16.1.9 Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E6011-J081-201
Study Protocol Title:	A Dose Response Study of E6011 in Subjects With Rheumatoid Arthritis Inadequately Responding to Methotrexate
Date:	19 Mar 2018
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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.

Statistical methods of Treatment 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 only once (6 administrations of E6011 400 mg every 2 weeks).

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 and had at least 1 postdose primary efficacy measurement
- The Per Protocol Analysis Set(PPS) is the subset of subjects in the corresponding FAS who do not meet any of following criteria:
  - Subjects who have any major protocol violations (major inclusion/exclusion violations or other major protocol deviation that affect the evaluation of efficacy
  - Subjects who are <80% compliant with study drug during treatment phase

  A comprehensive list of excluded subjects from the PPS will be verified by the sponsor's medical officer before database lock.
- The Safety Analysis Set is the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment

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 numbers of subjects who have provided informed consent, and who are screen failures together with reasons for screening failure will be summarized. The numbers of randomized subjects and the numbers of treated subjects will be summarized for each treatment group and overall. The number and percentage of subjects who completed treatment 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

Determination of covariates are as follows:

- Prior Use of Biologics Treatment (Yes/No)
- RA Duration (< 5 years, >= 5 years)
- CRP Level at Baseline (< 0.6mg/dL, >= 0.6mg/dL)

In case that the number of subjects in each category of covariates for logistic regression models and ANCOVA is very small, to integrate the categories will be planned.

5.3.3 Multiple Comparisons/Multiplicity

Hochberg method will be used to control the overall type I error rate for the comparison between placebo and either E6011 200 mg or 400 mg in primary efficacy analysis. The *P*values from the comparisons will be calculated using SAS PROC MULTTEST.

5.3.4 Examination of Subgroups

The primary efficacy endpoint, ACR50, ACR70 and mTSS will be summarized and analyzed by subgroups defined by section 5.2.1 for categorical variables. Also, forest plot will be created by subgroups for comparison of response rate at primary efficacy endpoint and the changes from baseline at mTSS.

Additional subgroup analyses may also be conducted, if deemed appropriate.

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 52 will be extrapolated from values of baseline and values of postbaseline, which will be used in summary statistics and ANCOVA.

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 and Week 52). 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; thus, there will be no observed data for the placebo arm for the structural comparison at subsequent time points. Therefore, baseline data and the most recent radiographic data prior to initiation of the new therapy, adjusted for time, will be used for linear extrapolation at Week 52. The linear extrapolation method has been established as an appropriate missing data imputation method in other Phase 3 RA trials (Keystone et al. 2004, 2008, 2009; Cohen et al. 2006; Smolen et al. 2008, 2009). 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 52 = (Postbaseline) + (Postbaseline – Baseline) * ((52 – (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 as the primary population for the efficacy analyses, while the PPS will be used as a supportive analysis.

5.4.1 Primary Efficacy Analyses

ACR20 response rate at Week 12 will be analyzed using a logistic regression model, baseline CRP, RA Duration and Prior Use of Biologics Treatment as covariates, for the comparison between placebo and either E6011 200 mg or 400 mg. Overall significance level is α=0.025 (one-sided). Hochberg method will be used to control the overall type I error rate.

Hypothesis for logistic regression model is:

- Primary hypothesis

$$\begin{cases} H_0: & \frac{Odds_{400\,mg}}{Odds_{Placebo}} = 1 \; and \; \frac{Odds_{200\,mg}}{Odds_{Placebo}} = 1 \\ H_1: & \frac{Odds_{400\,mg}}{Odds_{Placebo}} > 1 \; or \; \frac{Odds_{200\,mg}}{Odds_{Placebo}} > 1 \end{cases}$$

Subjects with missing primary efficacy endpoint due to early discontinuation or other reasons will be considered non-responders. In case that the number of subjects in each category of covariates is very small, to integrate the categories will be planned. ACR20 response rate and its 2-sided 95% confidence interval for each treatment group will be calculated. The difference in ACR20 response rate between each of E6011 dose and placebo and its 2-sided 95% confidence interval will also be calculated. Subgroup analyses or sensitivity analyses will be conducted.

