RAJ3**	**RAJ4**	
TEAEs[1, 3]	X	X	X	preceding studies and overall
TEAEs of special interest[2] ● Serious Infections ● Malignancies ● Herpes Zoster Related Disease (Herpes Zoster and Varicella) ● Herpes Zoster ● Varicella ● Infections That Require Intravenous Anti-infectious Therapy	X	X	X	preceding studies and overall
TEAEs of special interest by subgroups [2] ● Sex (Male, Female,) ● Age Group at Week 0 (< 65 years, >= 65 years) ● Concomitant Steroid at Week 0 (No, Yes) ● Prednisone Dose (mg/day) at Week 0 (None, 0 <- 5 mg/day, > 5 mg/day)	X	X	X	preceding studies and overall
[1] According to Definition 2 [2] According to Definition 1 [3] Patient-years analysis will be displayed by time intervals and by overall period.				

10.3 Appendix 3: Overview of Clinical Laboratory Evaluation, Vital Signs, and Electrocardiograms (ECGs) analyses

Table below summarizes the analyses of Clinical Laboratory Evaluation, Vital Signs, and Electrocardiograms (ECGs), with "X" indicating that the variable will be analyzed. All analyses will be based on the SAF and presented by preceding studies and overall, unless otherwise specified.

The overview of Clinical Laboratory Evaluation, Vital Signs, and Electrocardiograms (ECGs) analyses

	Study for Analysis			Analysis Group
	RAJ1	RAJ3	RAJ4	
Clinical Laboratory Evaluation				
Quantitative Laboratory Test Results in SI Units, Hematology; Actual and Change from Week 0	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Hematology; Actual and Change from Week 0 By study region	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Biochemistry; Actual and Change from Week 0	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Biochemistry; Actual and Change from Week 0 By study region	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Urinalysis; Actual and Change from Week 0	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Urinalysis; Actual and Change from Week 0 By study region	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Fasting Lipids Profile; Actual and Change from Week 0	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Fasting Lipids Profile; Actual and Change from Week 0 By study region	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, T-Chol/HDL, LDL/HDL Ratio; Actual and Change from Week 0	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, T-Chol/HDL, LDL/HDL Ratio; Actual and Change from Week 0 By study region	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Erythrocyte Sedimentation Rate (ESR) ; Actual and Change from Week 0	X	X	X	preceding studies and overall
Quantitative Laboratory Test Results in SI Units, Erythrocyte; Actual and Change from Week 0 By study region	X	X	X	preceding studies and overall
Qualitative Laboratory Test Results, Urinalysis; By study region (Japan)	X	X	X	preceding studies and overall
Qualitative Laboratory Test Results, Urinalysis For subjects shifted from RAJ3, by study region (Korean/Taiwan)		X		RAJ3
Shift-from-Week 0 Table for Laboratory Test Results, Hematology; Week 0 to Lowest Value up to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for Laboratory Test Results, Hematology; Week 0 to Highest Value up to ET	X	X	X	preceding studies and overall

	Study for Analysis			Analysis Group
	RAJ1	RAJ3	RAJ4	
Shift-from-Week 0 Table for Laboratory Test Results, Biochemistry; Week 0 to Lowest Value up to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for Laboratory Test Results, Biochemistry; Week 0 to Highest Value up to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for Laboratory Test Results, Urinalysis; Week 0 to Lowest Value up to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for Laboratory Test Results, Urinalysis; Week 0 to Highest Value up to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for Laboratory Test Results, Fasting Lipids Profile; Week 0 to Lowest Value up to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for Laboratory Test Results, Fasting Lipids Profile; Week 0 to Highest Value up to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for Selected Laboratory Variables using NCI-CTCAE Toxicity Grade (version 4.0) ; Week 0 to ET	X	X	X	preceding studies and overall
Shift-from-Week 0 Table in Pre-Specified Reference Range Laboratory test Results by Visit, Selected Laboratory Variables ● Aspartate Aminotransferase (AST) ● Alanine Aminotransferase (ALT) ● Alkaline Phosphatase (ALP) ● Total Bilirubin Category 1 ● Total Bilirubin Category 2 ● Low-Density Lipoprotein (LDL) Category 1 ● Low-Density Lipoprotein (LDL) Category 2 ● Hemoglobin (HGB) Category 1 ● Hemoglobin (HGB) Category 2 ● Hemoglobin (HGB) Category 3 ● Creatine Phosphokinase (CPK) Category 1 ● Creatine Phosphokinase (CPK) Category 2 ● Creatine Phosphokinase (CPK) Category 3 ● Creatinine ● Absolute Neutrophil Count (ANC) ● Lymphocytes Category 1 ● Lymphocytes Category 2 ● Platelets Category 1 ● Platelets Category 2	X	X	X	preceding studies and overall
Liver Function Analysis for Overall Period ● Clinically Significant Values in Liver Function Tests ● Summary of Moderate and Marked Liver Abnormalities by Visit	X	X	X	preceding studies and overall
Liver Functions Plots	X	X	X	preceding studies and overall
Vital Signs				
Vital Signs; Actual and Change from Week 0	X	X	X	preceding studies and overall
ECG Results				
Interpretation of 12- Lead ECG Results, Assessment by Investigator	X	X	X	preceding studies and overall
Shift-from-Week 0 Table for 12-Lead ECG	X	X	X	preceding studies and overall

10.4 Appendix 4: Computation of HAQ-DI Score

The HAQ-DI is composed of 20 items in 8 categories (Dressing and Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, and Activities). Each category has at least two questions. Within each category, subjects report the amount of difficulty they have in performing the specific question items.

