STATISTICAL ANALYSIS PLAN

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Study Protocol Title:	A Dose Response Study of E6011 in Subjects With Rheumatoid Arthritis Inadequately Responding to Methotrexate
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2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACR	American College of Rheumatology
AE	adverse event
ATC	anatomical therapeutic class
ANCOVA	analysis of covariance
Ang2	angiopoietin 2
ATC	anatomical therapeutic class
BLQ	below the limit of quantification
BMI	body mass index
BP	Blood pressure
CCP	cyclic citrullinated peptide
CDAI	clinical disease activity index
CI	confidence interval
CRF	case report form
CRP	C-reactive Protein
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DAS28	disease activity score in 28 joints,
DP	Decimal places
EGF	epidermal growth factor
ESR	Erythrocyte Sedimentation Rate
EULAR	European League Against Rheumatism
FAS	full analysis set
γ-GTP	γ-glutamine transpeptidase
HAQ	Health Assessment Questionnaire
HAQ-DI	Health Assessment Questionnare Disability Index
IL	Interleukin
LLOQ	lower limit of quantification
LOCF	last observation carried forward

Abbreviation	Term
LRG1	leucine-rich alpha-2 glycoprotein 1
MedDRA	Medical Dictionary for Regulatory Activities
MMP	matrix metalloproteinase
mTSS	modified total sharp score
MTX	Methotrexate
NCI	National Cancer Institute
NRI	non-responder imputation
OC	observed cases
PD	pharmacodynamics
PK	Pharmacokinetic
PPS	per protocol set
PT	preferred term
RA	rheumatoid arthritis
RF	rheumatoid factor
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDAI	simple disease activity index
SI	Système International
SJC	swollen joint counts
SJC28	swollen joint counts in 28 joints
SJC66	swollen joint counts in 66 joints
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory value
TJC	tender joint counts
TJC28	tender joint counts in 68 joints
TJC68	tender joint counts in 28 joints
TLG	tables, listings, and graphs
TNF-RI	tumor necrosis factor receptor-I

Abbreviation	Term
TRACP-5b	tartrate resistant acid phosphatase 5b
VAS	visual analog scale
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol E6011-J081-201. Since the Version 6 of the protocol defined that it was unnecessary to conduct assessments other than safety assessment, all the efficacy analysis will be conducted until Week 84, that is the latest Visit of ongoing subjects at the time of amendment of the protocol.

Statistical methods of Extension Phase are provided in this document.

3.1 Study Objectives

3.1.1 Primary Objectives

- To evaluate the efficacy of E6011 compared with placebo by ACR20 response rate at Week 12 as a primary endpoint
- To evaluate the safety and tolerability of E6011

3.1.2 Secondary Objectives

- To evaluate the effect of E6011 on suppressing radiographic progression of joint destruction at Week 24
- To evaluate the pharmacokinetics (PK) and immunogenicity of E6011

3.1.3 Exploratory Objective

- To explore the PK/pharmacodynamics (PD) and biomarkers of E6011

3.2 Overall Study Design and Plan

This study is a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison study. The following 4 treatment groups are selected for the study: E6011 100 mg, 200 mg, 400 mg, and placebo. In the E6011 100 mg, 200 mg, and placebo groups, subjects will receive 100 mg, 200 mg, or placebo at Weeks 0, 1, 2, and every 2 weeks subsequently. In the E6011 400 mg group, subjects will receive 400 mg at Weeks 0, 1, 2, 4, 6, 8, 10 and then 200 mg every 2 weeks subsequently.

The study consists of Screening, Observation, Treatment, Extension, and Follow-up Phases.

Undergoing screening assessments within 42 days prior to the study treatment, subjects with the certain eligibility confirmed in the Observation Phase will be allocated into any of the 100 mg, 200 mg, 400 mg, or placebo groups at a 1:2:2:2 ratio through dynamic allocation using the following factors: C- reactive protein (CRP) level at Screening, Rheumatoid Arthritis (RA) Duration, and Prior Use of Biologics Treatment.

In the Treatment Phase (24 weeks), subjects will receive either E6011 or placebo at Weeks 0, 1, 2, and every 2 weeks until Week 22 in a double-blind manner.

Subjects who complete evaluations at Week 24 of the Treatment Phase will enter the Extension Phase. The Extension Phase is up to Week 104 from the starting of the study treatment, and subjects will receive an open-label E6011 200 mg every 2 weeks until Week 102. When subjects insufficiently respond to the treatment or when their disease relapses in the Extension Phase (show no improvement from Observation Phase in both of tender joint counts (TJC) and swollen joint counts (SJC) at 2 consecutive assessments with an interval of ≥1 week), a dose escalation will be allowed.

Follow-up investigations will be conducted on-site 28 days after the completion of the study or the discontinuation of the treatment, and either an on-site or telephone-interview investigation will be conducted 70 days after the last dosing.

4 DETERMINATION OF SAMPLE SIZE

The sample size was based on an expected ACR20 response rate of 30% at Week 12 in the placebo group and at least 60% in both of the E6011 200 mg and 400 mg groups, as per previous Study 103 and the results from other drugs for treatment of RA. Although multiplicity adjustment using Hochberg method will be carried out in the primary analysis, sample size was calculated at a 1-sided significance level of α=0.0125 (α=0.025/2) conservatively. The sample sizes of 50 for E6011 200 mg, 400 mg, and placebo will have 91% power to detect a difference in response rate of 35% between placebo and each E6011 group and will have 79% power to detect a difference in response rate of 30% based on a chi-square test.

