STATISTICAL ANALYSIS PLAN

Protocol title:	**An Open-Label, Randomized, Parallel Group Study to Assess the Safety and Efficacy of Hectorol® (doxercalciferol capsules) in Pediatric Patients with Chronic Kidney Disease Stages 3 and 4 with Secondary Hyperparathyroidism Not Yet on Dialysis**
Protocol number:	**LPS14314**
Compound number (INN/Trademark):	**GZ427397 doxercalciferol/Hectorol®**
Study phase:	**III**
Short Title:	**Safety and Efficacy of Hectorol in Pediatric Patients with Chronic Kidney Disease Stage 3 and 4 with Secondary Hyperparathyroidism Not Yet on Dialysis**
Statistician:	[redacted]
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VERSION HISTORY

This statistical analysis plan (SAP) for study LPS14314 is based on the protocol dated 29-Mar-2016. There are no major changes to the statistical analysis features in this SAP.

The first participant was randomized on 14-Sep-2017.

Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	13-Sep-2022	In protocol amendment 2 dated 29-Mar-2016, the objectives and endpoints are not organized in a table. In SAP section 1.2, objectives and endpoints are re-organized to match each other.	To clarify the study objectives and endpoints.
		The definition of baseline in protocol amendment 2 is “the last available value before randomization” and is revised to “the last available value before the first dose of investigational medicinal product”.	To accommodate Sanofi statistical analysis convention.
		The definition of screened participants in protocol amendment 2 is “who met the inclusion criteria and signed the informed consent” and is revised to “who signed the ICF”.	To accommodate Sanofi statistical analysis convention.
		In protocol amendment 2, PCSA analysis is planned for on-treatment period, and it’s revised to treatment-emergent period.	To accommodate Sanofi statistical analysis convention.

1 INTRODUCTION

There are no major changes to the analyses described in the protocol.

1.1 STUDY DESIGN

This is a randomized, multinational, open-label, parallel group, active comparator study in participants aged 5 -18 years with chronic kidney disease (CKD) Stages 3 and 4 and SHPT not yet on dialysis. The study will include a Screening Period (4 days to 4 weeks), a Primary Efficacy Period (12 weeks), and a Safety Continuation Period (12 weeks). Eligible participants will be randomized either to the Hectorol® or Rocaltrol® treatment groups in a 2:1 ratio and will be stratified by age and CKD Stage at baseline as follows:

- At least 30% of participants < 12 years of age and at least 30% of participants ≥ 12 years of age
- At least 30% of participants with Stage 3 (GFR = 30 – 59 ml/min/1.73m^2) CKD and at least 30% of participants with Stage 4 (GFR = 15 – 29 ml/min/1.73m^2) CKD

All participants will be treated with either Hectorol® or Rocaltrol® from randomization until Week 24, which represents the end of treatment visit.

The Rocaltrol® active comparator treatment group is included for qualitative comparison purposes only. No formal statistical comparison between the Hectorol® and Rocaltrol® treatment group will be made.

Hectorol® and Rocaltrol® dosing will be adjusted to the iPTH plasma levels measured bi-weekly in all participants. For this pediatric study, the starting dose of Hectorol and all potential titration increases are less than those used in adults and have been modeled to provide weekly exposures comparable to those predicted in adults. The starting dose and titration instructions for Rocaltrol® capsules will follow the pediatric pre-dialysis SHPT label instructions.

Study primary analysis will be conducted after study completion.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
• The primary objective of this study is to evaluate the effect of Hectorol® capsules in reducing elevated levels of intact parathyroid hormone (iPTH)	• The primary efficacy endpoint is the percentage of participants achieving two consecutive ≥ 30% reductions in iPTH from baseline up to Week 12. • The secondary efficacy endpoints are: - Percentage change in iPTH from baseline to Weeks 12 and 24.