Classification of HAQ Question and Checkbox for computation of HAQ-DI Score

Category	Question	Checkbox
1. Dressing and Grooming	1) Dress yourself, including shoelaces and buttons 2) Shampoo your hair	● 1 "aids or devices" check box: o Devices used for dressing (button hook, zipper pull, etc.) ● 1 "help from another person" checkbox: o Dressing and grooming
2. Arising	1) Stand up from a straight chair 2) Get in and out of bed	● 1 "aids or devices" checkbox: o Special or built up chair ● 1 "help from another person" checkbox: o Arising
3. Eating	1) Cut your own meat 2) Lift a full cup or glass to your mouth 3) Open a new milk carton	● 1 "aids or devices" checkbox: o Built up or special utensils ● 1 "help from another person" checkbox: o Eating
4. Walking	1) Walk outdoors on flat ground 2) Climb up five steps	● 4 "aids or devices" checkboxes: o Cane o Walker o Crutches o Wheelchair ● 1 "help from another person" checkbox: o Walking
5. Hygiene	1) Wash and dry your body 2) Take a tub bath 3) Get on and off the toilet	● 4 "aids or devices" checkboxes: o Raised toilet seat o Bathtub seat o Bathtub bar o Long-handled appliances in bathroom ● 1 "help from another person" checkbox: o Hygiene

Category	Question	Checkbox
6. Reach	1) Reach and get down a 5 pound object (such as a bag of sugar) from above your head 2) Bend down to pick up clothing from the floor	● 1 "aids or devices" checkbox: ○ Long-handled appliances for reach ● 1 "help from another person" checkbox: ○ Reach
7. Grip	1) Open car doors 2) Open previously opened jars 3) Turn faucets on and off	● 1 "aids or devices" checkbox: ○ Jar opener (for jars previously opened) ● 1 "help from another person" checkbox: ○ Gripping and opening things
8. Activities	1) Run errands and shop 2) Get in and out of a car 3) Do chores such as vacuuming or yard work	● 1 "help from another person" checkbox: ○ Errands and chores

For each question, there are four response options ranging from "Without Any Difficulty" to "Unable to Do", scored 0 - 3. Details are as follows.

Response	Score
Without Any Difficulty	0
With Some Difficulty	1
With Much Difficulty	2
Unable to Do	3

The patient must have a score for >= 6 of the 8 categories. If there are less than 6 categories completed, a HAQ-DI cannot be computed, whether the missing categories are due to missing values or they do not apply to the respondent. Individual questions within a category are not imputed. Therefore the maximum score in each category is based on non-missing questions, and a category score is missing when all questions within a category are missing.

There are three steps to compute the HAQ-DI score.

1. For each category, compute the category score by using the highest question score.

- For example, in the category "Eating" there are 3 questions, a subject responds with a 1, 2, and 0, respectively.

Category	Question	Subject Reported Response
Eating	1) Cut your own meat	1
	2) Lift a full cup or glass to your mouth	2
	3) Open a new milk carton	0

- The highest score is 2, so the category score is 2 for this subject.

2. Adjust for use of "aids or devices" and/or "help from another person" when indicated in the checkbox(es)
   - If the category score is < 2 but at least one "aids or devices" or "help from another person" box is checked, the category score is set equal to 2.
   - If the category score is < 2 and none of the "aids or devices" or "help from another person" boxes is checked, the category score remains.
   - If the category score is 2, it remains 2, and if a three, it remains a three.
3. Divide the summed category scores by the number of categories answered (must be a minimum of 6) to obtain a HAQ-DI score of 0 – 3, with higher scores indicating greater disability (3 = worst functioning).

10.5 Appendix 5: Computation of SF-36v2® Score

The SF-36v2® will be scored for the 8 scales according to the standard SF-36v2® scoring algorithm (0-100 scale) explained in the SF-36v2® Japanese Manual (Fukuhara et al., 2011). The physical component score (PCS), mental component score (MCS) and role/social component score (RCS) will be scored according to the standard SF-36v2® scoring algorithm (0-100 scale) explained in the same Manual. A higher score indicates a better health state. Prior to the analysis, the responses will be scored according to the following four steps.

1. Item recoding for the 10 items which require recoding
2. Computing raw scale scores by summing across items within the same scale (raw scale scores)
3. Transforming the raw scale scores into a 0-100 scale (transformed scale scores)
4. Normalizing the transformed scale scores with a mean of 50 and a standard deviation of 10 in the general Japanese population (norm-based scale scores)

Questions, coding and scoring of the 8 scales (Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, Metal Health), PCS and MCS are presented below.

