NCT03001011

STATISTICAL ANALYSIS PLAN

A randomized, double blind, parallel group study for assessing the efficacy and safety of Renvela® tablets for the treatment of hyperphosphatemia in patients with chronic kidney disease not on dialysis versus placebo (RECOVER Study)

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Renvela® /sevelamer carbonate

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ATC:	anatomic category
BP:	blood pressure
CKD:	Chronic Kidney Disease
DBTP:	double blind treatment period
eCRF:	electronic case report form
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
IMP:	investigational medicinal product
iPTH:	intact parathyroid hormone
IVRS:	interactive voice response system
IWRS:	interactive web response system
LDL-C:	low density lipoprotein cholesterol
LLT:	Low level term
LOCF:	last observation carried forward
MedDRA:	Medical Dictionary for Regulatory Activities
mITT:	modified Intent To Treat
PCSA:	potentially clinically significant abnormality
PT:	preferred term
Q1:	first quartile
Q3:	third quartile
SAE:	serious adverse event
SD:	standard deviation
SOC:	system organ class
TEAE:	treatment emergent adverse event
TID:	3 times per day

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a phase III, multi-center, randomized, double blind, placebo-controlled, balanced (1:1, Renvela: placebo), parallel-group study to evaluate the efficacy and safety of Renvela versus placebo in hyperphosphatemic CKD patients not on dialysis in China.

Eligible patients who are taking a phosphate binder at screening visit will enter a 2-week phosphate binder washout period. Eligible patients who are not taking a phosphate binder at screening visit will proceed directly to the start of the 8-week treatment period (Day 1).

Randomization will be stratified according to baseline serum phosphorus (≥5.5 – 6.0 mg/dL [1.78 – 1.94 mmol/L] and >6.0 mg/dL [1.94 mmol/L]). After randomization, patients will receive double-blind study treatment (either Renvela or placebo) over a period of 8 weeks.

Patients will be followed for 2 weeks after the last visit of the Double Blinded Treatment Period (DBTP).

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate efficacy of Renvela tablets in the reduction of serum phosphorus in hyperphosphatemia in patients with CKD not on dialysis.

1.2.2 Secondary objectives

The secondary objectives are:

- To document the efficacy of Renvela tablets in the reduction of serum lipids (total cholesterol and low-density lipoprotein cholesterol [LDL-C]).
- To document the efficacy of Renvela tablets in the reduction of calcium-phosphorus product.
- To document the efficacy of Renvela tablets in the reduction of iPTH.
- To document the efficacy of Renvela tablets in proportion of patients reaching the target serum phosphorus level (4.6 mg/dL [1.49 mmol/L], inclusive).
- To evaluate safety of Renvela tablets.

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculations are based on the primary efficacy variable of serum phosphorus change from baseline to Week 8, with the following assumptions:

- A common standard deviation (SD) of 2 mg/dL, which is assumed based on the data from previous trials
- A 1 mg/dL mean difference between test and placebo in change from baseline in serum phosphorus
- A t-test at a 2-sided 5% significance level with 90% power
- Expected dropout rate = 15%.

Based on the above assumptions, 101 patients per arm are needed for this study. Calculations were made using nQuery Advisor 7.0.

1.4 STUDY PLAN

The following figure presents the graphical study design:

- R=Randomization
- Screening criteria:
- CKD patients not on dialysis
- Serum phosphorus level ≥5.5 mg/dL (1.78 mmol/L)
- Stratification factor, at the time of randomization, is screening serum phosphorus (≥5.5 – 6.0 mg/dL [1.78 – 1.94 mmol/L] and >6.0 mg/dL [1.94 mmol/L]). For eligible patients who are not taking phosphate binder(s) at screening visit, serum phosphorus at V1 will be used for stratification. For eligible patients who are taking phosphate binder(s) at screening visit, serum phosphorus at V1a will be used for stratification.
- Assessment of the primary efficacy (change from baseline in serum phosphorus level) endpoint is at Week 8.
- Wash out period is only for patients on phosphate binder(s) at screening. Patients not on phosphate binder(s) would proceed directly to the start of the 8-week treatment period (Day 1).
- During the Treatment Period, patients return to the investigative site every 2 weeks. Samples for laboratory measurements are collected at each site visit. After the results are received from the central laboratory, the serum phosphorus results are evaluated. Investigator will be informed by the IVRS/IWRS for dose titration. If the serum phosphorus is ≥4.6 mg/dL (≥1.49 mmol/L), the patient is to be instructed by the investigator to increase their study treatment dose by 1 tablet TID with meals. If the serum phosphorus is <2.7 mg/dL (<0.87 mmol/L), the patient is to be instructed by the investigator to decrease their study treatment dose by 1 tablet TID with meals.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