5 STATISTICAL METHODS

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 Study Endpoints

5.1.1 Primary Endpoint

- ACR20 response rate at Week 12

The ACR20 response is defined as if the following 3 criteria (ACR components) are met:

1. Greater than or equal to 20% reduction from baseline in the TJC in 68 joints (TJC68)
2. Greater than or equal to 20% reduction from baseline in the SJC in 66 joints (SJC66)
3. Greater than or equal to 20% reduction from baseline in at least 3 of the following 5 assessments:
   - Physician's Global Assessment of Disease Activity (VAS)
   - Patient's Global Assessment of Disease Activity (VAS)
   - Patient's Assessment of Pain (VAS)
   - HAQ-DI
   - CRP

5.1.2 Secondary Endpoints

- ACR20, ACR50, and ACR70 response rate at each visit (excluding ACR20 at Week 12)
- Values and change from baseline in ACR components (TJC, SJC, VAS [patient's assessment of pain, patient's global assessment of disease activity and physician's global assessment of disease activity], functional assessment by subjects [HAQ-DI], and CRP·ESR), DAS28-ESR, DAS28-CRP, SDAI, and CDAI at each visit
- EULAR response criteria at each visit; subjects will be classified based on DAS28-ESR or DAS28-CRP
- DAS28-ESR, DAS28-CRP, SDAI, CDAI, and Boolean remission rates at each visit
- Values and change from baseline in modified total sharp score (mTSS) at each visit

The ACR50 response is defined similar to the ACR20 with a 50% reduction.

The ACR70 response is defined similar to the ACR20 with a 70% reduction.

The DAS28-CRP calculates on the following formula, and disease activity is categorized as High at > 4.1, Moderate at > 2.7 and ≤4.1, Low at <= 2.7, and Remission at <= 2.3.

> 0.56 × sqrt{TJC in 28 joints (TJC28)} + 0.28×sqrt{SJC in 28 joints (SJC28)} + 0.36 × ln{CRP (mg/dL) × 10 + 1} + 0.014 × Patient's Global Assessment of Disease Activity (VAS) (mm) + 0.96

The DAS28-ESR will be calculated on the following formula, and disease activity is categorized as High at > 5.1, Moderate at > 3.2 and <= 5.1, Low at <= 3.2, and Remission at < 2.6.

0.56 × sqrt{TJC28}+ 0.28 × sqrt{SJC28}+0.70×ln{ESR (mm/h)}+0.014 × Patient's Global Assessment of Disease Activity (VAS) (mm)

EULAR Response Criteria:

Present DAS28	DAS28 change from baseline		
	<–1.2	>= –1.2 and <–0.6	>= –0.6 (missing included)
Low	Good response	Moderate response	No response
Moderate	Moderate response	Moderate response	No response
High	Moderate response	No response	No response

The CDAI will be calculated on the following formula, and disease activity is categorized as High at > 22, Moderate at >10 and <= 22, Low at <= 10, and Remission at <= 2.8.

SJC28+ TJC28
+ Patient's Global Assessment of Disease Activity (VAS) (mm)/10
+ Physician's Global Assessment of Disease Activity (VAS) (mm)/10

The SDAI will be calculated on the following formula, and disease activity is categorized as High at > 26, Moderate at > 11 and <= 26, Low at <= 11, and Remission at <= 3.3.

SJC28+ TJC28
+ Patient's Global Assessment of Disease Activity (VAS) (mm)/10
+ Physician's Global Assessment of Disease Activity (VAS) (mm)/10 + CRP (mg/dL)

The Boolean remission is defined as satisfied all of the following conditions:

1. TJC68 <= 1
2. SJC66 <= 1
3. CRP (mg/dL) <= 1
4. Disease activity assessments VAS (mm) by subjects <= 10

5.2 Study Subjects

5.2.1 Definitions of Analysis Sets

Definition of analysis sets are as follows:

- The Full Analysis Set (FAS) is the group of randomized subjects who received at least 1 dose of study drug after 24 weeks to 104 weeks and had at least 1 postdose efficacy measurement after 24 weeks to 104 weeks
- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug after 24 weeks to 104 weeks and had at least 1 postdose safety assessment after 24 weeks to 104 weeks

The number of subjects randomized, the number and the percentage of subjects included in each analysis set, and the number and the percentage of subjects excluded from each analysis set will be presented by treatment group and overall.

5.2.2 Subject Disposition

The number and percentage of subjects who completed extension phase and discontinued the study, and reasons for discontinuation will be summarized for each treatment group and overall.

5.2.3 Protocol Deviations

Major protocol deviation criteria will be established and subjects with major protocol deviations will be identified and documented before the database lock. The protocol deviations identified according to the criteria at study entry and during treatment will not be included in tables, listings, and graphs (TLGs) covered by SAP, but presented in the clinical study report (CSR).

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group and overall using descriptive statistics.

