## 16.1.9 Documentation of Statistical Methods


# STATISTICAL ANALYSIS PLAN

| | |
|---|---|
| **Study Protocol Number:** | E7080-J081-112 |
| **Study Protocol Title:** | Phase 1 Study of lenvatinib in Combination with Everolimus in Subjects with Unresectable Advanced or Metastatic Renal Cell Carcinoma |
| **Date:** | 08 Feb 2016 |
| **Version:** | Version 2.0 |

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# 2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Term |
|---|---|
| AE | adverse event |
| ATC | anatomical therapeutic chemical |
| AUC | area under the plasma concentration-time curve |
| BLQ | below the limit of quantification |
| BOR | best overall response |
| CI | confidence interval |
| CL/F | apparent total clearance following oral administration |
| $C_{max}$ | maximum observed plasma concentration |
| CR | complete response |
| CRF | case report form |
| CSR | clinical study report |
| $C_{ss,av}$ | average steady-state concentration |
| $C_{ss,max}$ | maximum observed plasma concentration at steady state |
| $C_{ss,min}$ | minimum observed plasma concentration at steady state |
| CTCAE | common toxicity criteria for adverse events |
| CV | coefficient of variation |
| DCR | disease control rate |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| LLOQ | lower limit of quantification |
| LLT | lower level term |
| LVEF | left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NE | not evaluable |
| ORR | objective response rate |
| PD | pharmacodynamic(s) / progressive disease |
| PFS | progression free survival |
| PK | pharmacokinetic(s) |
| PR | partial response |
| PS | performance status |
| PT | preferred term |
| PTF | peak-trough fluctuation |
| QD | quaque die |
| $R_{ac}$ | accumulation index |
| RCC | renal cell carcinoma |
| RECIST | response evaluation criteria in solid tumor |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation / stable disease |
| SI | système international |
| SOC | system organ class |

| Abbreviation | Term |
|---|---|
| $t_{1/2}$ | terminal elimination phase half-life |
| TEAE | treatment-emergent adverse event |
| TEMAV | treatment-emergent markedly abnormal laboratory value |
| TLGs | tables, listings and graphs |
| $t_{max}$ | time at which the highest drug concentration occurs |
| $t_{ss,max}$ | time at which the highest drug concentration occurs at steady state |
| $V_z/F$ | apparent volume of distribution at terminal phase |
| WHO DD | World Health Organization drug dictionary |
| $\lambda_z$ | terminal phase rate constant |

# 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 E7080-J081-112.

## 3.1 Study Objectives

### 3.1.1 Primary Objectives

- To investigate tolerability and safety of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic renal cell carcinoma (RCC).

### 3.1.2 Secondary Objectives

- To assess the pharmacokinetic (PK) of lenvatinib and everolimus
- To assess the preliminary anticancer effects of lenvatinib in combination with everolimus

## 3.2 Overall Study Design and Plan

### 3.2.1 Overall Study Design and Plan

This is a non-randomized, open-label, multi-center Phase 1 study (E7080-J081-112) of lenvatinib in combination with everolimus in subjects with unresectable advanced or metastatic RCC. Subjects will be enrolled in this study after informed consent is obtained and eligibility is confirmed.

One treatment cycle is defined as 28 days. Lenvatinib will be administered at starting dose of 18 mg in combination with everolimus at starting dose of 5 mg both orally once daily continuously. DLT will be observed during Cycle 1 (28 days following the initial dosing) to investigate tolerability and safety. Treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by sponsor.

A total of six subjects will be initially enrolled. Enrollment will be interrupted when DLT is observed in two or more subjects. Investigators and sponsor will review the nature and severity of all the DLTs and make a decision if enrollment of up to six subjects and further additions of three to six subjects are feasible and necessary. Suggestions by the independent medical advisor will be collected, if necessary.

The study sponsor and investigators will consider the nature and severity of DLT during Cycle 1 as well as unacceptable toxicities that cannot be managed with dose interruption and/or reduction and overall toxicities up to Cycle 2 on the evaluation of tolerability in

combination therapy. The suggestions by the independent medical advisor can be collected, if necessary.

Additional subjects maybe enrolled to the lower cohort (lenvatinib 14 mg and everolimus 5 mg once daily administration) in the following cases: over one-third of subjects experiences DLTs during Cycle 1, development of unacceptable, development of unmanageable toxicity with dose interruption and/or reduction up to Cycle 2, tolerability cannot be confirmed with dose level of lenvatinib 18 mg/everolimus 5 mg QD.

If a subject has no DLT but fails to receive ≥ 75% of the planned dosage of lenvatinib and/or everolimus up to Cycle 1 Day 21, due to a reason other than treatment related toxicity, this subject will not be included in the DLT assessment population and a new subject will be added for replacement.

Subjects will discontinue study treatment at the time of disease progression, development of unacceptable toxicity, withdrawal of consent, or qualifies any of the criteria described in 'Discontinuation for Individual Subjects' in protocol. The discontinuation assessments will occur within 7 days and off-treatment visit on 30$^{th}$ day after the final dose of study treatment.

DLT is defined as toxicity related to this combination therapy as indicated in Table 1.