Objectives	Endpoints
	- Frequency of hypercalcemia, defined as albumin corrected serum calcium >10.2 mg/dL, up to Weeks 12 and 24.
Secondary	
• To evaluate the safety profile of Hectorol® capsules versus Rocaltrol® (calcitriol) capsules • To determine the pharmacokinetics profile of 1,25-dihydroxyvitamin D_2 after administration of Hectorol®.	• The safety endpoints are: - Adverse Events (AEs) - Vital signs - Clinical laboratory assessments • The pharmacokinetics endpoint is: - Serum 1,25-dihydroxyvitamin D_2 concentration-time data

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 2 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Randomized Population	The randomized population comprises all participants randomized either into the Hectorol® or Rocaltrol® group. Participants will be analyzed according to the intervention allocated by randomization.
Full Analysis Set (FAS)	The Full Analysis Set (FAS) comprises all treated participants with at least 2 assessments of iPTH after use of study drug. Participants will be analyzed according to the intervention allocated by randomization.
Per Protocol Set (PPS)	The Per Protocol Set (PPS) comprises all full analysis set-evaluable participants with no significant protocol deviations. Participants will be analyzed according to the intervention allocated by randomization.
Safety Population	The Safety Population comprises all randomized participants who have taken at least one Hectorol® or Rocaltrol® dose. Participants will be analyzed according to the intervention they actually received.
Pharmacokinetic (PK) Population	The PK population will consist of Hectorol® patients in the safety population with at least one post-dose, non-missing concentration value.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization (except if the first randomization is done by error) will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the intervention group as randomized if the participant received at least one administration as randomized.

Participants with the following protocol deviations will be excluded from PPS: The list of deviations leading to exclusion of participants from PPS is included in the appendix Section 5.5. Final decision will be made for each participant in the data review meeting prior to the database lock.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before the first dose of investigational medicinal product (IMP). For participants randomized but not treated, the baseline value is defined as the last available value before randomization.

Unless otherwise specified, analyses will be performed by intervention group (and by overall for baseline and demographics characteristics).

In statistical outputs, intervention group will be presented with the generic name of Hectorol® or Rocaltrol®, i.e., Doxercalciferol or Calcitriol.

The on-treatment strategy will be applied to the efficacy analysis, which will exclude the data 14 days after the last dose of IMP from analysis.

Observation period

The observation period will be divided into 3 segments:

- The **pre-treatment period** is defined as the period up to first investigational medicinal product (IMP) administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 4 days.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

3.2.1 Definition of endpoint

The primary endpoint is the percentage of participants achieving two consecutive ≥ 30% reductions in iPTH from baseline up to Week 12.

3.2.2 Main analytical approach

Primary endpoint will be summarized using the FAS and the PPS.

The percentage of participants meeting the iPTH ≥ 30% reduction from baseline at 2 consecutive study visits up to Week 12 will be calculated. Two consecutive ≥ 30% reductions in iPTH from

baseline up to Week 12 is defined as two consecutive 30% or greater reductions at any two consecutive measurements from baseline up to Week 12 with on-treatment strategy applied. For participants who have missing iPTH data for one or more analysis, the missing iPTH will not be imputed, and the primary endpoint will be analyzed with available data.

A 95% confidence interval will be constructed for the proportion of participants achieving the primary endpoint by Hectorol® and Rocaltrol® treatment groups by Clopper-Pearson method. The difference of proportions achieving the primary endpoint between treatment groups with associated 2-sided 95% CI will be estimated by Mantel-Haenszel method stratified on randomization stratum of age group (5 to <12, 12 to 18, years of age) and randomization stratum of CKD stage (3, 4). No formal statistical comparison will be made between the Hectorol® and Rocaltrol® treatment groups.

3.2.3 Sensitivity analysis

Sensitivity analysis is not planned for this study.

3.2.4 Supplementary analyses

Supplementary analyses are not planned for this study.