There are no major changes to the protocol statistical section.

The first patient was screened on 7 Jun 2016. The first patient was randomized on 21 July 2016. There are no planned interim analyses.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value obtained up to the date and time of the first double-blind investigational medicinal product (IMP) administration. For patients randomized and not treated, the baseline value is defined as the last available value obtained up to the date and time of randomization.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with summary statistics in the safety and efficacy sections (Section 2.4.4 and Section 2.4.5).

Demographic characteristics

Demographics and baseline characteristics will be listed and summarized by treatment group and overall for randomized patients. Standard descriptive statistics will be presented for the following continuous variables:

- age (years)
- weight (kg);
- height (cm);
- body mass index [BMI] (kg/m^2) [calculated as ($weight/height^2$) where weight is in kg and height is in m];

The total counts and percentages of patients will be presented for the categorical variables of:

- age group (years) : <45, ≥45 to <65, ≥65 to <75, and ≥75 years; and <65, and ≥65 years.
- gender (Male, Female);
- race (Asian, other).
- Alcohol use within 12 months.

Disease characteristics at baseline

Disease characteristics at baseline will be listed and summarized by treatment group and overall for randomized patients. Standard descriptive statistics will be presented for eGFR and total counts and percentages of patient will be presented for the CKD stage at baseline.

Medical and Renal history

Medical and renal history findings at Screening will be tabulated overall and by treatment group for randomized patients, including any past and/or concomitant diseases or past surgeries, primary cause of chronic kidney disease (CKD) and parathyroid gland resection.

2.1.2 Prior or concomitant medications

As specified in the protocol, all medications and therapies taken by the patient from 30 days prior to the signing of the informed consent through the end of the study will be recorded.

Medications will be coded to anatomic therapeutic class (ATC) term and generic name using the World Health Organization (WHO) Drug dictionary using the latest version at the date of DBL. Tables will be sorted first by alphabetical ATC and then by descending frequency of generic name within ATC based on the prevalence across all treatment groups. The highest ATC level for each medication will be used for summary. Multiple records of the same drug (based on generic name) used by a patient are counted once within a drug class and within a generic name.

Prior medications will be summarized, both overall and by treatment group for the Safety Set, by ATC and generic name for all medications.

Prior medications are defined as follows:

- Prior medications include any medications that were used within 30 days of screening visit and prior to the date of first dose of study drug.

Concomitant medications will be summarized by treatment group for the Safety Set, by ATC and generic name for all medications.
Concomitant medications are defined as follows:

- Concomitant medications include any medications used between study drug start and end of study.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 Primary efficacy endpoint(s)

The primary endpoint is the change from baseline in serum phosphorus level at Week 8.

The baseline of serum phosphorus value will be the last serum phosphorus level obtained before the first double-blind IMP dosing.

The serum phosphorus at Week 8 will be the serum phosphorus level obtained within the Week 8 analysis window.

All serum phosphorus values (scheduled or unscheduled) may be used to provide a value for the primary endpoint if appropriate according to above definition. The analysis window used to allocate a time point to a measurement is defined in Section 2.5.3.

2.1.3.2 Secondary efficacy endpoint(s)

The secondary efficacy endpoints are:

- The change from baseline in total cholesterol at Week 8
- The change from baseline in LDL-C at Week 8
- The change from baseline in calcium-phosphorus product at Week 8
- The change from baseline in iPTH level at Week 8
- Percentage of patients reaching the target serum phosphorus level (4.6 mg/dL [1.49 mmol/L], inclusive) at Week 8
- The change from baseline in serum phosphorus level at Week 4.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AEs) and other safety information, such as clinical laboratory data and vital signs.