**Table 1 Dose Limiting Toxicity**

| **Toxicity Category** | **Toxicity/CTCAE Grade** |
|---|---|
| Hematologic | • Grade 4 neutropenia lasting > 7 days<br>• Grade 3 febrile neutropenia (axillary temperature ≥ 38.5ºC and neutrophils < 1 x$10^3$/μL (< 1000/$mm^3$)<br>• Grade ≥ 3 thrombocytopenia lasting > 7 days or requiring blood transfusion |
| Non-hematologic toxicity | • Grade 3 non-hematologic toxicities lasting > 7 days except for the following:<br>➢ Clinically insignificant or transient abnormal laboratory findings<br>➢ Able to be controlled by maximal supportive therapy<br>Grade ≥ 3 hyperamylasemia or hyperlipasemia without clinical or other evidence of pancreatitis are not regarded as a DLT.<br>➢ Grade ≥ 3 nausea, vomiting or diarrhea lasting 7 days which persist despite maximal medical therapy<br>• Hypertension uncontrolled by medication<br>• Any thromboembolic event including cerebrovascular hemorrhage/events |
| Medication compliance | • Failure to administer ≥ 75% of the planned dosage of lenvatinib or everolimus as a result of treatment related toxicity |

Overall study design is presented in Figure 1.

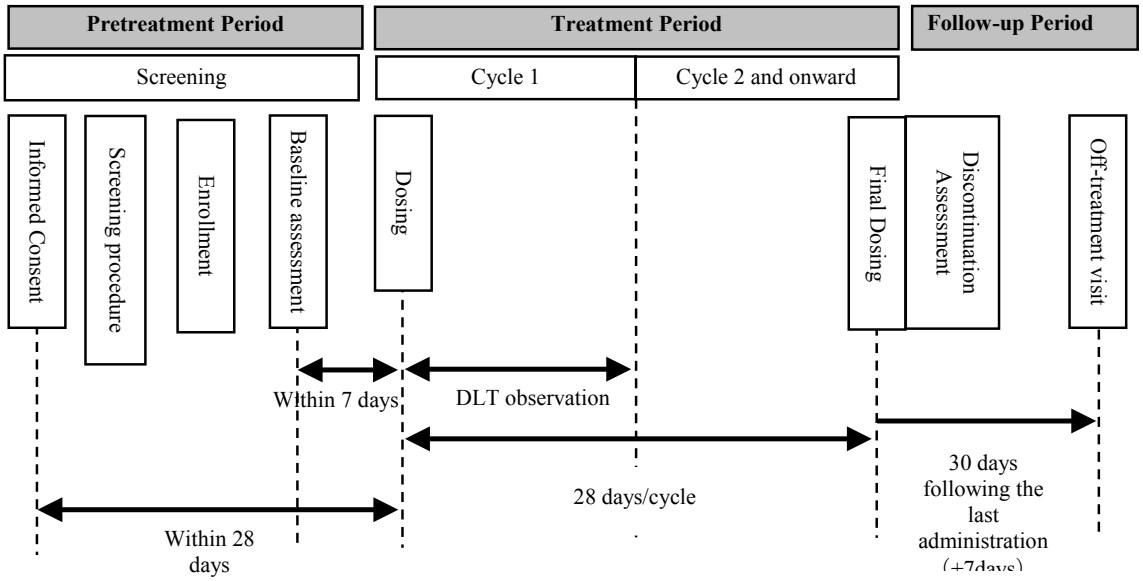


**Figure 1 Overview of Study Design**

### 3.2.2 Pretreatment Period

Pretreatment Period will consist of obtaining informed consent, screening procedures, subject enrollment and baseline assessments. Each subject must be explained the nature of the study and sign an informed consent form before any study-specific procedures are performed. Investigators must confirm the eligibility of each subject during screening procedures.

All Screening procedures are to be completed within 28 days prior to the Cycle 1 Day 1 and eligible subjects will be enrolled. All Baseline assessments are to be completed within 7 days prior to the Cycle 1 Day 1 and subjects' eligibility will be confirmed.

### 3.2.3 Treatment Period

Treatment Period will consist of two parts: Cycle 1 and following cycles.

One treatment cycle is defined as 28 days. Lenvatinib will be administered at starting dose of 18mg in combination with everolimus at starting dose of 5 mg both orally once daily continuously. Dose limiting toxicity (DLT) will be observed during Cycle 1 (28 days following the initial dosing) to investigate tolerability and safety. Treatment will continue until disease progression, development of unacceptable toxicity, subject requests to discontinue, withdrawal of consent, or study termination by sponsor.

Subjects will be required to stay at the clinic during Cycle 1 as a general rule, however, they may be allowed to go home temporarily, be discharged or receive treatment as outpatient per investigators' discretion.

### 3.2.4 Follow-up Period

Follow-up Period will include discontinuation assessments and off-treatment visit. Subject will discontinue study treatment if he/she qualifies for any of the criteria listed in Section 9.3.3.1. The discontinuation assessments will occur within 7 days and off-treatment visit on 30th day (+ 7 days) after final dose of study treatment.

# 4 DETERMINATION OF SAMPLE SIZE

The primary objective of this study is to investigate the tolerability and safety of lenvatinib in combination with everolimus. Hence neither clinical hypothesis nor judgment criteria are set, the sample size is not based on statistical consideration. The 6 to 12 subjects per initial dose group are considered to be adequate to obtain some preliminary data for the assessment of safety.

# 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.

All analysis will be performed for total subjects and by initial dose group ( if applicable ).

## 5.1 Study Endpoints

### 5.1.1 Primary Endpoint

- DLTs
- Safety endpoints ( adverse events, clinical laboratory parameters, vital signs, weight, 12-lead ECG, ECOG-PS and left ventricular ejection fraction [LVEF])

### 5.1.2 Secondary Endpoints

- PK parameters of lenvatinib and everolimus
- Best overall response (BOR), objective response rate (ORR), disease control rate (DCR), and percent change from baseline in the sum of the diameters of target lesions ( if applicable ).