Continuous demographic and baseline variables include:

- Age (year)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) at Screening
- Rheumatoid Arthritis (RA) Duration (years)
- Dose of MTX (mg/week)
- Serum Rheumatoid Factor (RF) Concentration (IU/mL)

- Serum Anti-Cyclic Citrullinated Peptide (CCP) Antibody Concentration (U/mL)
- Oral Steroid[*1] (mg/day)
- ACR Components
  - TJC68 at Baseline
  - SJC66 at Baseline
  - TJC28 at Baseline
  - SJC28 at Baseline
  - CRP (mg/dL) at Screening
  - CRP (mg/dL) at Baseline
  - ESR (mm/h) at Baseline
  - Physician's Global Assessment of Disease Activity (VAS) (mm) at Baseline
  - Patient's Global Assessment of Disease Activity (VAS) (mm) at Baseline
  - Patient's Assessment of Pain (VAS) (mm) at Baseline
  - HAQ-DI at Baseline
- DAS28-CRP at Baseline
- DAS28-ESR at Baseline
- CDAI at Baseline
- SDAI at Baseline
- Joint Space Narrowing at Baseline
- Number of Bone Erosions at Baseline
- mTSS at Baseline
- mTSS divided by RA Duration (/year)

Categorical variables include:

- Age group (18<= <35, 35<= <50, 50<= <75)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Race (White, Black or African American, Japanese, Chinese, Other Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Other)
- RA Duration (< 5 years, 5 years <=)
- RA Duration (< 1 year, 1 year <= < 5 years, 5 years <= < 10 years, 10 years <= < 15 years, >= 15 years)

- Smoking History (Current, Former, Never)
- Current Medical Conditions (Yes, No)
- Prior Use of Biologics Treatment (Yes - TNF*2/Non-TNF, No)
- Drug experience of MTX (Yes, No)
- Dose of MTX (< 6 mg/week, 6 mg/week <= < 12 mg/week, >= 12 mg/week)
- Drug experience of DMARDs within 12 weeks before informed consent except MTX (Yes - 1/2/…, No)
- Continuation of Steroid
- Serum RF Concentration (Seropositive - High Positive/Low Positive, Seronegative)*3
- Anti-CCP Antibody (Seropositive - High Positive/Low Positive, Seronegative)*4
- Classification of Global Functional Status in RA
- DAS28-CRP Category (High: >4.1, Moderate: 2.7 < <= 4.1, Low: <= 2.7)
- DAS28-ESR Category (High: >5.1, Moderate: 3.2 < <= 5.1, Low: <= 3.2)
- CDAI (High: > 22, Moderate: 10 < <= 22, Low: <= 10)
- SDAI (High: > 26, Moderate: 11 < <= 26, Low: <= 11)
- CRP level at Screening (< 0.6mg/dL, >= 0.6mg/dL)
- CRP level at Baseline (< 0.6mg/dL, >= 0.6mg/dL)
- ESR level at Baseline (< 28mm/h, >= 28mm/h)

*1 Prednisone-equivalent dose

*2 Refer section 8.5 "TNF agent"

*3 Categories of Serum RF Concentration are derives as follows:

Seropositive: > 15 (IU/mL)

High Positive: < 45 (IU/mL)

Low Positive: 15 <= <= 45 (IU/mL)

Seronegative: <= 15 (IU/mL)

*4 Categories of Anti-CCP Antibody are derives as follows:

Seropositive: >= 4.5 (U/mL)

High Positive: < 13.5 (U/mL)

Low Positive: 4.5 < <= 13.5 (U/mL)

Seronegative: < 4.5 (U/mL)

Subject data listings will be provided.

MEDICAL HISTORY

A subject data listing will be provided.

5.2.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the case report form (CRF) will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) version (Mar2016 or later). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the FAS by treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term. Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug. A subject data listing of all medications will be provided.

5.2.6 Treatment Compliance

Treatment compliance will be described in section 5.6.1.

5.3 Data Analysis General Considerations

5.3.1 Pooling of Centers

Subjects from all centers will be pooled for all analyses.

5.3.2 Adjustments for Covariates

No covariates are planned for analyses for extension phase.

5.3.3 Multiple Comparisons/Multiplicity

No multiplicity are planned for analyses for extension phase.

5.3.4 Examination of Subgroups

No subgroup analyses are planned for analyses for extension phase.

5.3.5 Handling of Missing Data, Dropouts, and Outliers

For the efficacy analyses, approaches to handling missing data for continuous variables, except mTSS, will be the observed cases (OC) method and the last observation carried forward (LOCF) method; binary variables and EULAR response criteria will be the observed cases (OC) method, the last observation carried forward (LOCF) method and the non-responder imputation (NRI) method as each visit.

mTSS value at Week 24, Week 52 and Week 76 will be extrapolated from values of baseline and values of postbaseline, which will be used in summary statistics. The linear extrapolation method will be used for analysis of the structural progression endpoint (van der Heijde mTSS) to impute missing data at time points when analyses are conducted (including the analyses at Week 24, Week 52 and Week 76). For patients who discontinue the study or the study treatment or for patients who miss a radiograph for any reason, baseline data and the most recent radiographic data prior to discontinuation or the missed radiograph, adjusted for time, will be used for linear extrapolation to impute missing data at subsequent time points. All patients originally randomized to placebo will be switched to active treatment at Week 24; Missing postbaseline values will be imputed only if both a baseline value and a postbaseline value from another time point are available, as long as the patient was on the same treatment at each applicable time point.

Calculation for value of mTSS extrapolation will be derived by follow formula:

- Week 24 = (Postbaseline) + (Postbaseline – Baseline) * ((24 – (Study Day of Postbaseline / 7) / Study Day of Postbaseline / 7)
- Week 52 = (Postbaseline) + (Postbaseline – Baseline) * ((52 – (Study Day of Postbaseline / 7) / Study Day of Postbaseline / 7)
- Week 76 = (Postbaseline) + (Postbaseline – Baseline) * ((76 – (Study Day of Postbaseline / 7) / Study Day of Postbaseline / 7)

The two individual components of mTSS (Erosion and joint space narrowing [JSN] score) will be analyzed in the same way as the mTSS.