Physical Functioning: Verbatim Items and Scoring Information

Question Number	Verbatim Items
3.	The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?
3a.	*Vigorous activities*, such as running, lifting heavy objects, participating in strenuous sports
3b.	*Moderate activities*, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
3c.	Lifting or carrying groceries
3d.	Climbing *several* flights of stairs
3e.	Climbing *one* flight of stairs
3f.	Bending, kneeling, or stooping
3g.	Walking *more than a mile*
3h.	Walking *several hundred yards*
3i.	Walking *one hundred yards*
3j.	Bathing or dressing yourself

Precoded and Final Values for Items 3a through 3j		
Response Choices	**Precoded Item Value**	**Final Item Value**
Yes, limited a lot	1	1
Yes, limited a little	2	2
No, not limited at all	3	3

Role-Physical: Verbatim Items and Scoring Information

Question Number	Verbatim Items
4.	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
4a.	Cut down the *amount of time* you spent on work or other activities
4b.	*Accomplished less* than you would like
4c.	Were limited in the *kind* of work or other activities
4d.	Had *difficulty* performing the work or other activities (for example, it took extra effort)

Precoded and Final Values for Items 4a through 4d		
Response Choices	**Precoded Item Value**	**Final Item Value**
All of the time	1	1
Most of the time	2	2
Some of the time	3	3
A little of the time	4	4
None of the time	5	5

Bodily Pain: Verbatim Items and Scoring Information

Question Number	Verbatim Items
7.	How much bodily pain have you had during the past 4 weeks?
8.	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

Precoded and Final Values for Item 7		
Response Choices	**Precoded Item Value**	**Final Item Value**
None	1	6.0
Very mild	2	5.4
Mild	3	4.2
Moderate	4	3.1
Severe	5	2.2
Very Severe	6	1.0

Scoring for Item 8 if both Items 7 and 8 are Answered			
Response Choices	**If Item 8 Precoded Item Value**	**And Item 7 Precoded Item Value**	**Then Final Item Value**
Not at all	1	1	6
	1	2 through 6	5
A little bit	2	1 through 6	4
Moderately	3	1 through 6	3
Quite a bit	4	1 through 6	2
Extremely	5	1 through 6	1

Scoring for Item 8 if Item 7 is Not Answered		
Response Choices	**Precoded Item Value**	**Then Final Item Value**
Not at all	1	6.0
A little bit	2	4.75
Moderately	3	3.5
Quite a bit	4	2.25
Extremely	5	1.0

General Health: Verbatim Items and Scoring Information

Question Number	Verbatim Items
1.	In general, would you say your health is :
11.	How TRUE or FALSE is each of the following statements for you?
11a.	I seem to get sick a little easier than other people
11b.	I am as healthy as anybody I know
11c.	I expect my health to get worse
11d.	My health is excellent

Precoded and Final Values for Items 1 and 11a through 11d			
Item 1	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	Excellent	1	5.0
	Very good	2	4.4
	Good	3	3.4
	Fair	4	2.0
	Poor	5	1.0
Items 11a and 11c	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	Definitely True	1	1
	Mostly True	2	2
	Don't Know	3	3
	Mostly False	4	4
	Definitely False	5	5
Items 11b and 11d	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	Definitely True	1	5
	Mostly True	2	4
	Don't Know	3	3
	Mostly False	4	2
	Definitely False	5	1

Vitality: Verbatim Items and Scoring Information

Question Number	Verbatim Items
9.	These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks …
9a.	Did you feel full of life?
9e.	Did you have a lot of energy?
9g.	Did you feel worn out?
9i.	Did you feel tired?

Precoded and Final Values for Items 9a, 9e, 9g and 9i			
Item 9a and 9e	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	All of the time	1	5
	Most of the time	2	4
	Some of the time	3	3
	A little of the time	4	2
	None of the time	5	1
Items 9g and 9i	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	All of the time	1	1
	Most of the time	2	2
	Some of the time	3	3
	A little of the time	4	4
	None of the time	5	5

Social Functioning: Verbatim Items and Scoring Information

Question Number	Verbatim Items
6.	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
10.	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

Precoded and Final Values for Items 6 and 10			
Item 6	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	Not at all	1	5
	Slightly	2	4
	Moderately	3	3
	Quite a bit	4	2
	Extremely	5	1
Item 10	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	All of the time	1	1
	Most of the time	2	2
	Some of the time	3	3
	A little of the time	4	4
	None of the time	5	5

Role-Emotional: Verbatim Items and Scoring Information

Question Number	Verbatim Items
5.	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
5a.	Cut down on the *amount of time* you spent on work or other activities
5b.	*Accomplished less* than you would like
5c.	Did work or other activities *less carefully than usual*

Precoded and Final Values for Items 5a through 5c			
Item 5a through 5c	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	All of the time	1	1
	Most of the time	2	2
	Some of the time	3	3
	A little of the time	4	4
	None of the time	5	5

Mental Health: Verbatim Items and Scoring Information

Question Number	Verbatim Items
9.	These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks …
9b.	Have you been very nervous?
9c.	Have you felt so down in the dumps that nothing could cheer you up?
9d.	Have you felt calm and peaceful?
9f.	Have you felt downhearted and depressed?
9h.	Have you been happy?