In addition, following analyses will be conducted for ACR20 response rate at Week 12.

- To compare ACR20 response between E6011 100 mg and placebo using logistic regression model same as above. The difference in ACR20 response rate between E6011 100 mg and placebo and its 2-sided 95% confidence interval will also be calculated.

  Additional hypothesis:

$$\begin{cases} H_0: & \frac{Odds_{100\,mg}}{Odds_{Placebo}} = 1 \\ H_1: & \frac{Odds_{100\,mg}}{Odds_{Placebo}} > 1 \end{cases}$$

- To evaluate the overall dose response relationship using a logistic regression model with treatment as continuous variable(placebo=0, 100mg=100, 200mg=200 and 400mg=400), and baseline CRP, RA Duration and Prior Use of Biologics Treatment as covariates.

5.4.2 Secondary Efficacy Analyses

The multiplicity adjustment will not be considered for secondary efficacy analyses. For ACR20 (excluding Week 12), ACR50, and ACR70, similar analyses as primary analyses will be conducted. 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. The changes from baseline will also be analyzed using ANCOVA with baseline value, CRP Level at Baseline, RA Duration, and Prior Use of Biologics Treatment as covariates. The significance level for comparisons between placebo and each treatment group of E6011 (100 mg, 200 mg, and 400 mg) is α=0.05 (2-sided).

For mTSS, values and changes from baseline will be summarized by treatment group. The changes from baseline will be analyzed using rank ANCOVA same as above. In this analysis, all mTSS score will first be rank transformed for both baseline and changes from baseline separately. The Hodges-Lehman method will be used in this analysis concerning the median changes from baseline in mTSS score to show treatment differences and associated 95% confidence intervals (CI) for each active treatment group. Also, frequency and percentage of proportion for changes from baseline (criteria: <= 0.5/year) 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. For remission rates in DAS28-ESR, DAS28-CRP, SDAI, CDAI, and Boolean, similar analyses as primary analyses will be conducted.

The mean of variables (ACR components, DAS28-CRP, DAS28-ESR, CDAI and SDAI) and change from baseline - visit will be displayed by treatment group. ACR response rate - visit, including week 12, will be displayed by treatment group. Bar chart of each variables (ACR response rate, remission rate in DAS28-CRP, DAS28-ESR, CDAI, SDAI and Boolean) will be displayed at week 12 and week 24. Stacked bar chart of DAS28-CRP and DAS28-ESR by EULAR response criteria will be displayed at week 12 and week 24. Stacked bar chart of

category of DAS28-CRP and DAS28-ESR will be displayed at baseline and week 12 and week 24. Cumulative probability of the change from baseline in mTSS will be displayed at week 24.

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).

The Safety Analysis Set will be used for PK analyses.

<Table>

Individual serum concentration values of E6011 will be listed and summarized using descriptive statistics (n, mean, standard deviation, median, minimum and maximum) by dose and nominal time point. The data of time points in subject with interruption will not be included on calculation of summary statistics.

<Listing>

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

<Figure>

The individual serum E6011 concentration–time profile will be displayed in linear and semi–log scales using actual sampling times in the same graph by dose.

The mean serum concentrations of E6011 will be displayed using nominal blood sampling times with standard deviation in linear and semi–log scales by dose in the same graph.

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 Treatment 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.

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 12/24 weeks analysis, the AEs emerged until disposition on Week 12/24 are intended, but for patients who discontinued in Treatment Phase, 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.

5.9 Extension Phase Analyses

SAP for extension phase will be separately prepared and finalized before each database lock.

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:

- Regarding primary efficacy analysis, baseline CRP will be used as covariate instead of CRP at screening.