#### 5.1.2.1 Pharmacokinetic (PK) Endpoints

PK parameters derived by non-compartmental analysis using plasma concentrations of lenvatinib and blood concentrations of everolimus which include, but are not limited to, are shown as below:

| | |
|---|---|
| $C_{max}$ | maximum observed concentration |
| $t_{max}$ | time at which the highest drug concentration occurs |
| $AUC_{(0-t)}$ | area under the concentration-time curve from zero time to time of last quantifiable concentration |
| $AUC_{(0-ti)}$ | area under the concentration-time curve from zero (pre-dose) to a given sampling time (ti) |
| $AUC_{(0-inf)}$ | area under the concentration-time curve from zero time extrapolated to infinite time |
| $t_{1/2}$ | terminal elimination phase half-life |
| CL/F | apparent total clearance following oral dosing |
| $V_z$/F | apparent volume of distribution at terminal phase |

| | |
|---|---|
| $C_{ss,max}$ | maximum observed concentration at steady state |
| $C_{ss,min}$ | minimum observed concentration at steady state |
| $t_{ss,max}$ | time at which the highest drug concentration occurs at steady state |
| $AUC_{(0-\tau)}$ | area under the concentration-time curve over the dosing interval |
| $CL_{ss}/F$ | apparent total clearance following oral administration at steady state |
| $C_{ss,av}$ | average steady-state concentration |
| $R_{ac}(C_{max})$, $R_{ac}(AUC)$ | accumulation index |
| PTF ratio | peak-trough fluctuation ratio |

## 5.2 Study Subjects

### 5.2.1 Definitions of Analysis Sets

DLT Analysis Set is the group of subjects who have completed treatment Cycle 1 without major protocol deviation with at least 75% of treatment compliance and were assessed for DLT, and subjects who have experienced DLT during Cycle 1. Subjects with less than 75% treatment compliance to lenvatinib or everolimus due to a reason other than toxicity up to Cycle 1 Day 28 will not be included in this analysis set.

Safety Analysis Set/Efficacy Analysis Set is the group of subjects who received at least 1 dose of lenvatinib

Pharmacokinetic Analysis Set is the group of subjects who received at least 1 dose of lenvatinib and had sufficient PK data to derive at least 1 PK parameter.

The number of subjects enrolled, the number and the percentage of subjects included in each analysis set will be presented. Subject data listings will be provided.

### 5.2.2 Subject Disposition

Screening subjects table will include the number of subjects who are enrolled (i.e., subjects who signed informed consent), failed screening, and the primary reason for screen failures. Subject disposition table will include the number of subjects who are treated, completed/discontinued the study. Similarly, the number of subjects who completed/discontinued the study treatment, and the primary reason for the study treatment discontinuation will also be summarized.

A subject who completed the study is defined as whose DLT assessment has been completed adequately. A subject who completed the study treatment is defined as who discontinued study treatment due to radiological or disease progression or were on-going at the study cut-off.

Subject data listings will be provided.

### 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. All protocol deviations identified according to study entry criteria and during treatment will be 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 Pharmacokinetic Analysis Set will be summarized using summary statistics. Continuous demographic and baseline variables include age, height, and weight; categorical variables include sex, race, ethnicity, ECOG PS, NYHA, diagnostic information (metastatic sites, number of metastatic site, histological type, time since RCC diagnosis to first dose of study treatment, TNM categories and stage), prior therapy (nephrectomy [yes or no], radiotherapy [yes or no], sites of radiotherapy, anti-cancer medication [yes or no], type of anti-cancer medication [axitinib, everolimus, and so on.],number of VEGF targteted therapy [1 regimen, 2regimens, 3 regimens]and other therapies [yes or no]), treatment duration and reason for discontinuation of last anti-cancer medication, hypertension (yes or no), and creatinine clearance ( >= LLN, < LLN and >= 60 mL/min, and 60-40 mL/min).

The categories for metastatic site, site of previous radiotherapy, type of prior anti-cancer medication depend on actual data.

Subject data listings 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). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by Anatomical Therapeutic Chemical (ATC) class (anatomical class, pharmacological class, and pharmacological sub-class) and WHO DD preferred term. Prior medications are defined as medications that stopped before the first dose of study treatment. Concomitant medications are defined as medications that (1) started before the first dose of study treatment and were continuing at the time of the first dose of study treatment, or (2) started on or after the date of the first dose of study treatment up to 30 days after last dose. Medications received after 30 days of last dose will be considered as post treatment medications. All medications will be presented in subject data listings.

### 5.2.6 Treatment Compliance

Treatment related protocol deviations will be presented in CSR as provided in section “5.2.3 Protocol Deviations “.

## 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 adjustment for covariates will be performed.

### 5.3.3 Multiple Comparisons/Multiplicity

No statistical comparison is planned in this study.

### 5.3.4 Examination of Subgroups

No subgroup analysis is planned in this study.

### 5.3.5 Handling of Missing Data, Dropouts, and Outliers

No imputation will be performed for missing data.

### 5.3.6 Other Considerations

Not applicable.

## 5.4 Efficacy Analyses

### 5.4.1 Primary Efficacy Analysis

Since this study is phase 1, primary endpoint is not defined.

Efficacy analyses will be based on the Efficacy Analysis Set. Based on the tumor assessments according to response evaluation criteria in solid tumor (RECIST) 1.1, BOR will be summarized. BOR are complete response (CR), partial response (PR) stable disease (SD), progression of disease (PD) and not evaluable (NE). ORR, DCR and their corresponding 2-sided 95% confidence intervals (CIs) will be calculated using Cropper-Pearson's exact method. ORR is defined as the proportion of subjects who achieved BOR of CR or PR. DCR is defined as the proportion of subjects who achieved BOR of CR, PR or SD. Subjects with non-target disease only will be assigned to SD category if the BOR is non-CR/non-PD. SD has to be achieved at ≥ 7 weeks after first dose. CR and PR do not have to be confirmed at ≥ 4 weeks later assessment. If applicable, a spaghetti plot will be presented for the percent changes from baseline in the sum of the diameters of target lesions by subject.