For the safety analyses for continuous value, descriptive statistics are used OC method and LOCF method, this is applied only the last observation of each phase, in tables and figures.

In the cases of laboratory result contains less (or more) than quantitation limit value is treated as:

a. zero, when less than quantitation limit value,

b. quantitation limit value, when more than quantitation limit value.

In the cases of pharmacokinetic data, refer "8.2 Convention for Pharmacokinetic data handling".

5.3.6 Other Considerations

5.3.6.1 Total number of joints

For the calculation of the total number of joints that are tender/swollen, if any joints are not evaluable, the score is prorated by taking the number of joints that are tender/swollen divided by the number of evaluable joints and multiplied by the target number of joints, rounded to nearest integer. If assessment of joints are "Not Done", the joints will be handled as tender and swollen.

5.3.6.2 HAQ subcategory score

The HAQ-DI is composed of 20 items in 8 categories (Dressing and Grooming, Arising, Eating, Walking, Hygiene, Reach, Grip, Activities). To calculate the HAQ-DI, the highest sub-category score determines the value for each category, there must be responses in at least 6 of the 8 categories or else a HAQ-DI cannot be computed. The category scores are then averaged into an overall HAQ-DI.

HAQ-DI = (Amount of score with all categories) / (Number of categories scored)

5.4 Efficacy Analyses

The FAS will be used for the efficacy analyses.

5.4.1 Primary Efficacy Analyses

No primary efficacy analyses are planned for analyses for extension phase.

5.4.2 Secondary Efficacy Analyses

For each component of ACR (TJC, SJC, VAS [patient's assessment of pain, patient's global

assessment of disease activity and physician's global assessment of disease activity], functional assessment by subjects (HAQ) and CRP·ESR), DAS28-ESR, DAS28- CRP, SDAI, and CDAI in each visit, the values and the changes from baseline will be summarized by treatment group.

For mTSS, values and changes from baseline will be summarized by treatment group. For DAS28-ESR and DAS28-CRP, frequency and percentage of each classification (no response, moderate response, good response) by EULAR response criteria will be summarized by treatment group and visit in a shift table. For DAS28-ESR, DAS28-CRP, SDAI and CDAI, frequency and percentage of each category (Remission, Low, Moderate, High) will be summarized by treatment group and visit in a shift table.

The mean change from baseline of ACR components, DAS28-CRP, DAS28-ESR, CDAI and SDAI - visit will be displayed by treatment group. ACR response rate - visit will be displayed by treatment group. Cumulative probability of the change from baseline in mTSS will be displayed at week 52 and Week 76.

All efficacy endpoints for the treated subjects will be listed.

5.4.3 Other Efficacy Analyses

No other efficacy analyses are planned for this study.

5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.1 Pharmacokinetic Analyses

Serum E6011 Concentration

Serum PK samples for PK analyses will be collected on Week 0 (predose), Week 1 (predose), Week 2 (predose), Week 4 (predose), Week 8 (predose), Week 12 (predose) , Week 16 (predose), Week 20 (predose), Week 24 (predose) to Week 104 (predose) by 4 Weeks.

The Safety Analysis Set will be used for PK analyses.

<Table>

No Tables are planned for analyses for extension phase.

<Listing>

Actual sampling time and serum concentrations of E6011 for each subject will be listed.

<Figure>

No figures are planned for analyses for extension phase.

5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

5.5.2.1 Pharmacodynamic, Pharmacogenomic Analyses

No Pharmacodynamic and Pharmacogenomic analyses are planned for this study.

5.5.2.2 Other Biomarker Analyses

All biomarker analyses will be performed using the Full Analysis Set.

For the Extension Phase, summary statistics for serum RF concentration, serum anti-CCP antibody concentration, and serum matrix metalloproteinase-3 concentration, serum tartrate resistant acid phosphatase 5b (TRACP-5b) concentration, serum cytokine concentration, serum leucine-rich alpha-2 glycoprotein 1 (LRG1) concentration, serum angiopoietin 2 (Ang2) concentration, Vectra™ DA and it's component (vascular cell adhesion molecule-1 (VCAM-1), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF)-A, interleukin (IL)-6, tumor necrosis factor receptor-I (TNF-RI), serum matrix metalloproteinase-1, serum matrix metalloproteinase-3, YKL-40, leptin, resistin, SA and CRP) value, change from baseline and percent change from baseline, by treatment group and time point, will be calculated. Exploratory investigations of the relationship between efficacy and biomarkers will be conducted. The analysis plan for CX3CR1 is out of scope of this document. All other biomarkers will be collected on baseline and postbaseline, referring section 8.1.3 "Time window".

Subject data listings will be provided.

5.5.2.3 Immunogenicity Analyses

All immunogenicity analyses will be performed using the Safety Analysis Set.

The percentage and frequency of occurrences will be calculated for serum anti-E6011 antibodies and E6011-induced anti-E6011 antibodies by treatment group and time point. If anti-E6011 antibody develops, the frequency and percentage of any anti-E6011 antibody neutralization activity and isotypes will be calculated.

These are analyzed by Week 84.

Subject data listings will be provided.

5.6 Safety Analyses

All safety analyses will be performed on the Safety Analysis Set. Safety data, presented by treatment group, will be summarized on an "as treated" basis using descriptive statistics (eg, n, mean, SD, median, minimum, maximum for continuous variables; n [%] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, 12-lead ECG results, chest x-ray, neurological findings, and blood CD4 positive cell count. Day 1 for all safety analyses will be defined as the date of the first dose of study drug.