Observation period

The observation of safety data will be as follows:

- Pre-treatment period: The pre-treatment observation period is defined from the signed informed consent up to the first dose of double-blind IMP.
- Treatment Emergent Adverse Event (TEAE) period: The TEAE observation period is defined as the time from the first dose of double-blind IMP to the last dose of double-blind IMP+3 days.
- Post-treatment period: The post-treatment observation period is defined as the time starting the day after the end of the TEAE period up to the end of the study (see definition in Protocol Section 6.2.1).

2.1.4.1 Adverse events variables

All adverse events (including serious adverse events [SAE], and AEs of special interest) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Record the occurrence of adverse events (including serious adverse events and AEs of special interest) from the time of signed informed consent until the end of the study.

Adverse event observation period

Pre-treatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of the IMP.

Treatment-emergent adverse events (TEAE) are adverse events that developed or worsened or became serious during the treatment period.

Post-treatment adverse events are adverse events that developed or worsened or became serious during the post-treatment period

Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that:

- Results in death, or
- Is life-threatening, or

Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

Adverse event of special interest

An AESI is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them.

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count). Renvela is a non-absorbed drug, thus it is not possible to define a symptomatic overdose prospectively. However, the investigator may use his or her judgment to report an event that he or she considers to be a symptomatic overdose using the corresponding screens in the e-CRF using the Term "Symptomatic OVERDOSE (accidental [or intentional])". The patient should be monitored and appropriate symptomatic treatment instituted. The circumstances of the overdose should be clearly

specified in the verbatim. Of note, asymptomatic overdose has to be reported as a standard AE.

- Increase in alanine transaminase (ALT) (see the "Increase in ALT" flow chart in Appendix A of the protocol).

2.1.4.2 Deaths

The deaths observation period are defined as below.

- Death on-study: deaths occurring during the on-study observation period (defined as the time from start of treatment until the end of the study)
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period

2.1.4.3 Laboratory safety variables

The clinical laboratory data consist of hematology (complete blood count [CBC], differential, platelet and prothrombin time), chemistry (serum phosphorus, calcium [adjusted for albumin], albumin, calcium-phosphorus product, chloride, bicarbonate, uric acid, sodium, potassium, glucose, blood urea nitrogen [BUN], alanine aminotransferase [ALT], aspartate aminotransferase [AST], creatinine), and lipid panel (total cholesterol, LDL-C, high-density lipoprotein cholesterol [HDL-C], non-high-density lipoprotein cholesterol [non-HDL-C] and triglycerides). Laboratory variables which are defined as efficacy variables will not be included in the safety analysis.

Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at Visit 1 (Week -4), Visit 2 (Week 0), Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 6 (Week 8) and/or early termination unless otherwise specified.

2.1.4.4 Vital signs variables

Vital signs include: heart rate (HR), systolic blood pressure (BP) and diastolic BP, and body temperature in sitting position.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients;
- Screen failure patients and reasons for screen failure;
- Nonrandomized but treated patients, if any;
- Randomized patients;
- Randomized but not treated patients;
- Randomized and treated patients;
- Patients who did not complete the study treatment period as per protocol;
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation (For the case of treatment discontinuation due to adverse event which is provided in CRF by investigators, medical expert will conduct a blinded review on the adverse event or pre-specify a rule to distinguish the “adverse event” or “CKD worsening underwent dialysis” before database lock);
- Status at last study contact.

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator divided by the number of exposed patients.

Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, the analysis populations for safety, efficacy will be summarized in a table by number of patients on the randomized population:

- Randomized population
- Efficacy population: modified intent-to-treat (mITT) population
- Safety population

Definitions of the study population are provided in Section 2.3.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR
2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population.

Patients who are dispensed study drug without calling the IRT or before calling the IRT are considered nonrandomized patients. They are excluded from any population for analysis, including safety. However, if these patients experienced any significant safety event, they should be documented separately in the clinical study report.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the mITT population.