Precoded and Final Values for Items 9b, 9c, 9d, 9f and 9h			
Items 9b, 9c and 9f	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	All of the time	1	1
	Most of the time	2	2
	Some of the time	3	3
	A little of the time	4	4
	None of the time	5	5
Item 9d and 9h	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	All of the time	1	5
	Most of the time	2	4
	Some of the time	3	3
	A little of the time	4	2
	None of the time	5	1

Reported Health Transition: Verbatim Items and Scoring Information

Question Number	Verbatim Items
2.	Compared to one year ago, how would you rate your health in general now?

Precoded and Final Values for Item 2			
Item 2	**Response Choices**	**Precoded Item Value**	**Final Item Value**
	Much better now than one year ago	1	1
	Somewhat better now than one year ago	2	2
	About the same as one year ago	3	3
	Somewhat worse now than one year ago	4	4
	Much worse now than one year ago	5	5

Use Table below to compute simple algebraic sums of the presented final item scores.

Formulas for Scoring and Transforming Scales

SF-36v2 Scale	Sum Final Item Values (after recoding items as in Tables above)	Lowest and Highest Possible Raw Scores	Possible Raw Score Range
Physical Functioning	3a + 3b + 3c + 3d + 3e + 3f + 3g + 3h + 3i + 3j	10, 30	20
Role-Physical	4a + 4b + 4c + 4d	4, 20	16
Bodily Pain	7 + 8	2, 12	10
General Health	1 + 11a + 11b + 11c + 11d	5, 25	20
Vitality	9a + 9e + 9g + 9i	4, 20	16
Social Functioning	6 + 10	2, 10	8
Role-Emotional	5a + 5b + 5c	3, 15	12
Mental Health	9b + 9c + 9d + 9f + 9h	5, 25	20

Formula for transformation of raw scale scores to 0-100 scale scores

$$\text{Transformed Scale} = \frac{\text{(Actual raw score – lowest possible raw score)}}{\text{(Possible raw score range)}} \times 100$$

After calculating the transformed scale score, the next step is to compute a z-score transformation. A z-score for each scale is computed by subtracting the 2007 General Japanese Population Means for each SF-36v2® scale and dividing the difference by the corresponding scale standard deviation (Table 20) from the 2007 General Japanese Population Means and Standard Deviations Used to Derive SF-36v2® Z-score. Formulas are listed below.

2007 General Japanese Population Means and Standard Deviations Used to Derive SF-36v2® Z-score

SF-36v2 Scale	Mean	Standard Deviation
Physical Functioning (PF)	89.13446	13.85045
Role-Physical (RP)	89.24007	18.80773
Bodily Pain (BP)	73.77098	22.39818
General Health (GH)	62.91007	18.76562
Vitality (VT)	62.82787	19.46255
Social Functioning (SF)	86.38347	19.40441
Role-Emotional (RE)	87.84637	20.01521
Mental Health (MH)	71.60598	18.62983

Step 1. Formulas for Z-score Standardization of SF-36v2® Scales

PF_Z	=	(PF – 89.13446) / 13.85045
RP_Z	=	(RP – 89.24007) / 18.80773
BP_Z	=	(BP – 73.77098) / 22.39818
GH_Z	=	(GH – 62.91007) / 18.76562
VT_Z	=	(VT – 62.82787) / 19.46255
SF_Z	=	(SF – 86.38347) / 19.40441
RE_Z	=	(RE – 87.84637) / 20.01521
MH_Z	=	(MH – 71.60598) / 18.62983

Means and standard deviations are from previous Table.

Step 2. Norm-based Transformation of SF-36v2® Z-scores

The next step involves transforming each SF-36v2® z-score to the norm-based (50, 10) scoring. This is accomplished by multiplying each z-score from Step 1 by 10 and adding the resulting product to 50. Formulas are listed below.

Norm-Based Physical Functioning (PF)	=	50 + (PF_Z × 10)
Norm-Based Role-Physical (RP)	=	50 + (RP_Z × 10)
Norm-Based Bodily Pain (BP)	=	50 + (BP_Z × 10)
Norm-Based General Health (GH)	=	50 + (GH_Z × 10)
Norm-Based Vitality (VT)	=	50 + (VT_Z × 10)
Norm-Based Social Functioning (SF)	=	50 + (SF_Z × 10)
Norm-Based Role-Emotional (RE)	=	50 + (RE_Z × 10)
Norm-Based Mental Health (MH)	=	50 + (MH_Z × 10)

PCS, MCS and RCS are scored in three steps as explained below:

Step 1. Z-score Standardization of SF-36v2® Scales

The first consists of standardizing each of the 8 SF-36v2® scales using a z-score transformation. This is the same as Step 1 used in the norm-based scoring of the 8 SF-36 scales.

Step 2. Aggregating Scales in Estimating Aggregate Physical, Mental, and Role/social Component Scores

After a z-score has been computed for scale, the second step involves computation of aggregate scores for the physical,mental and role/social components using the physical and mental factor score coefficients from 2002 survey as given in next Table.