5.6.1 Extent of Exposure

The extent of exposure to study drug will be characterized by duration of exposure, number of injection dose and study medication compliance for each treatment group. Definition of analysis items are as follows:

- Duration of exposure (weeks) = (Date of Last Dose - Date of First Dose + 14) / 7
- Number of Injection = Count of records with non-zero treatment
- Study Medication Compliance (%) = Number of Injection / Number of Expected Injection * 100

Subject data listings will be provided.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be coded to the MedDRA (Version 19.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database. A treatment-emergent adverse event (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or

- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables.

A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT.

The TEAEs will be summarized by treatment group and E6011 overall. The incidence of follow TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT:

- TEAEs
- TEAEs by maximum intensity
- Serious TEAEs
- TEAEs leading to study drug withdrawn
- TEAEs leading to interruption of study drug
- TEAEs leading to reduction from study drug
- Treatment Related, TEAEs
- Treatment Related, TEAEs by maximum grade
- Treatment Related, Serious TEAEs
- Treatment Related, TEAEs leading to study drug withdrawn
- Treatment Related, TEAEs leading to interruption of study drug
- Treatment Related, TEAEs leading to reduction from study drug

In the analysis, the AEs emerged until 70 days after the last dose are intended

Subject data listings of All AEs, SAEs, AEs leading to death, leading to study drug withdrawn or leading to interruption from study drug will be provided.

5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For quantitative parameters listed in protocol Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference

range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will be used to compare the baseline LNH classification to the LNH classification for the highest and lowest value during the study.

The Sponsor's Grading for Laboratory Values using CTCAE v4.0 presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

Laboratory results versus visit by treatment group will be displayed using box-plot.

Subject data listings of Laboratory test results and TEMAV will be provided.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (systolic and diastolic BP, pulse, temperature, and weight) and changes from baseline will be presented by visit and treatment group.

Subject data listings will be provided.

5.6.5 Electrocardiograms

Shift tables will be presented changes from baseline in 12-lead ECG interpretation (normal/abnormal, not clinically significant/abnormal, not clinically significant) by visit and treatment group.

Subject data listings will be provided.

5.6.6 Other Safety Analyses

5.6.6.1 Chest X-Ray

Shift tables will be presented changes from baseline in chest x-ray (normal/abnormal, not clinically significant/abnormal, not clinically significant) by visit and treatment group.

Subject data listings will be provided.

5.6.6.2 Neurological findings

Descriptive statistics for neurological findings will be presented by visit and treatment group.

Subject data listings will be provided.

5.6.6.3 Blood CD4 positive cell counts

For Blood CD4 positive cell counts, the actual value and the change from baseline to each postbaseline visit will be summarized by visit and treatment group using descriptive statistics. Blood CD4 positive cell counts will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the it's reference range. Within-treatment comparisons will be based shift tables that compare the baseline LNH classification to the LNH classification at each postbaseline visit.

Subject data listings will be provided.

5.7 Other Analyses

5.7.1 Anti-JCV Antibody Test

Anti-JCV antibody test result (positive or negative) is judged according to the results of screen assay and inhibition assay.

Subject data listings will be provided.

5.8 Exploratory Analyses

Exploratory analyses may be conducted as appropriate. Any exploratory analyses that are performed will be appropriate titled and labeled as exploratory and will be clearly distinguished from planned analyses when results are reported in the Clinical Study Report.

6 INTERIM ANALYSES

No interim analyses are planned for this study.

7 CHANGES IN THE PLANNED ANALYSES

Changes in the planned analyses for protocol are as follows:

- Based on the protocol amendment Version 6, all efficacy results will be summarized until week 84.
- Regarding the PK analysis for extension phase, only listing will be created.

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 Baseline, Time Windows for statistical analyses

8.1.1 Definition of baseline value

The baseline value was defined as the most recent value reported just before first dosing.

8.1.2 Definition of change from baseline and percent change from baseline

Change from baseline is defined as postbaseline value minus baseline value. Percent change from baseline is defined as follows:

% Change from baseline = (Change from baseline/Baseline) * 100

For any Baseline value of 0, the subject's corresponding percent change from baseline will not be included in the summary statistics table.

8.1.3 Time windows

Time windows are defined as Table 8.1 to Table 8.8 for each assessment. Observation that has the most recent date-time on base date-time is adopted if plural observations exist in the time window. Observation recorded later is adopted if they recorded in that same period.

Table 8.1 Definition of time windows and calculated visits for vital signs and Serum E6011 concentration

Visit	Base date	Time windows
Week 1 (Day 8)	Date of first drug administration + 7 days	Base date - 3 days <= < Base date + 3 days
Week 2 (Day 15)	Date of first drug administration + 14 days	Base date - 4 days <= < Base date + 7 days

Week 4 (Day 29)	Date of first drug administration + 28 days	Base date - 7 days <= < Base date + 14 days
Week 8 - Week 104 by 4 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days

Table 8.2 Definition of time windows and calculated visits for Physical findings, administration site finding

Visit	**Base date**	**Time windows**
Week 1 (Day 8)	Date of first drug administration + 7 days	Base date - 3 days <= < Base date + 3 days
Week 2 (Day 15)	Date of first drug administration + 14 days	Base date - 4 days <= < Base date + 7 days
Week 4 (Day 29)	Date-time of first drug administration + 28 days	Base date - 7 days <= < Base date + 14 days
Week 8 - Week 12 by 4 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days
Week 24 - Week 36 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days
Week 52 - Week 88 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 168 days	Base date - 14 days <= < Base date + 14 days