2.3.1.1 Modified intent-to-treat population

Modified Intent-to-treat (mITT) population: The mITT population consists of all patients who are randomized, receive at least one dose of IMP, and have both a baseline assessment and at least one post-baseline assessment of phosphorus measure.

2.3.2 Safety population

Safety population: The safety population consists of all randomized patients who receive at least one dose of IMP.

In addition:

- Nonrandomized but treated patients with IMP will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be in Renvela group.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. First quartile (Q1) and third quartile (Q3) will be provided for baseline serum phosphorus. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population and analyzed by the treatment group to which they were randomized. In the randomized population, parameters will also be summarized within each randomization stratum as per IVRS.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

All reported patient’s medical and surgical history will be presented by primary SOC and PT.

The tables will be sorted by SOC internationally agreed order and decreasing frequency of PT based on the overall incidence across treatment groups. In addition all medical history of specific interest (see Section 2.1.1) will be presented by treatment group.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the safety population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). A given medication may be classified in more than 1 ATC class. All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications and concomitant medications will be presented by anatomic category, therapeutic category and generic medication name, sorted by decreasing frequency of ATC and generic medication name based on the overall incidence in Renvela group. In case of equal frequency regarding ATCs (anatomic, therapeutic categories or generic medication name), alphabetical order will be used.

The use of concomitant Native Vitamin D will be summarized by treatment group.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure, and actual dose information.

Duration of IMP exposure is defined as last dose date – first dose date + 1 day, regardless of unplanned intermittent discontinuations (see Section 2.5.2 for calculation in case of missing or incomplete data). Non-integer values will be rounded to 1 decimal place.

Duration of IMP exposure will be summarized using number, mean, SD, median, minimum, and maximum. In addition, the durations of treatment exposure will be summarized the percentage of patients according to the following categories: ≤2 weeks, >2weeks and ≤4 weeks, >4weeks and ≤6 weeks, >6weeks and ≤8 weeks, and >8 weeks.

Titration

The number and percentage of patients with an up-titration or down-titration in the Renvela group will be described. Patients with a titration are defined as titrated patients according to IVRS/IWRS Week 3a, 4a and 5a, transaction with at least 1 tablet IMP intake afterwards.

Dose information will be assessed by the following variables:

- The actual dose received is defined as total IMP dose intake.

- The intended dose is defined as the intended dose according to the initial dose level adjustment and intended dose titration due to phosphorus level or adverse events.

Dose information including average dose, final dose and highest dose will be summarized descriptively (number, mean, SD, median, Q1:Q3, minimum, and maximum).

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

1) Planned dose according to serum phosphorous level per protocol:

Planned dose at visit *i*= planned daily dose per serum phosphorus level at visit *i* * duration of the planned dose at visit *i*

Planned daily dose per phosphorus level at visit *i* = planned daily dose adjusted per serum phosphorus level at visit *i* based on intended dose before serum phosphorus sampling at visit *i*

Duration of planned dose at visit *i* = date of next phone call visit (visit (*i*+1)a) - date of phone call visit soon after the serum phosphorus sample (visit *i*a)

Given no phone call visit for visit *i* or visit *i*+1, the projected dose start or end date will be the serum phosphorous sampling date +3 days.

- If the first dosing visit of visit 2, planned dose at visit 2= planned starting daily dose per serum phosphorus level at screening * (date of visit 2a - first dose date) + planned daily dose per serum phosphorus level at visit 2 * (date of visit 3a - date of visit 2a)
- For the last scheduled dosing visit, taking visit 5 as an example, planned dose at visit 5= planned daily dose per serum phosphorus level at visit 5 * [last dose date - date of last phone call visit (visit 5a)]

2) Compliance rate = cumulative actual dose during study / (sum of planned dose per serum phosphorous level for all visits across study) *100%

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized.

Cases of overdose will constitute adverse events and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint

2.4.4.1.1 Primary efficacy analysis

The change from baseline in serum phosphorus at Week 8 as defined in Section 2.1.3.1 will be compared between the Renvela group to the placebo group in the mITT population using stratified Wilcoxon rank sum tests considering randomization strata (screening serum phosphorus [≥5.5 - 6.0 mg/dL or >6.0 mg/dL]). The statistical test will be two-sided tests at a nominal 5% significance level.