Median, Q1, and Q3 for progression free survival (PFS) with its 95% CI will be evaluated. The number (percentage) of subjects with event/censored will be summarized. The PFS rate with its 95% CI at 4-month, 8-month and 12-month will be calculated using Kaplan-Meier

product limit estimates, if applicable. Kaplan-Meier plots with the number of subjects at risk will be presented for PFS.

PFS is defined as the time from the date of first dose to the date of first documented PD or death due to any cause (whichever occurs first). For subjects who do not have an event (documented PD or death from any cause), PFS will be censored. Censoring rules for PFS are shown in Table 2.

PFS (days) = Date of first documented PD/ death/ Censored date – Date of first dose + 1.

**Table 2 Censoring Rule of PFS**

| Situation | End Date | Censor/Event |
|---|---|---|
| Documented PD during the study | Date of the first assessment of the series of the tests that determined PD | Event[a] |
| Death during the study before PD | Date of death | Event[a] |
| No baseline or unreadable baseline tumor assessments | Date of first dose | Censor |
| Treatment discontinuation for other than PD or death, and no postbaseline tumor assessments | Date of first dose | Censor |
| Treatment discontinuation for other than PD or death with postbaseline tumor assessments | Date of last adequate[b] tumor assessment | Censor |
| New anticancer treatment started prior to PD or death | Date of last adequate[b] tumor assessment prior to or on date of new treatment | Censor |
| PD or death after two or more missed tumor assessments[c] | Date of last adequate[b] tumor assessment before missed tumor assessment | Censor |
| Subjects still on study without PD or death as of data cut off | Date of last adequate[b] tumor assessment prior to or on date of data cut off | Censor |

a: Earliest date among the two dates will be used in calculating the PFS.
b: Adequate tumor assessment is radiologic assessment of CR, PR, SD, non-CR/non-PD, or PD
c: Window of two or more missed tumor assessment is defined as duration between the last adequate tumor assessment and PD or death is ≥ 127 days, for scan schedule of every 8 weeks ( ±7 days)

Duration of response (DOR) is defined as the time from the date of first evaluation of PR or CR to the date of first documented PD or death due to any cause (whichever occurs first). DOR will be calculated for each subject and shown in only subject data listings. Only subjects who achieved at least one PR or CR will be include in calculation of DOR. For subjects who do not have an event (documented PD or death from any cause), DOR will be censored. Censoring rules for DOR are shown in Table 3.

**Table 3 Censoring Rules of DOR**

| Situation | End Date | Censor/Event |
|---|---|---|
| Documented PD during the study | Date of the first assessment of the series of the tests that determined PD | Event[a] |
| Death during the study before PD | Date of death | Event[a] |
| Treatment discontinuation for other than PD or death with postbaseline tumor assessments | Date of last adequate[b] tumor assessment | Censor |
| New anticancer treatment started prior to PD or death | Date of last adequate[b] tumor assessment prior to or on date of new treatment | Censor |
| PD or death after two or more missed tumor assessments[c] | Date of last adequate[b] tumor assessment before missed tumor assessment | Censor |
| Subjects still on study without PD or death as of data cut off | Date of last adequate[b] tumor assessment prior to or on date of data cut off | Censor |

a: Earliest date among the two dates will be used in calculating the DOR.
b: Adequate tumor assessment is radiologic assessment of CR, PR, SD, non-CR/non-PD, or PD
c: Window of two or more missed tumor assessment is defined as duration between the last adequate tumor assessment and PD or death is ≥ 127 days, for scan schedule of every 8 weeks ( ±7 days)

DOR (days) = Date of first documented PD/ death/ Censored date – Date of first evaluation of PR or CR + 1.

Subject data listings will be provided.

### 5.4.2 Secondary Efficacy Analysis

Not applicable.

### 5.4.3 Other Efficacy Analysis

Not applicable.

## 5.5 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

### 5.5.1 Pharmacokinetic Analyses

The Safety Analysis Set will be used for individual lenvatinib plasma concentrations and everolimus blood concentrations listings. The PK Analysis Set will be used for the summaries of lenvatinib plasma concentrations and everolimus blood concentrations and for summaries and listings of PK parameters.

#### 5.5.1.1 Plasma or Blood Concentration and its PK Parameter Analysis

<Concentration>

Plasma concentration values for lenvatinib and blood concentration values for everolimus will be summarized using summary statistics (n, mean, standard deviation [SD], median, minimum [min] and maximum [max]) by nominal time point.

Plasma concentrations of lenvatinib and blood concentrations of everolimus will be listed for each subject by actual sampling time.

<PK Parameter>

PK parameters will be derived by non-compartmental analysis using WinNonlin software (version 6.2.1 or later) according to SWP-SOCS-006.02.

The following pharmacokinetic parameters for lenvatinib and everolimus will be calculated: $C_{max}$ ,$t_{max}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}ti)}$, $AUC_{(0\text{-}inf)}$, $t_{1/2}$, CL/F, $V_z$/F, $C_{ss,max}$, $C_{ss,min}$, $t_{ss,max}$, $AUC_{(0\text{-}\tau)}$, $CL_{ss}$/F, $C_{ss,av}$, $R_{ac}(C_{max})$, $R_{ac}$(AUC), PTF ratio.

Other PK parameters may be calculated as appropriate.

Summary statistics will be tabulated for the PK parameters of lenvatinib and everolimus. Summary statistics (n, mean, SD, median, min, and max) will be presented for all parameters (apart from $t_{max}$ where mean and SD are not required). In addition, geometric mean and %CV will also be presented for all parameters apart from $t_{max}$.

PK parameters of lenvatinib and everolimus for each subject will be listed.