Table 8.3 Definition of time windows and calculated visits for Joint assessment, ESR, VAS, HAQ, Laboratory tests (include Hematology, blood chemistry, urinalysis, RF, anti-CCP antibody and matrix metalloproteinase -3)

Visit	**Base date**	**Time windows**
Week 2 (Day 15)	Date of first drug administration + 14 days	Base date - 4 days <= < Base date + 7 days
Week 4 (Day 29)	Date-time of first drug administration + 28 days	Base date - 7 days <= < Base date + 14 days

Visit	Base date	Time windows
Week 8 - Week 104 by 4 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days

Table 8.4 Definition of time windows and calculated visits for 12-lead ECG, Chest x-ray, Pregnancy test, Blood CD4 positive cells

Visit	Base date	Time windows
Week 12 - Week 24 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days
Week 52	Date of first drug administration + 334 days	Base date - 14 days <= < Base date + 14 days
Week 76	Date-time of first drug administration + 532 days	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 728 days	Base date - 14 days <= < Base date + 14 days

Table 8.5 Definition of time windows and calculated visits for body weight, Autoantibody

Visit	Base date	Time windows
Week 12 - Week 36 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date – 14 days <= < Base date + 14 days
Week 52	Date of first drug administration + 334 days	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 728 days	Base date - 14 days <= < Base date + 14 days

Table 8.6 Definition of time windows and calculated visits for Neurological findings, Vasculitis marker tests

Visit	Base date	Time windows
Week 12 - Week 36 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days

Week 52 - Week 88 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 728 days	Base date - 14 days <= < Base date + 14 days

Table 8.7 Definition of time windows and calculated visits for Serum KL-6, β D glucan, Serum TRACP-5b concentration, Vectra™ DA

Visit	**Base date**	**Time windows**
Week 12 - Week 24 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days
Week 52	Date of first drug administration + 334 days	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 728 days	Base date - 14 days <= < Base date + 14 days

Table 8.8 Definition of time windows and calculated visits for Serum anti-E6011 antibody

Visit	**Base date**	**Time windows**
Week 4 (Day 29)	Date-time of first drug administration + 28 days	Base date - 7 days <= < Base date + 14 days
Week 8 - Week 104 by 4 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days

Table 8.9 Definition of time windows and calculated visits for Serum cytokine concentration, LRG1, Ang2

Visit	Base date	Time windows
Week 4 (Day 29)	Date-time of first drug administration + 28 days	Base date - 7 days <= < Base date + 14 days
Week 12 - Week 24 by 12 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days
Week 52	Date of first drug administration + 334 days	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 728 days	Base date - 14 days <= < Base date + 14 days

Table 8.10 Definition of time windows and calculated visits for Anti-JCV antibody test

Visit	Base date	Time windows
Week 24	Date-time of first drug administration + 168 days	Base date - 14 days <= < Base date + 14 days
Week 52	Date of first drug administration + 334 days	Base date - 14 days <= < Base date + 14 days
Week 76	Date-time of first drug administration + 532 days	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 728 days	Base date - 14 days <= < Base date + 14 days

Table 8.11 Definition of time windows and calculated visits for Virus test, Syphilis test, Tuberculosis test

Visit	Base date	Time windows
Week 52	Date of first drug administration + 334 days	Base date - 14 days <= < Base date + 14 days
Week 104	Date-time of first drug administration + 728 days	Base date - 14 days <= < Base date + 14 days

Table 8.12 Definition of time windows and calculated visits for Joint x-ray

Visit	Base date	Time windows
Week 0	Date-time of first drug administration	Base date <= 28 days
Week 24	Date-time of first drug administration + 168 days	28 days < <= Base date + 28 days
Week 52	Date of first drug administration + 334 days	Base date - 28 days <= < Base date + 28 days
Week 76	Date-time of first drug administration + 532 days	Base date - 28 days <= < Base date + 28 days

8.2 Pharmacokinetic data handling

8.2.1 Lower Limit of Quantification of E6011 Serum Concentration

The LLOQ of E6011 serum concentration is 0.1 µg/mL.

8.2.2 BLQ Handling for Developing Concentration–Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to 302-104.00-MNL for non-compartmental pharmacokinetic analysis.

8.2.3 BLQ Handling for Developing Tables

When developing tables, BLQ values will be handled according to 302-104.00-MNL for non-compartmental pharmacokinetic analysis.

8.2.4 Handling of anomalous concentration values

Handling anomalous concentration values will follow the 302-104.00-MNL for non-compartmental pharmacokinetic analysis.

8.2.5 General Rules for Presentation of Drug Concentrations

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations, all summary statistics (mean, median, geometric mean, standard deviation (SD) and coefficient variation (CV)) will have 3 significant digits.