If a patient discontinues the treatment prematurely or does not have serum phosphorus value at Week 8, the last post-baseline on-treatment serum phosphorus measurement during the 8-week double-blind period will be used for the calculation of Week 8 (Last Observation Carried Forward [LOCF] procedure).

2.4.4.1.2 Sensitivity analysis of primary efficacy endpoint

The following sensitivity analyses will be performed for the primary endpoint.

An analysis of covariance (ANCOVA) with the missing data imputed by LOCF will be performed on the primary efficacy variable. The model will include treatment (Renvela or placebo) and screen serum phosphorus class (≥5.5 - 6.0 mg/dL [1.78 - 1.94 mmol/L] or >6.0 mg/dL [1.94 mmol/L]) and baseline serum phosphorus level as covariates. The adjusted mean difference of primary endpoint between two treatment groups will be provided as well as the 95% confidence interval and P-value.

The Markov Chain Monte Carlo (MCMC) method for multiple imputation will be used to account for missing values in change from baseline in serum phosphorus at Week 8. The imputation model will include baseline serum phosphorus level and all serum phosphorus level at all post-baseline visits stratified by treatment group and screen serum phosphorus class. The seed used for these imputations will be 14011. A minimum value of 0 will be specified in order to avoid negative imputed Phosphorus level.

Missing value in serum phosphorus will be imputed 100 times to generate 100 data sets with complete serum phosphorus values at Week 8. The change from baseline will be derived from observed and imputed serum phosphorus values. The completed data sets will be analyzed using an ANCOVA model with treatment groups, screen serum phosphorus class and baseline serum phosphorus level as covariates. The results from the 100 analyses will be combined using SAS PROC MIANALYZE.

2.4.4.1.3 Subgroup analysis

Subgroup analysis of primary endpoint will be conducted for exploratory purpose. The subgroup analysis include:

- Screening serum phosphorus level (≥5.5 - 6.0 mg/dL [1.78 - 1.94 mmol/L] or >6.0 mg/dL [1.94 mmol/L])
- Age (quartiles)
- Baseline eGFR (quartiles)
- Main cause of CKD (diabetes, hypertension and glomerulonephritis)
- Average daily dose (quartiles)
- Average daily dose (quartiles) * Screening serum phosphorus level (≥5.5 - 6.0 mg/dL [1.78 - 1.94 mmol/L] or >6.0 mg/dL [1.94 mmol/L])
- Screening serum phosphorus level (≤7.5 mg/dL[2.42mmol/L] or >7.5 mg/dL[>2.42mmol/L])

2.4.4.2 Analyses of secondary efficacy endpoints

All secondary endpoints will be analyzed using the mITT population.

Descriptive statistics (number, mean, SD, median, Q1, Q3, minimum, and maximum) will be provided by treatment for all continuous secondary variables at the scheduled visits.

All continuous secondary efficacy variables, ie, the change from baseline in serum lipids (total cholesterol and LDL-C), calcium-phosphorus product at Week 8, iPTH at Week 8 and serum phosphorus at Week 4 will be analyzed using the same test described in Section 2.4.4.1.1. For total cholesterol and LDL-C, sensitivity analysis of multiple imputation will not be applied. The same procedure for handling missing assessments/early discontinuation will also be applied as for the primary variable.

Proportion of patients reaching the target serum phosphorus level at Week 8 will be compared by treatment assignment (Renvela or placebo) using a Cochran-Mantel-Haensel method stratified by randomization strata (screening serum phosphorus: ≥5.5 - 6.0 mg/dL [1.78 - 1.94 mmol/L] or >6.0 mg/dL [1.94 mmol/L]), the proportion difference between Renvela and placebo group and 95% confidence intervals will be calculated.