#### 5.5.1.2 Pharmacokinetic Data Figures

The linear and semi-log plots of plasma concentration for lenvatinib and blood concentration for everolimus versus actual time will be displayed by individual subjects. The actual time will be plotted on the X axis and the concentrations of lenvatinib and everolimus will be plotted on the Y axis.

The linear and semi-log mean (+SD) plots of lenvatinib plasma concentration versus nominal time will be displayed. The nominal time will be plotted on the X axis and the mean (+SD) will be plotted on the Y axis on the same graph by visit (Cycle 1 Day 1 and Cycle1 Day 15).

The linear and semi-log mean (+SD) plots of everolimus blood concentration versus nominal time will be displayed. The nominal time will be plotted on the X axis and the mean (+SD) will be plotted on the Y axis on the same graph by visit (Cycle 1 Day 1 and Cycle1 Day 15).

### 5.5.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Not applicable.

## 5.6 Safety Analyses

The analysis for tolerability will be performed on the DLT Analysis Set. The Safety Analysis Set will be used for all other safety analyses. Safety data will be summarized on an "as treated" basis using summary statistics (e.g., n, mean, SD, median, Q1, Q3, minimum, maximum for continuous variables; number [percentage] for categorical variables). Safety variables include treatment-emergent adverse events (TEAEs), clinical laboratory parameters, vital signs, weight, LVEF, 12-lead ECG results, and ECOG PS. Study Day 1 for all safety analyses will be defined as the date of the first dose of lenvatinib.

### 5.6.1 Extent of Exposure

For lenvatinib and everolimus, the number of cycles, the cumulative number of cycles, duration of treatment per subject, number of subject months, total number of doses per subject, total doses per subject, dose intensity per subject, and relative dose intensity per subject will be summarized, separately. The calculations are below:

- Number of cycles = The last cycle with at least one study treatment dosing
- Duration of treatment (days) = Last dosing date – first dosing date + 1
- Duration of treatment (months) = (Last dosing date – first dosing date + 1) / (365.25/12)
- Number of subject months = (Total of Durations of treatment per subject) / (365.25/12)
- Total number of doses = Sum of days with study treatment dosing
- Total doses (mg) = Sum of all the actual dose
- Dose intensity (mg/days) = Total doses / Duration of treatment
- Relative dose intensity (%) = 100 × Dose intensity / defined starting dose for each dose group

The number (percentage) of subjects who experienced dose interruption, dose reduction of lenvatinib or everolimus will be provided. In addition, the cycle of first dose interruption, dose reduction, the number of subjects (percentage) with dose interruption, dose reduction by

cycle, the frequency of dose interruption, dose reduction during treatment of lenvatinib or everolimus will also be summarized.

Subject data listings will be provided.

### 5.6.2 Adverse Events

**DLTs**

The number (percentage) of subjects who experienced DLT will be summarized.

**Adverse events (AE)**

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 17.1 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database.

A treatment-emergent adverse event (TEAE), defined in "8.1 General Data Handling ", will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by MedDRA SOC and PT. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will be summarized by highest grade according to common toxicity criteria for adverse events (CTCAE) ver. 4.03. The number (percentage) of subjects with TEAEs with CTCAE grade 3 or above will also be summarized by highest grade.

The number (percentage) of subjects with treatment-related TEAEs will be summarized by MedDRA SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to lenvatinib or everolimus. The number (percentage) of subjects with treatment-related TEAEs will be summarized by highest CTCAE grade. The number (percentage) of subjects with treatment-related TEAEs with CTCAE grade 3 or above will also be summarized by highest grade.

The number (percentage) of subjects with DLTs will be summarized by MedDRA SOC and PT. All DLTs will be presented in subject data listings.

The number (percentage) of subjects with TEAEs leading to death, treatment-emergent serious adverse events (SAEs) will be summarized by MedDRA SOC and PT. The number (percentage) of subjects with treatment-related TEAEs leading to death, treatment-related treatment-emergent SAEs will also be summarized by MedDRA SOC and PT. A subject data listing of all serious adverse events, AEs leading to death will be provided.

The number (percentage) of subjects with TEAEs leading to dose reduction of lenvatinib and/or everolimus (A TEAE leading to discontinuation of only everolimus will be counted as a TEAE leading to dose reduction of lenvatinib and/or everolimus in this table), and dose interruption of lenvatinib and/or everolimus will be summarized by MedDRA SOC and PT.

As well as TEAEs, the number (percentage) of subjects with treatment-related TEAEs leading to dose reduction of lenvatinib and/or everolimus (A treatment-related TEAE leading to discontinuation of only everolimus will be counted as a treatment-related TEAE leading to dose reduction of lenvatinib and/or everolimus), and dose interruption of lenvatinib and/or everolimus will be summarized by MedDRA SOC and PT.

The number (percentage) of subjects with TEAEs leading to discontinuation from lenvatinib, dose reduction of lenvatinib, and dose interruption of lenvatinib, discontinuation from everolimus, dose reduction of everolimus, and dose interruption of everolimus will also be summarized by MedDRA SOC and PT.

In addition to TEAEs, the number (percentage) of subjects with treatment-related TEAEs leading to discontinuation from lenvatinib, dose reduction of lenvatinib, and dose interruption of lenvatinib will be summarized by MedDRA SOC and PT. For these analyses, treatment-related TEAEs include those events considered by the investigator to be related to lenvatinib. The number (percentage) of subjects with treatment-related TEAEs leading to discontinuation from everolimus, dose reduction of everolimus, and dose interruption of everolimus will also be summarized by MedDRA SOC and PT. For these analyses, treatment-related TEAEs include those events considered by the investigator to be related to everolimus.