Additions in the planned analyses for protocol are as follows:

- Efficacy Analysis
  - frequency and percentage of proportion for the changes from baseline (criteria: <= 0.5/year) in mTSS will be summarized by treatment group.
  - frequency and percentage of each category (Remission, Low, Moderate, High) of DAS28-ESR, DAS28-CRP, CDAI and SDAI will be summarized by treatment group and visit in a shift table.
  - The mean of variables (ACR components, DAS28-CRP, DAS28-ESR, CDAI and SDAI) and change from baseline - visit will be displayed by treatment group.
  - ACR response rate - visit, including week 12, will be displayed by treatment group.
  - Bar chart of each variables (ACR response rate, remission rate in DAS28-CRP, DAS28-ESR, CDAI, SDAI and Boolean) will be displayed at week 12 and week 24.
  - Stacked bar chart of DAS28-CRP and DAS28-ESR by EULAR response criteria will be displayed at week 12 and week 24.
  - Stacked bar chart of category of DAS28-CRP and DAS28-ESR will be displayed at baseline and week 12 and week 24.
  - Cumulative probability of the change from baseline in mTSS will be displayed at week 24.
  - ACR50, ACR70 and mTSS will be summarized and analyzed by subgroups defined by section 5.2.1 for categorical variables.
  - Forest plot will be created by subgroups for comparison of response rate at primary efficacy endpoint and the changes from baseline at mTSS.
  - logistic regression model with treatment as continuous variable(placebo=0, 100mg=100, 200mg=200 and 400mg=400), and baseline CRP, RA Duration and Prior Use of Biologics Treatment as covariates to evaluate the dose response relationship.
  - rank ANCOVA for the change from baselin in mTSS score with both baseline mTSS score and changes from baseline in mTSS score will be rank transformed.
  - The Hodges-Lehman estimates for the median difference and associated 95% confidence intervals (CI) in change from baseline in mTSS score.

- Extent of Exposure
  - The extent of exposure to study drug will be characterized by number of injection and study medication compliance for each treatment group.

- Adverse Events
  - The incidence of follow TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT:
    - Serious TEAEs
    - TEAEs leading to study drug withdrawn
    - TEAEs leading to interruption of study drug
    - TEAEs leading to reduction from study drug
    - 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

- Laboratory Values
  - 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.
  - Each subject will be counted once in the laboratory parameter high and in the laboratory parameter low categories.
  - Laboratory results versus visit by treatment group will be displayed using box-plot.

- Other Analyses
  - Anti-JCV antibody test result listings will be provided.

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 24 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	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
Week 8 - Week 24 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 body weight, 12-lead ECG, Chest x-ray, Pregnancy test, Neurological findings, Blood CD4 positive cells, Autoantibody, Serum KL-6, β D glucan, Vasculitis marker tests, 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

Table 8.5 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 24 by 4 weeks	Date-time of first drug administration + X * 7 days (Week X)	Base date - 14 days <= < Base date + 14 days

Table 8.6 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

Table 8.7 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

Table 8.8 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

* Assessment date for mTSS is prior to Base date -7 <= <= Base date + 28, value of Week 24 is extrapolated as follow formula:

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

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

Keystone, E., et al., Radiographic, Clinical, and Functional Outcomes of Treatment With Adalimumab (a Human Anti-Tumor Necrosis Factor Monoclonal Antibody) in Patients With Active Rheumatoid Arthritis Receiving Concomitant Methotrexate erapy Keystone EC, Kavanaugh AF, Sharp JT, Tannenbaum H, Hua Y, Teoh LS, Fischko SA, and Chartash EK Arthritis Rheum.2004 May; 50(5): p. 1400-11

Keystone, E., et al., Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week,

phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Arthritis Rheum, 2008. 58(11): p. 3319-29.

Keystone, E.C., et al., Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis, 2009. 68(6): p. 789-96.

Cohen, S.B., et al., Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. Arthritis Rheum, 2006. 54(9): p. 2793- 806.

Smolen, J.S., et al., Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet, 2008. 371(9617): p. 987-97.

Smolen, J.S., et al., Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. Lancet, 2009. 374(9685): p. 210-21.

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.

SIGNATURE PAGE

Author:

PPD

20 Mar 2018
Date

Approval:

PPD

20 Mar 2018
Date

20 Mar 2018
Date

Neurology Business Group

PPD

20 MAR 2018
Date