2002 Factor Score Coefficients Used to Derive PCS,MCS, and RCS Scale Scores

SF-36v2 Scale	PCS	MCS	RCS
Physical Functioning (PF)	0.67908	-0.20472	-0.13048
Role Physical (RP)	0.22298	-0.27243	0.40393
Bodily Pain (BP)	0.37244	0.14644	-0.21786
General Health (GH)	0.36992	0.33933	-0.41710
Vitality (VT)	-0.08420	0.46413	-0.13120
Social Functioning (SF)	-0.30769	0.06727	0.49261
Role Emotional (RE)	-0.14256	-0.15597	0.61022
Mental Health (MH)	-0.33155	0.44572	0.10326

Computation of an aggregate physical component score consists of multiplying each SF-36v2® scale z-score by its respective physical factor score coefficient and summing the eight products, as shown below. Similarly, an aggregate mental, and role/social component score is obtained by multiplying each SF-36v2® scale z-score by its respective mental factor score coefficient and summing the eight products.

Formulas for Aggregating Scales in Estimating Aggregate Physical, Mental, and Role/social Component Scores (Standard Form)

AGG_PHYS = (PF_Z × 0.67908) + (RP_Z × 0.22298) + (BP_Z × 0.37244) + (GH_Z × 0.36992) + (VT_Z × -0.08420) + (SF_Z ×-0.30769) + (RE_Z × -0.14256) + (MH_Z × -0.33155)

AGG_MENT = (PF_Z × -0.20472) + (RP_Z × -0.27243) + (BP_Z × 0.14644) + (GH_Z × 0.33933) + (VT_Z × 0.46413) + (SF_Z ×0.06727) + (RE_Z × -0.15597) + (MH_Z × 0.44572)

AGG_ROLE = (PF_Z × -0.13048) + (RP_Z × 0.40393) + (BP_Z × -0.21786) + (GH_Z × -0.41710) + (VT_Z × -0.13120) + (SF_Z × 0.49261) + (RE_Z × 0.61022) + (MH_Z ×0.10326)

Step 3. Formulas for T-score Transformation of Component Scores (Standard Form)

The third step involves transforming each component score to the norm-based (50, 10) scoring. This is accomplished by multiplying each aggregate component scale score by 10 and adding the resulting product to 50.

Transformed Physical (PCS) = 50 + (AGG_PHYS × 10)
Transformed Mental (MCS) = 50 + (AGG_MENT × 10)
Transformed Role/Social (RCS) = 50 + (AGG_ROLE × 10)

Missing Data in an Individual Questionnaire

In the event that data is missing for an individual item from the scales of the SF-36v2® Health Status Survey, the average value of the completed items in the corresponding scale will be used as an estimate of the missing item. If more than 50 percent of the items from a scale are

missing for an individual questionnaire, the corresponding deficient scale(s) will be excluded from analyses.

Items in each scale are given below:

SF-36v2 Scale	No. Items	Items	Minimum No. Non-Missing Items for Imputation of Missing Values
PF	10	3a, 3b, 3c, 3d, 3e, 3f, 3g, 3h, 3i, 3j	5
RP	4	4a, 4b, 4c, 4d	2
BP	2	7, 8	1
GH	5	1, 11a, 11b, 11c, 11d	3
VT	4	9a, 9e, 9g, 9i	2
SF	2	6, 10	1
RE	3	5a, 5b, 5c	2
MH	5	9b, 9c, 9d, 9f, 9h	3

Example Showing the Mechanics of Imputation Technique:

Suppose for a subject the items 1, 3b, 3e, 3f, 4a, 4b, 11b, 11d, 5a and 5b are missing. First group the missing items according to the scale:

- GH: Items 1, 11b, 11d
- PF: Items 3b, 3e, 3f
- RP: Items 4a and 4b
- RE: Items 5a and 5b

GH consists of 5 items and 3 are missing. That is only 2 have non-missing scores. Since at least half of the items are not non-missing, missing items 1, 11a and 11d cannot be imputed. Therefore for this subject, the General Health scale score will be missing.

PF consists of 10 items. So, for this subject 7 of the items are non-missing. That is, at least half of the items are non-missing. Therefore replace the missing Items 3b, 3e and 3f scores by the average score of the non-missing items, i.e., replace by (3a + 3c + 3d + 3g + 3h + 3i + 3j) / 7.

RP consists of 4 items and two are missing. So at least half are non-missing. Therefore replace the missing item scores 4a and 4b by (4c+4d) / 2.

RE consists of 3 and two are missing. That is, more than half of the item scores are missing. Therefore, missing scores 5a and 5b cannot be imputed for this subject and thus RE scale score for this subject will be missing.

10.6 Appendix 6: Computation of FACIT-Fatigue Scale Score

Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale shown below, uses 13-item symptom-specific questionnaire to assess the burden of self-reported fatigue caused by a chronic disease and its impact upon daily activities and function. It's a reliable and valid instrument for measuring fatigue in subjects that has garnered interest in rheumatologic drug trials or its capacity to demonstrate decreases in fatigue associated with pharmacotherapy.