3.3 SECONDARY ENDPOINT(S) ANALYSIS

3.3.1 Key/Confirmatory secondary endpoint(s)

3.3.1.1 Definition of endpoint(s)

The secondary endpoints are:

- The percentage of change in iPTH from baseline to Weeks 12 and 24
- The frequency of hypercalcemia, defined as albumin corrected serum calcium >10.2 mg/dL, up to weeks 12 and 24

3.3.1.2 Main analytical approach

Secondary endpoints will be summarized using the FAS.

The percentage of change in iPTH from baseline to Weeks 12 and 24

The percentage change in iPTH from baseline to Weeks 12 and 24 will be summarized with descriptive statistics with on-treatment strategy applied. For the percentage changes from baseline iPTH, the effects over the treatment period time will be explored using a mixed model for repeated measures approach (MMRM) as appropriate.

The model will include baseline iPTH as a fixed-effect covariate, treatment group (Doxercalciferol, Calcitriol), randomization stratum of age group (5 to <12, 12 to 18, years of age), randomization stratum of CKD stage (3, 4), analysis visits (Week 2, Week 4, Week 6, Week 8, Week 10, Week 12, Week 18, Week 24) and treatment-by-visit interaction as fixed effect factors. An unstructured variance-covariance pattern will be assumed for the within-subject repeated measures. The Kenward-Roger method will be used to estimate the denominator degrees of freedom. Should the model fail to converge, then the variance-covariance structure will be assumed in the following order until the model converge: heterogeneous Toeplitz, heterogeneous compound symmetry, compound symmetry.

Overall model parameters will be presented, and lease squares (LS) means for percentage change from baseline iPTH, standard errors and 95% confidence interval will be presented by treatment group and visit. The difference in the LS means between Hectorol and Rocaltrol as well as accompanying standard errors and 95% CIs will be provided for week 12 and week 24.

Missing data will not be explicitly imputed because MMRM will extract and use the available information implicitly when estimating the variance-covariance matrix.

Plots of LS means and standard errors for percentage change from baseline in iPTH from the MMRM model will be presented by treatment.

Plots of means and standard errors in observed absolute value, absolute change from baseline, and percentage change from baseline will be presented by treatment and randomization stratum of CKD stage.

The frequency of hypercalcemia up to weeks 12 and 24

The number and percentage of participants with at least one event of hypercalcemia, and the number of hypercalcemia events, up to weeks 12 and 24, will be summarized descriptively with on-treatment strategy applied. Hypercalcemia is defined as albumin corrected serum calcium >10.2 mg/dL. For participants who have multiple consecutive test results that meet the criterion for hypercalcemia, each test result will be recognized as an individual event.

3.3.2 Supportive secondary endpoint(s)

Not applicable.

3.4 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

Not applicable.

3.4.1 Definition of endpoint(s)

Not applicable.

3.4.2 Main analytical approach

Not applicable.

3.5 MULTIPLICITY ISSUES

Not applicable.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2 , unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (e.g., exposed but not randomized) will be provided, if applicable.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 1 day, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically: ≤ 2 weeks, > 2 weeks and ≤ 4 weeks, > 4 weeks and ≤ 6 weeks, > 6 weeks and ≤ 8 weeks, > 8 weeks and ≤ 10 weeks, > 10 weeks and ≤ 12 weeks, > 12 weeks and ≤ 18 weeks, > 18 weeks and ≤ 24 weeks, and > 24 weeks.

Dose information will be assessed by the following variable:

- Intended and actual starting weekly dose by age group (5 to < 12 years, 12 to 18 years).
- Dose titration, including dose increase, dose reduction, and dose halt, will be analyzed based on both intended and actual weekly doses by exposure periods (Week 0 to week 2, Week 2 to week 4, Week 4 to week 6, Week 6 to week 8, Week 8 to week 10, Week 10 to week 12, Week 12 to week 18, Week 18 to week 24) and overall, and by baseline age and body weight group (5 to < 12 years (< 30 kg, ≥ 30 kg), 12 to 18 years).
  - Dose increase is defined as any increase, from either zero or non-zero dose.
  - Dose reduction is defined as any reduction to a non-zero dose.