2.4.4.3 Multiplicity issues

In order to handle multiple key endpoints, the overall type-I error will be controlled by the use of a fixed sequence approach. Statistical significance of the primary parameter at the 0.05 alpha level is required before drawing inferential conclusions about first secondary endpoint. Inferential conclusions about successive secondary endpoints require statistical significance of the prior one. The statistical inference order is as follows:

- The change from baseline in serum phosphorus at Week 8
- The change from baseline in total cholesterol at Week 8
- The change from baseline in LDL-C at Week 8
- The change from baseline in calcium-phosphorus product at Week 8
- The change from baseline in iPTH level at Week 8

- Percentage of patients reaching the target serum phosphorus level (4.6 mg/dL [1.49 mmol/L], inclusive) at Week 8
- The change from baseline in serum phosphorus level at Week 4

This fixed hierarchical approach will ensure a strong control of the overall type-I error rate at the 0.05 level. No further adjustments will be made for other secondary endpoints, for which p-values will be provided for descriptive purpose only (no claim).

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. No formal inferential testing will be performed. Summaries will be descriptive in nature.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately.
- The baseline value is defined as last available value obtained up to the date and time of the first double-blind IMP administration, except other specified.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (see 0). In case the threshold defined in the PCSA list for a given lab parameter is below the ULN, the following PCSA criterion will be used for the PCSA analysis: >PCSA threshold or > ULN (if ULN ≥ PCSA threshold).
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population.

All measurements, scheduled or unscheduled, will be assigned to analysis windows defined in Section 2.5.3, Table 2 in order to provide an assessment for Week 2 to Week 8 time points.

- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will also be provided for the last on-treatment value. The last on-treatment value is defined as the value collected at the same day/time of the last administration of IMP. If this value is missing, this endpoint value will be the closest value prior to the last dose intake.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event (AE) reporting will be on treatment-emergent adverse events (TEAEs). Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pre-treatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pre-treatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.2.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pre-treatment, treatment-emergent, and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the experimental treatment arm. The tables of AEs by SOC, HLGT, HLT, and PT will be sorted by the SOC internationally agreed order and the other levels (HLGT, HLT, and PT) will be presented in alphabetical order, unless otherwise specified.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order.
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event.

- All treatment-emergent adverse events related to IMP by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order.
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (i.e., mild, moderate, or severe), sorted by the sorting order defined above.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event.
- All treatment-emergent serious adverse events related to IMP, by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order.
- All treatment-emergent adverse events related to IMP leading to treatment discontinuation, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order.

Analysis of all treatment-emergent adverse event(s) of special interest

- All treatment-emergent adverse events of special interest, by primary SOC and PT, showing the number (%) of patients sorted by the internationally agreed SOC order.

Analysis of pre-treatment and post-treatment adverse events

- All pre-treatment AEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs (in the Renvela group) within each SOC.
- All post-treatment AEs by primary SOC and PT, sorted by the internationally agreed SOC order and decreasing incidence of PTs (in the Renvela group) within each SOC.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on TEAE period, post-study) and reasons for death if collected in the death report form.
- Deaths in nonrandomized patients or randomized but not treated patients.
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post baseline time point, last on-treatment) by treatment group. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in 0) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each post-baseline time point, last on-treatment) by treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.5 DATA HANDLING CONVENTIONS

2.5.1 Data handling conventions for secondary efficacy variables

See Section 2.4.4.2 Analysis of secondary endpoints.

2.5.2 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of missing/partial dates for medical history

Time from diagnosis of chronic kidney disease or resection (years) = (Date of informed consent –

Date of diagnosis*) / 365.25.
*In case the day of diagnosis would be missing, it will be imputed as to 01. In case the month of diagnosis would be missing, it will be imputed as 01JANUARY if the year of diagnosis equals the year of informed consent; it will be imputed as 01JULY if the year of diagnosis does not equal the year of informed consent.

Handling of baseline definition if time of first double-blind administration or time of assessment at Week 0 visit is missing

If the time of the first double-blind administration or time assessment at Week 0 visit is missing then the baseline value is defined as the last available value obtained before or on the day of the first double-blind IMP administration.

Handling of computation of treatment duration and compliance if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior and concomitant medication.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.
The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; e.g., for eosinophils the PCSA is > 0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.3 Windows for time points

Data analyzed by time point (including efficacy, laboratory safety data, and vital signs) will be summarized using the analysis windows given in Table 2. These analysis windows will be applicable for all analyses, and they are defined to provide more homogeneous data for time point-specific analyses.