A subject data listing of AEs leading to discontinuation from study treatment, dose reduction and dose interruption will be provided.

An overview table, including the incidence of and the number of subjects with TEAEs, treatment-related TEAEs, TEAEs with CTCAE grade 3 or above, treatment-emergent SAEs, deaths, and those TEAEs leading to treatment discontinuation, dose reduction, or dose interruption, and corresponding treatment-related TEAEs in above categories will be provided.

### 5.6.3 Laboratory Values

Laboratory results will be summarized using Système International (SI) units. For all quantitative parameters listed in protocol Section 9.5.1.3.5, the actual value and the change from baseline to each postbaseline visit, the highest and lowest postbaseline values will be summarized by visit using summary statistics. Qualitative parameters will be summarized by number and percentage of subjects, and changes from baseline to each postbaseline visit and the highest postbaseline result 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 is below (L), within (N), or above (H) the laboratory parameter's reference range. The result of LHN classification will be provided in a subject data listing.

Laboratory parameters will be graded by CTCAE ver. 4.03 in "13 APPENDICES". Changes from CTCAE grade at baseline to each postbaseline visit and worst postbaseline will be reported using shift tables. As for thyroid stimulation hormone, values at baseline and worst postbaseline will be categorized into ≤0.5, >0.5 – 2.0, >2.0 – 5.5, >5.5 (μIU/mL) and summarized.

CTCAE ver. 4.03 will be used to identify subjects with Treatment-emergent markedly abnormal laboratory value (TEMAV). TEMAV is defined as a value with postbaseline value with a grade increase from baseline by 2 or higher. (i.e., Increasing grade 0 to 2 or higher, grade 1 to 3 or higher, grade 2 to 4 or 5.) For phosphate, TEMAV is defined as a value with postbaseline value with a grade increase from baseline by 3 or higher. The number (percentage) of subjects with TEMAV (markedly abnormal high/low) will be summarized by visit. 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.

### 5.6.4 Vital Signs

Summary statistics for vital signs parameters (diastolic and systolic blood pressure, pulse, and temperature), and weight and changes from baseline will be presented by time point.

Subject data listings will be provided.

### 5.6.5 Electrocardiograms

The results of ECG assessments performed at each visit will be evaluated. Summary statistics for ECG parameters (Heart Rate, RR, PR, QRS, QT, and QTcF) and changes from baseline will be presented by time point.

Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to each visit.

In addition, the number (percentage) of subjects who met below criteria at least once in QTcF will be presented:

Absolute QTcF interval prolongation:

- QTcF interval >450 ms
- QTcF interval >480 ms
- QTcF interval >500 ms

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 ms

- QTcF interval increases from baseline >60 ms

Subject data listings will be provided.

### 5.6.6 Other Safety Analyses

**LVEF**

LVEF and change from baseline will be summarized at each time point.

The result of LVEF will be categorized into hyperdynamic (>70 %), normal (≥50 – 70%), mild dysfunction (≥40 – 50%), moderate dysfunction (≥30 – 40%), Severe dysfunction (<30%), and shift from baseline to worst postbaseline will be reported using shift table with below levels.

- Hyperdynamic/Normal
- Mild Dysfunction
- Modetate Dysfunction
- Severe Dysfunction

Subject data listings will be provided.

**ECOG PS**

ECOG PS will be summarized by scale at each visit and by highest postbaseline scale.

Subject data listings will be provided.

## 5.7 Other Analyses

Not applicable.

## 5.8 Exploratory Analyses

No exploratory analyses are planned for this study.

# 6 INTERIM ANALYSES

No interim analysis is planned for this study.

# 7 CHANGES IN THE PLANNED ANALYSES

The below analyses were added from protocol to establish analyses for CSR:

- The items of demographic and other baseline characteristics were detailed.
- The analysis for dose interruption and dose reduction were added.
- The analysis for PFS and calculation of DOR were added.
- A waterfall plot for the percent changes from baseline in the sum of the diameters of target lesions was replaced to spaghetti plot.
- An overview table of TEAEs was added.
- The analysis for TEAEs and treatment-related TEAEs were enhanced.
- The shift table of laboratory values based on CTCAE grades was added.
- The analysis for TEMAV and its definition were added.
- The categorical analysis for LVEF was added.

The below analysis was deleted from protocol

- The analysis for time course change in tumor marker was deleted as the amount of data is not sufficient.

# 8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The data will be handled as follows. The sponsor will determine how to handle all data prior to data base lock.

## 8.1 General Data Handling

**Baseline**

Baseline is defined as the last non-missing value observed prior to the first dose of study treatment for a given parameter.

**Change from Baseline, Percent Change from Baseline**

Change from baseline is defined as post-baseline 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.

**Handling of Missing data**

No imputation will be performed for missing data.

**Handling of data not within specified periods or within the follow-up period**

All the safety parameters will be used for summary statistic tabulation, except when it is irrelevant like the situation that tests scheduled to be conducted before administration of the investigational drug are actually conducted after its administration. Data obtained not within the time window specified in the protocol will be handled as missing data for summary tables by visit. Data obtained after the follow-up assessment, which is scheduled for 30 days after the last administration of study treatment, will not be used for analysis.

**Handling of multiple data**

In the case of multiple observations within the specified time window of a specific analysis visit, the observation closest in date and time to the target visit day will be used in summary tables by visit. If two or more observations have the same distance to the target visit day, the one that has the highest CTCAE grade or is furthest away from the normal range will be used for safety analyses. If there are still multiple observations, the handling will be considered individually.

**Handling of below lower quantification values in laboratory results**

In the cases of laboratory result contains below lower quantification (BLQ) value, it will be replaced to the lower limit of quantification (LLOQ) for summarizing tables.