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI 12	I feel weak all over	0	1	2	3	4
An 1	I feel listless ("washed out")	0	1	2	3	4
An 2	I feel tired	0	1	2	3	4
An 3	I have trouble starting things because I am tired	0	1	2	3	4
An 4	I have trouble finishing things because I am tired	0	1	2	3	4
An 5	I have energy	0	1	2	3	4
An 7	I am able to do my usual activities	0	1	2	3	4
An 8	I need to sleep during the day	0	1	2	3	4
An 12	I am too tired to eat	0	1	2	3	4
An 14	I need help doing my usual activities	0	1	2	3	4
An 15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An 16	I have to limit my social activity because I am tired	0	1	2	3	4

As each of the 13 items of the FACIT-Fatigue scale ranges from 0 – 4, the range of possible scores is 0 – 52, with 0 being the worst possible score and 52 the best.

To obtain the 0 – 52 score, each negatively worded item response is recoded so that 0 is a bad response and 4 is good response. Therefore, specifically, prior to calculation of the FACIT-Fatigue scale score, all questions with the exception of "I have energy" and "I am able to perform usual activities" will have their responses recoded specified as follows so that:

Response	Recoded Score
Not at all	4
A little bit	3
Somewhat	2
Quite a bit	1
Very much	0

For the questions "I have energy" and "I am able to do my usual activities", the following 5-point Likert-type scale as follows will be used:

Response	Score
Not at all	0
A little bit	1
Somewhat	2
Quite a bit	3
Very much	4

All responses are added with equal weight to obtain the total score. Lower values of the FACIT-Fatigue score denote higher fatigue.

10.7 Appendix 7: Computation of WPAI Scale Score

Work Productivity and Activity Impairment Questionnaire: WPAI

In this study, the following scoring methods are applied. These scoring methods are based on the specific health problem version of WPAI (WPAI:SHP).

Question Number	Contents
1.	1. Are you currently employed (working for pay)?
2.	2. During the past seven days, how many hours did you miss from work because of problems associated with your rheumatoid arthritis?
3.	3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?
4.	4. During the past seven days, how many hours did you actually work?
5.	5. During the past seven days, how much did your rheumatoid arthritis affect your productivity while you were working?
6.	6. During the past seven days, how much did your rheumatoid arthritis affect your ability to do your regular daily activities, other than work at a job?

Scores:

Multiply scores by 100 to express in percentages.

- Percent work time missed due to problem: Q2/(Q2+Q4)
- Percent impairment while working due to problem: Q5/10
- Percent overall work impairment due to problem: Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4))x(Q5/10)]
- Percent activity impairment due to problem: Q6/10

10.8 Appendix 8: AE of Special Interest

1. Serious Infections
   AE which belongs to SOC of Infections and infestations (10021881) and regarded as serious.
2. Malignancies
   Following PT terms are included.
   Diffuse large B-cell lymphoma (10012818), Bladder cancer (10005003), Breast cancer (10006187), Carcinoma in situ (10061450), Colon cancer (10009944), Gastric cancer (10017758), Renal cancer (10038389), Squamous cell carcinoma (10041823), Small cell lung cancer stage unspecified (10041071), Extraskeletal chondrosarcoma (10015838), Lymphoma (10025310), Thyroid cancer (10066474).
3. Herpes Zoster Related Disease (Herpes Zoster and Varicella)
   Following PT terms are included.
   Herpes zoster (10019974), Herpes zoster iridocyclitis (10019980), Herpes zoster ophthalmic (10019983), Herpes zoster multi-dermatomal (10058428), Herpes zoster infection neurological (10061208), Herpes zoster oticus (10063491), Herpes zoster disseminated (10065038), Encephalitis post varicella (10014603), Varicella (10046980), Varicella post vaccine (10063522).
4. Herpes Zoster
   Following PT terms are included.
   Herpes zoster (10019974), Herpes zoster iridocyclitis (10019980), Herpes zoster ophthalmic (10019983), Herpes zoster multi-dermatomal (10058428), Herpes zoster infection neurological (10061208), Herpes zoster oticus (10063491), Herpes zoster disseminated (10065038)
5. Varicella
   Following PT terms are included.
   Encephalitis post varicella (10014603), Varicella (10046980), Varicella post vaccine (10063522).
6. Infections That Require Intravenous Anti-infectious Therapy
   All PTs which belong to SOC of Infections and Infestations (10021881) for which there is an intravenous concomitant medication (antibiotics, antivirals, antifungals, etc.) associated with that event for that patient.