Table 1 - Analysis windows definition

Time point	Targeted study day	Analysis window in study days
Week 2	15	2 to 22
Week 4	29	23 to 36
Week 6	43	37 to 50
Week 8	57	51 to 64
Follow-up	71	65 ~

For the case multiple visit dates fall into the same analysis window, the one close to the targeted study day is applied. In case of two visit dates are equally close to targeted date, the original record of visit will be applied. For the Week 8, the analysis visit should use the one close to the last IMP dose intake.

2.5.4 Unscheduled visits

For efficacy, safety laboratory data, and vital signs, unscheduled visit measurements may be used to provide a measurement for a time point, a baseline, a last or a worst value, if appropriate according to their definitions. The measurements may also be used to determine abnormal/PCSA.

2.5.5 Pooling of centers for statistical analyses

Not applicable.

3 INTERIM ANALYSIS

Not applicable.

4 DATABASE LOCK

The database is planned to be locked 5 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

6 REFERENCES

Not applicable.

7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria
Appendix B: Summary of statistical analyses

Appendix A Potentially clinically significant abnormalities criteria

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.

Parameter	PCSA	Comments
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cokcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - < 60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 μ mol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	 >408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	

Parameter	PCSA	Comments
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥ 40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Parameter	PCSA	Comments
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥ 20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension Orthostatic SDB Orthostatic DBP	≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm <40 bpm <40 bpm and decrease from baseline ≥20 bpm <30 bpm <30 bpm and decrease from baseline ≥20 bpm	Categories are cumulative
	>90 bpm >90 bpm and increase from baseline ≥20bpm >100 bpm >100 bpm and increase from baseline ≥20bpm >120 bpm >120 bpm and increase from baseline ≥20 bpm	Categories are cumulative
PR	>200 ms >200 ms and increase from baseline ≥25% > 220 ms >220 ms and increase from baseline ≥25% > 240 ms > 240 ms and increase from baseline ≥25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline ≥25% >120 ms >120 ms and increase from baseline ≥25%	Categories are cumulative
QT	>500 ms	
QTc	Absolute values (ms) >450 ms >480 ms >500 ms Increase from baseline Increase from baseline]30-60] ms Increase from baseline >60 ms	To be applied to any kind of QT correction formula. Absolute values categories are cumulative QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.

Appendix B Summary of statistical analyses

EFFICACY ANALYSIS

Endpoint	Analysis population	Primary analysis	Supportive analysis	Subgroup analysis	Other analyses
Primary endpoint					
Serum Phosphorus Level Change from baseline at Week 8	mITT	Stratified Wilcoxon rank sum tests	ANCOVA Multiple Imputation	Yes	No
Secondary endpoints					
Total cholesterol change from baseline at Week 8	mITT	Stratified Wilcoxon rank sum test	ANCOVA	No	No
LDL-Cat change from baseline at Week 8	mITT	Stratified Wilcoxon rank sum test	ANCOVA	No	No
Calcium-phosphorus product change from baseline at Week 8	mITT	Stratified Wilcoxon rank sum test	ANCOVA Multiple Imputation	No	No
iPTH level change from baseline at Week 8	mITT	Stratified Wilcoxon rank sum test	ANCOVA Multiple Imputation	No	No
Serum Phosphorus level change from baseline at Week 4	mITT	Stratified Wilcoxon rank sum test	ANCOVA Multiple Imputation	No	No
Percentage of patients reaching target serum phosphorus level at Week 8	mITT	Cochran-Mantel-Haensel Method	Yes Multiple Imputation	No	No

SAFETY ANALYSES

Endpoint	*Analysis population*	*Primary analysis*	*Supportive analysis*	*Subgroup analysis*	*Other analyses*
Adverse events	*Safety*	*Follow safety guidelines*	*No*	*No*	*No*
Deaths	*Safety*	*Follow safety guidelines*	*No*	*No*	*No*
Laboratory safety	*Safety*	*Follow safety guidelines*	*No*	*No*	*No*
Vital signs	*Safety*	*Follow safety guidelines*	*No*	*No*	*No*

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