**Calculation of creatinine clearance**

To calculate a creatinine clearance (mL/min), the Cockcroft & Cault formula will be used.

Males: ((140 – age (years))×weight(kg)) / ( Creatinine (serum:mg/dL)×72)

Females: ((140 – age (years))×weight(kg) ×0.85) / (Creatinine (serum:mg/dL)×72)

**Treatment-emergent adverse event**

A TEAE is defined as an AE that emerged during treatment, having been absent at pretreatment or

- Reemerged during treatment, having been present at pretreatment but stopped before treatment, or
- Worsened in severity during treatment relative to the pretreatment state, when the AE was continuous.

All the adverse events will be considered as TEAE if the AE onset date was on or after the first dose of lenvatinib up to 30 days after last dose of lenvatinib.

## 8.2 Pharmacokinetic Data Handling

### 8.2.1 Lower Limit of Quantification of lenvatinib Plasma Concentration and Everolimus Blood and Concentration

The LLOQ of lenvatinib plasma concentrations is 0.250 ng/mL

The LLOQ of everolimus blood concentrations is 0.300 ng/mL

### 8.2.2 BLQ Handling for Calculation of PK Parameters

While calculating PK parameters in WinNonlin, BLQ values will be handled according to SWP-SOCS-006.02, for non-compartmental pharmacokinetic analysis.

### 8.2.3 BLQ Handling for Developing Concentration-Time Profiles

When developing individual concentration-time profiles, BLQ values will be handled according to SWP-SOCS-006.02 for non-compartmental pharmacokinetic analysis.

### 8.2.4 Handling of Anomalous Concentration Values

The handling of anomalous concentration values will follow the guidance in the SWP for non-compartmental pharmacokinetic analysis (SWP-SOCS-006.02).

### 8.2.5 General Rules for Presentation of Drug Concentrations and PK Parameters

When presenting individual/raw (raw, hereafter) values and summary statistics, the following rule will be applied: for drug concentrations and concentration-dependent pharmacokinetic parameters, all summary statistics (mean, median, geometric mean, SD and coefficient variation (CV) ) will have 3 significant digits. For $t_{max}$, raw values and their median are shown in fixed 2 decimal places.

| Variable | Unit | N | Digit rule | Raw/ Minimum/ Maximum | Mean Median | SD | Geometric Mean | CV (%) |
|---|---|---|---|---|---|---|---|---|
| drug concentration | ng/mL | X | Significant digits | 3 | 3 | 3 | - | - |
| $C_{max}$, $C_{ss,max}$, $C_{min}$, $C_{ss,av}$ | ng/mL | X | Significant digits | 3 | 3 | 3 | 3 | 3 |
| $t_{max,}$ $t_{ss,max}$ | h | X | Fixed decimal places | 2 | 3 | - | - | - |
| $\lambda_z$(C1D1&D15) | 1/h | X | Significant digits | 3 (Listing only) | - | - | - | - |
| $t_{1/2}$(C1D1&D15) | h | X | Significant digits | 3 | 3 | 3 | 3 | 3 |
| $AUC_{(0-t)}$, $AUC_{(0-inf)}$, $AUC_{(0-ti)}$ $AUC_{(0-\tau)}$ | ng•h/mL | X | Significant digits | 3 | 3 | 3 | 3 | 3 |
| CL/F, $CL_{ss}$/F | L/h | X | Significant digits | 3 | 3 | 3 | 3 | 3 |
| $V_z$/F(C1D1&D15) | L | X | Significant digits | 3 | 3 | 3 | 3 | 3 |
| $R_{ac}$ | | X | Significant digits | 3 | 3 | 3 | 3 | 3 |
| PTF ratio | | X | Significant digits | 3 | 3 | 3 | 3 | 3 |

Mean, SD, geometric mean and CV will not be calculated for $t_{max}$, $t_{ss,max}$.

CV(%)= sqrt(exp[SD**2 of log transformed data]-1)*100

**NOTE**

1. The following parameters are reported in the CSR, but appear in Listings only. They are important information to confirm that individual $t_{1/2}$ and its related parameters such as$AUC_{(0-inf)}$ are appropriately derived and allow those PK parameters to be reproduced when necessary.
   a. Time points used for estimation of $\lambda_z$ (lower and upper)
   b. Number of the time points used for $\lambda_z$
   c. Adjusted regression coefficient ($R_{2adj}$)

In Listings, a) are shown in same digits as actual sampling time after dosing used for calculation of PK parameters. For b), integer number is used in Listings. For c), significant 3 digits are used in Listing.

# 9 PROGRAMMING SPECIFICATIONS

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

# 10 STATISTICAL SOFTWARE

All statistical Analyses will be conducted by Takumi Information Technology, using validated standard programs or double programming. For analyses needed in data review, single programming will be used.

All statistical analyses will be performed using WinNonlin version 6.2.1 or later SAS v 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

- FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, May 2007 [internet; cited 3 March 2011] Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf.

# 13 APPENDICES

## 13.1 National Institute for Health: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03

National Cancer Institute (NCI) Cancer therapy evaluation program Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 May 2009 (v4.03 June 2010) is available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_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.