10.9 Appendix 9: Standard Toxicity Grading for Laboratory Tests According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0

Standard Toxicity Grading for Laboratory Tests According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0

Test Name	Test Code	Units [1]	Direction of Change / AE Term	CTCAE Grade [2]					NCI Ref.		
				0	1	2	3	4	Version	Page	Units
Alanine Aminotransferase(ALT/SGPT)	ALT	n/a	Increase/ Alanine aminotransferase increased	WNL	>ULN - <= 3.0×ULN	>3.0×ULN - <= 5.0×ULN	>5.0×ULN - <= 20.0×ULN	>20.0 ×ULN	4.0	107	n/a
Albumin	ALB	g/dL	Decrease/ Hypoalbuminemia	WNL	>=3 - <LLN	>=2 - <3	<2		4.0	116	g/dL
Alkaline Phosphatase	ALKP	n/a	Increase/ Alkaline phosphatase increased	WNL	>ULN - <= 2.5×ULN	>2.5×ULN - <= 5.0×ULN	>5.0×ULN - <= 20.0×ULN	>20.0 ×ULN	4.0	107	n/a
Amylase	AMY	n/a	Increase/ Serum amylase increased	WNL	>ULN - <= 1.5×ULN	>1.5×ULN - <= 2.0×ULN	>2.0×ULN - <= 5.0×ULN	>5.0× ULN	4.0	112	n/a
Aspartate Aminotransferase(AST/SGOT)	AST	n/a	Increase/ Aspartate aminotransferase increased	WNL	>ULN - <=3.0×ULN	>3.0×ULN - <=5.0× ULN	>5.0×ULN - <=20.0 ×ULN	>20.0 ×ULN	4.0	107	n/a
Calcium Corrected [3]	CACOR	mg/dL	Increase/ Hypercalcemia	WNL	>ULN - <= 11.5	>11.5 - <=12.5	>12.5 - <= 13.5	>13.5	4.0	115	mg/dL
Calcium Corrected [3]	CACOR	mg/dL	Decrease/ Hypocalcemia	WNL	>=8.0 - <LLN	>=7.0 - <8.0	>=6.0 - <7.0	<6.0	4.0	116	mg/dL
Total Cholesterol	TCHOL	mg/dL	Increase/ Cholesterol high	WNL	>ULN - <=300	>300 - <= 400	>400- <=500	>500	4.0	109	mg/dL
Creatine Phosphokinase	CPK	n/a	Increase/ CPK increased	WNL	>ULN - <= 2.5×ULN	>2.5×ULN - <= 5×ULN	>5×ULN - <= 10×ULN	>10× ULN	4.0	109	n/a
Creatinine	CREAT	n/a	Increase/ Creatinine increased	WNL	>ULN - <= 1.5×ULN or >ULN- <=1.5× Week 0 value	>1.5×ULN - <= 3.0×ULN or >1.5×ULN - <=3.0× Week 0 value	>3.0×ULN - <=6.0× ULN or >3.0× Week 0 value	>6.0× ULN	4.0	109	n/a

Test Name	Test Code	Units [1]	Direction of Change / AE Term	CTCAE Grade [2]					NCI Ref.		
				0	1	2	3	4	Version	Page	Units
Estimated glomerular filtration rate	GFR	mL/min per 1.73 m^2	Decrease/ Chronic kidney disease	*Not applicable* [8]	*Not applicable* [8]	30 - 59	15 - 29	<15	4.0	147	mL/min per 1.73 m^2
Gamma Glutamyl Transferase (GGT)	GGT	n/a	Increase/ GGT increased	WNL	>ULN - <=2.5×ULN	>2.5×ULN - <=5.0× ULN	>5.0×ULN - <=20.0 ×ULN	>20.0 ×ULN	4.0	110	n/a
Glucose	GLUC	mg/dL	Decrease/ Hypoglycemia	WNL	>=55 - <LLN	>=40 - <55	>=30- <40	<30	4.0	117	mg/dL
Hemoglobin	HGB	g/dL	Increase/ Hemoglobin increased	WNL	Increase in >0 - 2 g/dL above ULN or above Week 0 value if Week 0 value is above ULN	Increase in >2 - 4 g/dL above ULN or above Week 0 value if Week 0 value is above ULN	Increase in >4 g/dL above ULN or above Week 0 value if Week 0 value is above ULN		4.0	111	g/dL
Hemoglobin	HGB	g/dL	Decrease/ Anemia	WNL	>=10 - <LLN	>=8 - <10.0	<8		4.0	3	g/dL
Leukocytes (WBC)	WBC	$10^3/\mu L$	Decrease/ White blood cell decreased	WNL	>=3.0 - <LLN	>=2.0 - <3.0	>=1.0 - <2.0	<1.0	4.0	113	$10^3/\mu L$
Lymphocytes, Absolute Units	LYMPHAB	$10^3/\mu L$	Decrease/ Lymphocyte count decreased	*Not applicable* [8]	*Not applicable* [8]	>=0.5 - <0.8	>=0.2 - <0.5	<0.2	4.0	111	$10^3/\mu L$
Lymphocytes, Absolute Units	LYMPHAB	$10^3/\mu L$	Increase/ Lymphocyte count increased	*Not applicable* [8]		>4 - 20	>20		4.0	111	$10^3/\mu L$
Magnesium	MG	mg/dL	Increase/ Hypermagnese-mia	WNL	>ULN - <=3.0		>3.0 - <=8.0	>8.0	4.0	115	mg/dL
Magnesium	MG	mg/dL	Decrease/ Hypomagnesemia	WNL	>=1.2 - <LLN	>=0.9 - <1.2	>=0.7 - <0.9	<0.7	4.0	117	mg/dL
Absolute Neutrophil Count	ANC	$10^3/\mu L$	Decrease/ Neutrophil count decreased	*Not applicable* [8]	*Not applicable* [8]	>=1.0 - <1.5	>=0.5 - <1.0	<0.5	4.0	112	$10^3/\mu L$
Phosphate (Phosphorus)	PHOS	mg/dL	Decrease/ Hypophosphatemia	WNL	*Not applicable* [8]	>=2.0 - <2.5	>=1.0 - <2.0	<1.0	4.0	117	mg/dL