8.3 Imputation rule for partial date

8.3.1 Date of Diagnosis

Imputation rule for date of diagnosis is as follows:

- Complete date: Date as reported on CRF.
- Year and Month are not missing but Day is missing: Year and Month as reported on CRF, Date as 15th
- Year is not missing but Month and Day are missing: Year as reported on CRF, Month and Day as July 1st.
- Year is missing or Date is completely missing: Missing

8.3.2 Medication

Imputation rule for medication start date is as follows:

- Complete date: Date as reported on CRF
- Year and Month are not missing but Day is missing: Year and Month as reported on CRF, Day as 1st
- Year is not missing but Month and Day are missing: Year as reported on CRF, Month and Day as January 1st
- Year is missing or Start Date is completely missing: Missing

Imputation rule for medication end date is as follows:

- Complete date: Date as reported on CRF
- Year and Month are not missing but Day is missing: Date of death or Year and Month as reported on CRF, last day of the reported month, which is earlier
- Year is not missing but Month and Day are missing: Year as reported on CRF, Month and Day as December 31st
- Year is missing or Start Date is completely missing: Missing

8.3.3 Adverse Events

Imputation rule for adverse event start date is as follows:

- Year and Month are not missing but Day is missing
  - Year and Month are the same as year and month of the earliest among non-missing values of first dosing date of study Treatment and imputed AE end date: The earliest among non-missing values of first dosing date of study Treatment and imputed AE end date
  - Year and Month are not the same as year and month of the earliest among non-missing values of first dosing date of study Treatment and imputed AE end date: Year and Month as reported on CRF, Day as 1st
- Year is not missing but Month and Day are missing
  - Year is the same as year of the earliest among non-missing values of first dosing date of study Treatment and imputed AE end date: The earliest among non-missing values of first dosing date of study Treatment and imputed AE end date
  - Year is not the same as year of the earliest among non-missing values of first dosing date of study Treatment and imputed AE end date: Year as reported on CRF, Month and Day as January 1st
- Completely missing: First dosing date or imputed AE end date, which is earlier

Imputation rule for adverse event end date is as follows:

- Outcome is 'fatal' and End Date is not complete date: Date of death
- Outcome is 'fatal' and End Date is complete date
  - different from the date of death: Confirm to CDM
  - same as the date of death: Date of death
- Outcome is not 'fatal' and date of death is not missing
  - Year and Month are the same as the year and month of date of death: Date of death
  - Year and Month are not the same as the year and month of date of death: Year and Month as reported on CRF, Day as the last day of the month
  - Year is the same as the year of date of death: Date of death
  - Year is not the same as the year of date of death: Year as reported on CRF, Month and Day as December 31st
  - Completely missing: Date of death
- Outcome is not 'fatal' and date of death is missing

  - Year and Month are not missing but Day is missing: Year and Month as reported on CRF, Day as the last day of the month
  - Year is not missing but Month and Day are missing, and Year is before the Year of date of discontinuation from study: Year as reported on CRF, Month and Day as December 31st
  - Year is not missing but Month and Day are missing, and Year is same as the Year of date of discontinuation from study: Date of discontinuation from study
- Outcome is marked 'Recovered' or 'Recovered with sequelae': Date of discontinuation from study
- Outcome is missing or is 'Not recovered', 'Recovering' or 'Unknown', or Year is missing or Start Date is completely missing: Missing
- Year, Month and Day are all missing and date of death is not missing: Date of death

8.4 Decimal places

Decimal places (DP) for descriptive statistics, except PK analysis, is defined as follows:

- Mean: Significant digits + 1
- SD: Significant digits + 2
- Median: Significant digits + 1
- Min, Max: Significant digits
- Percentage of frequency: fixed one decimal place

Significant digits for the derived parameter is defined as follows:

- TJC68, SJC66, TJC28, SJC28: Integer
- DAS28-CRP, DAS28-ESR, CDAI, SDAI, Calcium Corrected: 2 DP
- HAQ-DI: 1 DP

DP for the other calculated result is defined as follows:

- Confidence Interval: fixed 2 DP
- *P*value: fixed 3 DP(truncated below 4 DP) , except < 0.001. When < 0.001, as is.

Summary of change from baseline is based on significant digits of each parameter, and percent change from baseline is defined as 1 DP.

8.5 TNF Agent

Medications as TNF agent are extracted at ATC4 Code = L04AB.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS version 9.3 or later.

11 MOCK TABLES, LISTINGS, AND GRAPHS

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

Not applicable.

13 APPENDICES

13.1 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

National Cancer Institute (NCI) CTCAE version 4.0 May 2009 is available online at:

https://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.0_2009-05-29_QuickReference_5x7.pdf

CTCAE grades for selected laboratory parameters are listed in the table below, where ULN is the upper limit of normal and LLN is the lower limit of normal.

	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
Lab Parameter	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hematology					
Hemoglobin (low)	< LLN - 100 (g/L)	< 100 - 80 (g/L)	< 80 - 65 (g/L)		Death
Hemoglobin (high)	Increase in > 0 - 20 (g/L) above ULN or above baseline if baseline is above ULN	Increase in >20 - 40 (g/L) above ULN or above baseline if baseline is above ULN	Increase in > 40 (g/L) above ULN or above baseline if baseline is above ULN		
Platelet Count (PLT) (low)	< LLN - 75.0 (10^9/L)	< 75.0 - 50.0 (10^9/L)	< 50.0 - 25.0 (10^9/L)	< 25.0 (10^9/L)	
White Blood Cell Count (WBC) (low)	< LLN - 3.0 (10^9/L)	< 3.0 - 2.0 (10^9/L)	< 2.0 - 1.0 (10^9/L)	< 1.0 (10^9/L)	
White Blood Cell Count (WBC) (high)			> 100 (10^9/L)		Death
Lymphocytes (low)	< LLN - 0.8 (10^9/L)	< 0.8 - 0.5 (10^9/L)	< 0.5 - 0.2 (10^9/L)	< 0.2 (10^9/L)	
Lymphocytes (high)		> 4 - 20 (10^9/L)	> 20 (10^9/L)		
Neutrophils (low)	< LLN - 1.5 (10^9/L)	< 1.5 - 1 (10^9/L)	< 1 - 0.5 (10^9/L)	< 0.5 (10^9/L)	
Blood Chemistry					
Albumin (low)	< LLN - 3 (g/dL) ; < LLN - 30 (g/L)	< 3 - 2 (g/dL) ; < 30 - 20 (g/L)	< LLN - 2 (g/dL) ; < 20 (g/L)		Death
Alkaline Phosphatase (high)	> ULN - 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN	
Alanine Aminotransferase (high)	> ULN - 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN	
Amylase (high)	> ULN - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN	