- Dose halt is defined as any dose change from non-zero to zero.

Treatment compliance

Percentage of treatment compliance for a participant will be defined as the number of cumulative actual doses (capsules) divided by the number of cumulative intended doses (capsules).

On CRF page "Exposure_Study Treatment", Intended Weekly Dose (capsule) and Actual Weekly Dose (capsule) will be reported for each log line. For each log line, the actual doses (capsules) and intended doses (capsules) will be calculated as:

- Actual doses (capsules) = (End Date – Start Date + 1) * Actual Weekly Dose (capsule) / 7
- Intended doses (capsules) = (End Date – Start Date + 1) * Intended Weekly Dose (capsule) / 7

The cumulative actual doses (capsules) and the cumulative intended doses (capsules) will be calculated as the sum of actual doses (capsules) and sum of intended doses (capsules) of all log lines, respectively.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80% and ≤100%, >100%.

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) 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 Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary AE analyses will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the intensity is missing for 1 of the treatment-emergent occurrences of an AE, the intensity will be imputed with the maximal intensity of the other occurrences. If the severity is missing for all the occurrences, the intensity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 3.

Table 3 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a,b]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the GZ427397 intervention group
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any treatment-emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation
- Any treatment emergent AESI
- Any treatment-related TEAE

The AE summaries of Table 4 will be generated with number (%) of participants experiencing at least one event.

Table 4 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity[a]	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent SAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Pretreatment AE	Overview[b]
	Primary SOC and PT
Pretreatment SAE	Primary SOC and PT
Post-treatment AE	Overview[b]
	Primary SOC and PT
Post-treatment SAE	Primary SOC and PT

a In case of several occurrences for the same PT in a participant, the maximal intensity will be used.
b Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AESI

Analysis of deaths

In addition to the analyses of deaths included in Table 3 the number (%) of participants in the following categories will be provided, if applicable:

- Deaths during the treatment-emergent and post-treatment periods
- Deaths in non-randomized participants or randomized but not treated participants

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) will be selected for analyses as indicated in Table 5. Number (%) of participants experiencing at least one event will be provided. Tables will be sorted as indicated in Table 3.

Table 5 - Selections for AESIs

AESIs	Selection
• Pregnancy of a female participant entered into the study. It will qualify as an SAE only if it fulfills one of the seriousness criteria. • Symptomatic overdose (serious or non-serious) with Hectorol®/Rocaltrol® • Increase in alanine transaminase (ALT): ALT ≥3ULN (if baseline < ULN) or, ALT ≥ 2 times the baseline value (if baseline ALT ≥ULN) will be monitored according to the guidance provided in Appendix A of the protocol. • Other project specific AESI(s): Albumin corrected serum calcium > 10.2 mg/dl	e-CRF specific tick box on the AE page

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables and vital signs

The following laboratory variables and vital signs variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets: red blood cell count, reticulocyte count, hemoglobin, hematocrit, platelets
  - White blood cells: white blood cell count with differential blood count
- Clinical chemistry:
  - Metabolism: albumin, blood glucose, 25-hydroxyvitamin D, albumin-corrected serum calcium, calcium-phosphorus product
  - Electrolytes: sodium, potassium, calcium, bicarbonate, chloride, phosphorus
  - Renal function: serum creatinine, blood urea nitrogen and GFR calculation, according to the Schwartz equation: GFR (mL/min/1.73 m2) = (0.41 × Height in cm) / Creatinine in mg/dL
  - Liver function: ALT, AST, total and direct bilirubin, alkaline phosphatase, GGTP
- Vital signs: systolic and diastolic blood pressure according to position (supine), heart rate, temperature

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

Quantitative analyses

When relevant, for laboratory variables and vital signs above, descriptive statistics for results and changes from baseline will be provided for each analysis window, the last value and the worst

value (minimum and/or maximum value depending on the parameter) during the treatment-emergent period.