Test Name	Test Code	Units [1]	Direction of Change / AE Term	CTCAE Grade [2]					NCI Ref.		
				0	1	2	3	4	Version	Page	Units
Platelets	PLT	$10^3/\mu L$	Decrease/ Platelet count decreased	WNL	>=75.0 - <LLN	>=50.0 - <75.0	>=25.0 - <50.0	<25.0	4.0	112	$10^3/\mu L$
Potassium	K	mEQ/L	Increase/ Hyperkalemia	WNL	>ULN - <=5.5	>5.5 - <=6.0	>6.0 - <=7.0	>7.0	4.0	115	mEQ/L [7]
Potassium [4]	K	mEQ/L	Decrease/ Hypokalemia	WNL		>=3.0 - <LLN	>=2.5 - <3.0	<2.5	4.0	117	mEQ/L [7]
Urine Protein[5]	UPROT		Increase/ Proteinuria	WNL	+	++	+++ or ++++		4.0	149	n/a
Sodium	NA	mEQ/L	Increase/ Hypernatremia	WNL	>ULN - <=150	>150 - <=155	>155 - <=160	>160	4.0	116	mEQ/L [7]
Sodium	NA	mEQ/L	Decrease/ Hyponatremia	WNL	>=130 - <LLN		>=120 - <130	<120	4.0	117	mEQ/L [7]
Total Bilirubin	TBILI	n/a	Increase/ Blood bilirubin increased	WNL	>ULN - <=1.5×ULN	>1.5×ULN - <=3.0× ULN	>3.0×ULN - <=10.0 ×ULN	>10.0 ×ULN	4.0	107	n/a
Triglycerides	TRIG	mg/dL	Increase/ Hypertriglyceridemia	WNL	> ULN [9] - <=300	>300 - <=500	>500 - <=1000	>1000	4.0	116	mg/dL
Uric Acid [6]	UACID	mg/dL	Increase/ Hyperuricemia	WNL			>ULN - 10	>10	4.0	116	mg/dL

[1] "n/a" is specified if the criteria are based strictly on a comparison of the value to its reference range.

[2] WNL = Within Normal Limits; LLN = Lower Limit of Normal; ULN = Upper Limit of Normal.

[3] **Calcium Corrected** will be derived using the following formula: Calcium Corrected = 0.8 × (4.0 – Albumin) + Calcium, where 4.0 represents the average albumin level in g/dL, Albumin is measured in unit of g/dL, and Calcium is measured in unit of mg/dL.

[4] Hypokalemia Grade 2 is the same as Grade1 but has additional clinical criteria that cannot be assessed. Therefore, it was decided to grade all criteria falling within >=3.0 - <LLN as grade 2.

[5] For Urine Protein, the maximum category is "++++", while NCI CTCAE version4.0 doesn't define "+++", "++++". So, these are defined as grade 3 per internal discussion.

[6] Hyperuricemia Grade 3 is the same as Grade1 but has additional clinical criteria that cannot be assessed. Therefore, it was decided to grade all criteria falling within >ULN – 10 mg/dL as grade 3.

[7] For hyperkalemia, hypokalemia, hypernatremia and hyponatremia, the unit in the NCI reference is mmol/L, which has been converted to mEQ/L by multiplying 1.

[8] For ANC, LYMPHAB, GFR, there are no reference range in central laboratory, so, NCI CTCAE grading scale is only defined for not-related reference range category. For PHOS, LLN=2.5mg/dL, while NCI Grade 1 is defined ">=2.5 - <LLN", so Grade 1 can't be defined.

[9] For TRIG, the upper limit of normal range is 149 mg/dL. Therefore, WNL for Grade 0 is up to 149 mg/dL. But the lower limit of Grade 1 is originally more than 150 mg/dL. So, the definition for the lower limit of grade 1 is

Test Name	Test Code	Units [1]	Direction of Change / AE Term	CTCAE Grade [2]					NCI Ref.		
				0	1	2	3	4	Version	Page	Units
changed from 150 mg/dL to ULN. ● Hyperuricemia (see pg. 116 of NCI document) cannot be assessed accurately without knowing whether or not the subject was experiencing physiologic consequences, so it is not included in the table. ● Hemoglobinuria (see pg. 148 of NCI document) cannot be assessed accurately without knowing clinical or diagnostic observations, so it is not included in the table. ● Troponin T (see pg. 109 of NCI document) cannot be assessed accurately without knowing manufacturer ranges, so it is not included in the table.											

10.10 Appendix 10: Key Contributors and Approvers

List of Key Contributors and Approvers

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