Lab Parameter	NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Aspartate Aminotransferase (high)	> ULN - 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN	
Total Bilirubin (high)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN	
Corrected Calcium*, serum-low (hypocalcemia)	< LLN - 2.0 (mmol/L) ; < LLN - 8.0 (mg/dL)	< 2 - 1.75 (mmol/L) ; < 8.0 - 7.0 (mg/dL)	< 1.75 - 1.5 (mmol/L) ; < 7.0 - 6.0 (mg/dL)	< 1.5 (mmol/L) ; < 6.0 (mg/dL)	Death
Corrected Calcium*, serum-high (hypercalcemia)	> ULN – 2.9 (mmol/L) ; > ULN – 11.5 (mg/dL)	> 2.9 – 3.1 (mmol/L) ; > 11.5 – 12.5 (mg/dL)	> 3.1 – 3.4 (mmol/L) ; > 12.5 – 13.5 (mg/dL)	> 3.4 (mmol/L) ; > 13.5 (mg/dL)	Death
Cholesterol (high)	> ULN - 300 (mg/dL) ; > ULN - 7.75 (mmol/L)	> 300 - 400 (mg/dL) ; > 7.75 - 10.34 (mmol/L)	> 400 - 500 (mg/dL) ; > 10.34 - 12.92 (mmol/L)	> 500 (mg/dL) ; > 12.92 (mmol/L)	
Creatinine (high)	> 1 - 1.5 x baseline ; > ULN - 1.5 x ULN	> 1.5 - 3.0 x baseline ; > 1.5 - 3.0 x ULN	> 3.0 x baseline ; > 3.0 - 6.0 x ULN	> 6.0 x ULN	
Gammaglutamyltransferase (high)	> ULN - 3.0 x ULN	> 3.0 - 5.0 x ULN	> 5.0 - 20.0 x ULN	> 20.0 x ULN	
Glucose, serum-low (hypoglycemia)	< LLN - 55 (mg/dL) ; < LLN - 3.0 (mmol/L)	< 55 - 40 (mg/dL) ; < 3.0 - 2.2 (mmol/L)	< 40 - 30 mg/dL ; < 2.2 - 1.7 mmol/L	< 30 mg/dL ; < 1.7 mmol/L	Death
Glucose, serum-high (hyperglycemia)	> ULN - 160 (mg/dL) ; > ULN - 8.9 (mmol/L)	> 160 - 250 (mg/dL) ; > 8.9 - 13.9 (mmol/L)	> 250 - 500 (mg/dL) ; > 13.9 - 27.8 (mmol/L)	> 500 (mg/dL) ; > 27.8 (mmol/L)	Death
Phosphate, serum-low (hypophosphatemia)	< LLN - 2.5 mg/dL; < LLN - 0.8 mmol/L	< 2.5 - 2.0 mg/dL; < 0.8 - 0.6 mmol/L	< 2.0 - 1.0 mg/dL; < 0.6 - 0.3 mmol/L	< 1.0 mg/dL; < 0.3 mmol/L;	Death
Potassium, serum-low (hypokalemia)	< LLN - 3.0 mmol/L		< 3.0 - 2.5 mmol/L	< 2.5 mmol/L	Death
Potassium, serum-high (hyperkalemia)	> ULN - 5.5 mmol/L	> 5.5 - 6.0 mmol/L	> 6.0 - 7.0 mmol/L	> 7.0 mmol/L	Death
Sodium (Hyponatremia) (low)	< LLN - 130 mmol/L		< 130 - 120 mmol/L	< 120 mmol/L;	Death
Sodium (Hypernatremia) (high)	> ULN - 150 mmol/L	> 150 - 155 mmol/L	> 155 - 160 mmol/L	> 160 mmol/L;	Death
Triglyceride (hypertriglyceridemia) (high)	150 - 300 (mg/dL) ; 1.71 - 3.42 (mmol/L)	> 300 - 500 (mg/dL) ; > 3.42 - 5.7 (mmol/L)	> 500 - 1000 (mg/dL) ; > 5.7 - 11.4 (mmol/L)	> 1000 (mg/dL) ; > 11.4 (mmol/L)	Death
Uric Acid (hyperuricemia) (high)	> ULN - 10 (mg/dL) ; > ULN - 0.59 (mmol/L)			> 10 (mg/dL) ; > 0.59 (mmol/L)	Death
Urinalysis					
Protein	1+	2+ or higher			
Other					
Blood CD4 Positive Cell Counts	< LLN - 0.5 (10^9/L)	< 0.5 - 0.2 (10^9/L)	< 0.2 - 0.05 (10^9/L)	< 0.05 (10^9/L)	

* Corrected serum calcium by albumin should be referred. If serum albumin is <4.0 g/dL, the corrected calcium will be calculated using the following formula:

Corrected calcium (mg/dL) = Total calcium (mg/dL) – 0.8 x [Albumin (g/dL) – 4]

As to Alkaline Phosphatase and γ-GTP, criteria for Grade 2 is changed from ULN x 2.5 (in the CTCAE) to ULN x 3.0.

13.2 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 3 or higher.

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