For phosphate, calcium, and calcium corrected, plots of means and standard deviations of observed value during the treatment-emergent period by visit will be presented by treatment, and by treatment and randomization stratum of age group (5 to <12, 12 to 18, years of age), respectively.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

Analyses according to PCSA will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For laboratory variables and vital signs above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

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

3.7 OTHER ANALYSES

3.7.1 Other variables and/or parameters

3.7.1.1 PK analyses

All PK analyses will be performed using the PK population.

For sparse PK samples, 1,25-dihydroxyvitamin D_2 concentration will be summarized using descriptive statistics including number, arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV) (%), minimum, median, and maximum for each visit overall, by randomization stratum of CKD stage (3, 4), and by randomization stratum of age group (5 to <12, 12 to 18, years of age). The samples will be considered non-eligible for these analyses if PK samples are not collected within 3 days of the most recent dose.

Concentrations below the lower limit of quantification (LLOQ) will be set to zero for samples at baseline. Post-baseline concentrations below LLOQ will be replaced by LLOQ/2. Plots of mean and standard deviation of 1,25-dihydroxyvitamin D_2 concentrations by visit will be presented.

For serial PK, the pharmacokinetics analyses will be performed separately.

3.7.2 Subgroup analyses

Subgroup analyses of the primary efficacy endpoint will be performed to assess the homogeneity of the treatment effect across the following subgroups:

- Randomization stratum of age group (5 to <12, 12 to 18, years of age)
- Randomization stratum of CKD stage (3, 4)
- iPTH level at the week -2 screening visit (>100 and ≤ 160, > 160, pg/mL)

3.8 INTERIM ANALYSES

Not applicable.

4 SAMPLE SIZE DETERMINATION

The Rocaltrol® active comparator treatment group is included for qualitative comparison purposes only for the safety profile.

The study is prospectively under powered for making statistical comparisons between the treatment groups for either the efficacy or safety outcomes. No formal statistical comparison between the Hectorol® and Rocaltrol® treatment group outcomes will be made.

Approximately 84 participants will be randomized in a 2:1 ratio to the Hectorol® and Rocaltrol® treatment groups. The study randomization scheme will be stratified by age group (i.e. 5 to <12, and 12 to 18, years of age) and CKD stage (i.e. 3 and 4).

A sample size of 39 participants for the Hectorol® treatment group provides 80% power to detect a difference, for the Hectorol® treatment group, from a value of <30% for the proportion of participants achieving the primary endpoint, assuming a 2-sided alpha = 0.05, using the normal approximation and that the true proportion for the Hectorol® treatment group is 50%. Approximately 56 participants will be randomized to the Hectorol® treatment group, allowing for 30% early terminations / unevaluable participants. The limits for a 95% confidence interval (CI) constructed for the proportion of Hectorol® treatment group participants achieving the primary endpoint would be ± 0.13, assuming 0.50 for the proportion and 56 Hectorol® treated participants. The estimate for the proportion of participants achieving the primary endpoint for the Hectorol® treatment group is extrapolated from the percent changes in plasma iPTH for the doxercalciferol treatment group summarized in Figure 1 of Coburn et al (1).

For the purpose of making a qualitative comparison of the Hectorol® safety profile to the active comparator treatment group, a sample size of 20 participants for the Rocaltrol® treatment group is based on the 2:1 randomization of participants to the Hectorol® treatment group and Rocaltrol® treatment group. To allow for 30% early terminations / unevaluable participants, approximately 28 participants will be randomized to the Rocaltrol® treatment group.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AE:	adverse event
AESIs:	adverse events of special interest
CI:	confidence interval
CKD:	chronic kidney disease
CV:	coefficient of variation
FAS:	Full Analysis Set
HLT:	high level term
IMP:	investigational medicinal product
iPTH:	intact parathyroid hormone
LLOQ:	lower limit of quantification
LLT:	lower-level term
LS:	lease squares
MedDRA:	medical dictionary for regulatory activities
MMRM:	mixed model for repeated measures
PCSA:	potentially clinically significant abnormality
PK:	pharmacokinetic
PPS:	Per Protocol Set
PT:	preferred term
SAP:	statistical analysis plan
SD:	standard deviation
SEM:	standard error of the mean
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 2 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Randomized but not exposed participants
- Randomized and exposed participants

- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation
- Participant status at last contact

The number (%) of exposed and not randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, randomized and with permanent intervention discontinuation will be provided.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, medical and surgical history and disease characteristics at baseline will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- age in years as quantitative variable and in categories (5 to <12, 12 to 18)
- sex (Male, Female)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple, Not Reported, Unknown)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)
- weight in kg as quantitative variable
- height in cm as quantitative variable
- body mass index (BMI) in kg/m^2 as quantitative variable, calculated as ($weight/height^2$) where weight is in kg and height is in m
- Chronic Kidney Disease (CKD) Stage (3, 4)
- iPTH level at the week -2 screening visit in pg/mL (>100 and ≤ 160, > 160)

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline includes:

- Age at initial diagnosis of chronic kidney disease stage 3 or 4, defined as: (Start Date* – Date of or birth + 1) / 365.25. For participants who reported both stage 3 and stage 4 CKD, the earlier start date will be used.
- Years since initial diagnosis of chronic kidney disease stage 3 or 4, defined as: (Date of informed consent – Start Date* + 1) / 365.25. For participants who reported both stage 3 and stage 4 CKD, the earlier start will be used.
- Age at initial diagnosis of secondary hyperparathyroidism, defined as: (Start Date* – Date of birth + 1) / 365.25.
- Years since initial diagnosis of secondary hyperparathyroidism, defined as: (Date of informed consent – Start Date* + 1) / 365.25.

*In case the day of diagnosis would be missing, it will be imputed as to 01. In case the month and day 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.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant received prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP from the first administration of IMP to the last IMP intake + 4 days.
- Post-treatment medications are those the participant received in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the safety population by anatomic and therapeutic class. The summaries will be sorted by decreasing frequency of anatomic category (ATC) based on incidence in the treatment group. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for time points

The following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy and safety variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. If multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 6 - Analyses window definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
Week 2 (Visit 3)	15	2 to 21
Week 4 (Visit 4)	29	22 to 35
Week 6 (Visit 5)	43	36 to 49
Week 8 (Visit 6)	57	50 to 63
Week 10 (Visit 7)	71	64 to 77
Week 12 (Visit 8)	85	78 to 105
Week 18 (Visit 9)	126	106 to 146
Week 24 (Visit 10)	168	147 to

Study days are calculated considering Day 1 as the day of first administration of intervention (or the day of randomization for participant not exposed).

Unscheduled visits

Unscheduled visit measurements of laboratory data and vital signs will be used for computation of baseline, the last value during the treatment-emergent period, analysis according to PCSAs, and the shift summaries for safety. They will also be included in the by-visit summaries if they are re-allocated to scheduled visits. For iPTH and albumin corrected serum calcium, unscheduled visits will also be included in the efficacy analyses.