| **Lab Parameter** | **NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units** | | | | |
|---|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| **Hematology** | | | | | |
| Hemoglobin (low) | 100 - <LLN (g/L) | 80 - <100 (g/L) | <80 (g/L) | __ | Death |
| Hemoglobin (high) | Increase in >0 - 20 g/L above ULN (i.e., Increase in >0 - 2 gm/dL above ULN) or above baseline if baseline is above ULN | Increase in >20 - 40 g/L above ULN (i.e., Increase in >2 - 4 gm/dL above ULN) or above baseline if baseline is above ULN | Increase in >40 g/L above ULN (i.e., Increase in >4 gm/dL above ULN) or above baseline if baseline is above ULN | __ | __ |
| Platelet Count (PLT) (low) | 75 - <LLN (x 10^9/L) | 50 - <75 (x 10^9/L) | 25 - <50 (x 10^9/L) | <25 (x 10^9/L) | __ |
| White Blood Cell Count (WBC) (low) | 3 - <LLN (x 10^9/L) | 2 - <3 (x 10^9/L) | 1 - <2 (x 10^9/L) | <1 (x 10^9/L) | __ |
| White Blood Cell Count (WBC) (high) | __ | __ | >100 x 10^9/L (i.e., >100,000/mm^3) | __ | Death |
| Lymphocytes (low) | 0.8 - <LLN (x 10^9/L) | 0.5 - <0.8 (x 10^9/L) | 0.2 - <0.5 (x 10^9/L) | <0.2 (x 10^9/L) | __ |
| Lymphocytes (high) | __ | >4 - 20 (x 10^9/L) (i.e., >4,000 - 20,000/mm^3) | >20 (x 10^9/L) (i.e., > 20,000/mm^3) | __ | __ |

| Lab Parameter | NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units | | | | |
|---|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Neutrophils (low) | 1.5 - <LLN (x 10^9/L) | 1 - <1.5 (x 10^9/L) | 0.5 - <1 (x 10^9/L) | <0.5 (x 10^9/L) | __ |
| **Blood Coagulation** | | | | | |
| INR (high) | >1 - 1.5 x ULN | >1.5 - 2.5 x ULN | >2.5 x ULN | __ | __ |
| **Blood Chemistry** | | | | | |
| Albumin (low) | 30 - <LLN (g/L) | 20 - <30 (g/L) | <20 (g/L) | __ | Death |
| Alkaline Phosphatase (ALP) (high) | >ULN - 2.5 x ULN | >2.5 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN | __ |
| ALT (SGPT) (high) | >ULN - 3 x ULN | >3 - 5.0 x ULN | >5.0 - 20.0 x ULN | >20.0 x ULN | __ |
| AST (SGOT) (high) | >ULN - 3 x ULN | >3 - 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 | __ |
| Calcium, serum-low (hypocalcemia) | 2.0 - <LLN (mmol/L) (i.e., 8.0 mg/dL - <LLN) * | 1.75 - <2 (mmol/L) (i.e., 7.0 - <8.0 mg/dL) * | 1.5 - <1.75 (mmol/L) (i.e., 6.0 - <7.0 mg/dL) * | <1.5 (mmol/L) (i.e., <6.0 mg/dL) * | Death |
| Calcium, serum-high (hypercalcemia) | >ULN – 2.9 (mmol/L) (i.e., >ULN – 11.5 mg/dL) * | >2.9 – 3.1 (mmol/L) (i.e., >11.5 – 12.5 mg/dL) * | >3.1 – 3.4 (mmol/L) (i.e., >12.5 – 13.5 mg/dL) * | >3.4 (mmol/L) (i.e., >13.5 mg/dL) * | Death |
| Cholesterol (high) | >ULN -7.75 mmol/L | >7.75 -10.34 mmol/L | >10.34 -12.92 mmol/L | >12.92 mmol/L | __ |
| CPK (high) | >ULN – 2.5 x ULN | >2.5 x ULN – 5 x ULN | >5 x ULN – 10 x ULN | >10 x ULN | __ |
| 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 | __ |
| Glucose, serum-low (hypoglycemia) | 3 - <LLN (mmol/L) | 2.2 - <3 (mmol/L) | 1.7 - <2.2 (mmol/L) | <1.7 (mmol/L) | Death |
| Glucose, serum-high (hyperglycemia) | ULN – 8.9 (mmol/L) | >8.9 – 13.9 (mmol/L) | >13.9 – 27.8 (mmol/L) | >27.8 (mmol/L) | Death |

| Lab Parameter | NCI Common Terminology Criteria for Adverse Events (CTCAE) - SI Units | | | | |
|---|---|---|---|---|---|
| | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
| Lipase (high) | >ULN - 1.5 x ULN | >1.5 - 2.0 x ULN | >2.0 - 5.0 x ULN | >5.0 x ULN | __ |
| Magnesium (low) | <LLN - 0.5 (mmol/L) | <0.5 - 0.4 (mmol/L) | <0.4 - 0.3 (mmol/L) | <0.3 (mmol/L) | Death |
| Magnesium (high) | >ULN - 1.23 (mmol/L) | __ | >1.23 - 3.30 (mmol/L) | >3.30 (mmol/L) | Death |
| Triglyceride (hypertriglyceridemia) (high) | 1.71 - 3.42 (mmol/L) | >3.42 - 5.7 (mmol/L) | >5.7 - 11.4 (mmol/L) | >11.4 (mmol/L) | Death |
| Phosphate, serum-low (hypophosphatemia) | 0.8 - <LLN (mmol/L) | 0.6 - <0.8 (mmol/L) | 0.3 - <0.6 (mmol/L) | <0.3 (mmol/L) | Death |
| Potassium, serum-low (hypokalemia) | 3.0 - <LLN (mmol/L) | __ | 2.5 - <3.0 (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, serum-low (hyponatremia) | 130 - <LLN (mmol/L) | __ | 120 - <130 (mmol/L) | <120 (mmol/L) | Death |
| Sodium, serum-high (hypernatremia) | >ULN - 150 (mmol/L) | >150 - 155 (mmol/L) | >155 - 160 (mmol/L) | >160 (mmol/L) | Death |
| **Urinalysis** | | | | | |
| Proteinuria (high) | 1+ proteinuria; urinary protein <1.0 g/24 hrs | ≥2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs | urinary protein >=3.5 g/24 hrs | __ | __ |

* 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]

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