5.5 APPENDIX 5 CRITICAL/MAJOR PROTOCOL DEVIATION LEADING TO EXCLUSION FROM PPS

Table 7 - Critical/major protocol deviation leading to exclusion from PPS

Category for Protocol Deviation (severity) (DVCATINI)	Protocol Deviation Coded Term (DVDECOD)	Deviation Number (DVSPID)	Protocol Deviation Term (DVTERM)	Notes
CRITICAL	Informed consent procedures	0101	Study Informed consent/ Assent form never obtained for the study and personal data collected or intervention(s) performed	
CRITICAL	Informed consent procedures	0104	Study Informed consent/Assent form not obtained for an amendment requiring a re-consent	
MAJOR	Informed consent procedures	0105	Study Informed consent/Assent form obtained with a misconduct in consent process or documentation	
CRITICAL	Inclusion/Exclusion criteria	0201	Male or female aged 5 to <18 years old[a]	
CRITICAL	Inclusion/Exclusion criteria	0202	Weight >= 15 kg[a]	
CRITICAL	Inclusion/Exclusion criteria	0203	CKD Stage 3 or 4 not on dialysis, defined as GFR between 15 and 59 mL/min/1.73m2 (established by Schwartz equation) at Week - 2 visit[a]	
CRITICAL	Inclusion/Exclusion criteria	0204	iPTH value > 100 pg/mL for CKD Stage 3 or > 160 pg/mL for CKD Stage 4, at Week -2 visit[a]	
CRITICAL	Inclusion/Exclusion criteria	0205	Signed informed consent / assent form[a]	
CRITICAL	Inclusion/Exclusion criteria	0206	The participant has a serum 25-hydroxyvitamin D level < 30 ng/mL at screening	
CRITICAL	Inclusion/Exclusion criteria	0207	The participant has a corrected calcium >= 10 mg/dL at the Week - 2 visit	
CRITICAL	Inclusion/Exclusion criteria	0208	The participant has a serum phosphorus > 4.5 mg/dL for children 13 to 18 years of age; > 5.8 mg/dL for children 5 to 12 years of age at the Week - 2 visit	
CRITICAL	Inclusion/Exclusion criteria	0210	The participant used cinacalcet or vitamin D sterol therapies such as calcitriol, doxercalciferol, or paricalcitol within 14 days prior to the baseline visit	
CRITICAL	Inclusion/Exclusion criteria	0212	The participant currently has a chronic gastrointestinal disease (ie, malabsorption, severe chronic diarrhea, chronic ulcerative colitis, or ileostomy)	
CRITICAL	Inclusion/Exclusion criteria	0213	The participant currently has primary hyperparathyroidism or has had a total parathyroidectomy	

Category for Protocol Deviation (severity) (DVCATINI)	Protocol Deviation Coded Term (DVDECOD)	Deviation Number (DVSPID)	Protocol Deviation Term (DVTERM)	Notes
MAJOR	Inclusion/Exclusion criteria	0215	The participant is unable to swallow a capsule in size similar to the Hectorol and Rocaltrol capsules	
CRITICAL	Inclusion/Exclusion criteria	0216	The participant has a history of sensitivity or allergy to doxercalciferol, calcitriol or other vitamin D analogs	
MAJOR	Inclusion/Exclusion criteria	0219	The participant is medically unstable or is not otherwise suitable for study participation, in the opinion of the Investigator	
MAJOR	Inclusion/Exclusion criteria	0220	The participant, in the opinion of the Investigator, is unable to adhere to the requirements of the study	
CRITICAL	Inclusion/Exclusion criteria	0221	Pregnant or breast-feeding female	
CRITICAL	Inclusion/Exclusion criteria	0223	All contraindications of Rocaltrol and warning/precaution of Rocaltrol use as per the US Rocaltrol Labeling (Rocaltrol package insert 2)	
CRITICAL	Inclusion/Exclusion criteria	0224	The participant currently uses aluminum or magnesium-based binders.	
CRITICAL	Concomitant Medications/ Therapy	0303	Protocol prohibited therapy/medication/vaccine/ administered	Discuss case by case before DBL.
MAJOR	IMP Management	0507	IMP not fit for use but dispensed/administered	
MAJOR	IMP Management	0510	IMP low compliance	Discuss case by case before DBL.
MAJOR	Randomization procedure	0601	IMP dispensed without Randomization	
MAJOR	Randomization procedure	0602	IMP dispensed prior to randomization	

a The inclusion criterion is described in DVTERM. Not meeting the inclusion criterion is a protocol deviation.

6 REFERENCES

1. Jack W Coburn, Hla M Maung, Logan Elangovan, Michael J Germain, Jill S Lindberg, Stuart M Sprague, et al. Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. Am J Kidney Dis. 2004;43(5):877-90.

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