NCT: NCT02859896

AMENDED CLINICAL TRIAL PROTOCOL 03

COMPOUND: GZ427397

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

STUDY NUMBER: LPS14314

STUDY NAME: VIDA

VERSION DATE / STATUS: 15-Jul-2021/ 2 for review

Version Number:	2 for review	IND number:	031423
Date:	15-Jul-2021	Total number of pages:	87

NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	Genzyme, a Sanofi Company 50 Binney Street Cambridge, MA 02142 USA
OTHER EMERGENCY TELEPHONE NUMBERS		

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country-specificity if applicable	Date, version
Amended protocol 03	All	15-Jul-2021, 2 for review (electronic 4.0)
Amended protocol 02	All	29-Mar-2016, version 1 (electronic 2.0)
Amended protocol 01	All	10-Feb-2016, version 1 (electronic 1.0)
Original Protocol		27-Oct-2015, version 1 (electronic 1.0)

AMENDED PROTOCOL 03 (15-JUL-2021)

This amended protocol 03 (amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The amendment is issued to accommodate FDA recommendation of changing eligibility criteria in efforts to facilitate recruitment of the study. The changes also consider feedback from the participating Investigators during various points of the study conduct that may support improved study participation and more aligned approach towards real life practice for better patient care along with reduced patient burden. Also, changes in IMP/NIMP clinical supply were implemented to accommodate any product unavailability or supply issues.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Title page	Study name added (VIDA)	Administrative change
Names and addresses	Updated Sponsor address	Administrative change
Clinical Trial Summary - Study design	Change of screening period duration to “10 days to 45 days (6 weeks)”	For recruitment flexibility
Duration of study period (per patient)	Addition of Post-Treatment Follow-Up Period/ EOS (24-28 weeks)	To reinforce patient safety

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary - Study design 6.5 Discussion of study design and choice of control groups	Addition of the below text: In case of product unavailability, Hectorol® and / or Rocaltrol® brand can be substituted by authorized generic forms for use in this trial. Substitute compounds are similar and equivalent as per CMC, therefore posing no changes in the overall efficacy, tolerability or safety.	To ensure trial continuity in case of product unavailability
Clinical Trial Summary - Study population, 7.1 Inclusion Criteria	Addition of 'at the time of randomization': I 01. Male or female aged 5 to 17 years old (both inclusive) at the time of randomization.	For clarification of eligibility
	Change of iPTH value: I 04. iPTH value >75 pg/mL (9.5 pmol/L) for CKD Stage 3 or >110 pg/mL (15.9 pmol/L) for CKD Stage 4, at Week -2 visit at screening.	To add clarity on the age definition of the pediatric population to the I 01 criteria
Clinical Trial Summary - Study population, 7.2 Exclusion Criteria	Change of serum 25-hydroxyvitamin D level: E.01 The patient has a serum 25-hydroxyvitamin D level <25 ng/mL at screening. Change of corrected calcium level: E 02. The patient has a corrected calcium ≥10.2 mg/dL at the Week -2 visit. Change of serum phosphorus level for children aged 13-17 years: E 03. The patient has a serum phosphorus >5.5 mg/dL (1.77mmol/L) for children 13 to 17 years of age; > 5.8 mg/dL (1.87mmol/L) for children 5 to 12 years of age at the Week -2 visit	To facilitate recruitment
	Below criteria deleted: E 05. The patient used cinacalcet or vitamin D sterol therapies such as calcitriol, doxercalciferol, or paricalcitol within 14 days prior to the baseline visit. To read as follows: E 05: Deleted in amended protocol 03	To facilitate recruitment eligibility: pre-dialysis patients taking cinacalcet is not a common practice due to the risk of hypocalcemia, therefore this criterion is deleted. Patients taking vitamin D therapies (or cinacalcet) prior to enrolment will go through the wash-out period of 45 days preceding the baseline visit.
	Addition of 'male' in E 17: E 17. Female or male patient who is sexually active and unwilling to abstain from sexual intercourse or is not protected by a highly effective contraceptive method of birth control.	To reinforce patient safety
	Addition of an EC as below: E 20. The patient has liver function abnormalities as defined by ALT >3x ULN	To reinforce patient safety

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary – Total expected number of patients Sample size determination	Reduced to 57	To facilitate study recruitment and completion
Clinical Trial Summary – Dose regimen: Investigational medicinal Product & Non-investigational medicinal product, 8.1 Investigational medicinal product, 8.1.1 Dose Titration, 8.2 Non-investigational medicinal product	Titration description changed to: The dosage will be increased If iPTH is reduced <30% comparing with the baseline value AND/OR does not reach the physician's clinically desired iPTH range for the patient. Otherwise the actual dosage will be maintained. Physicians can modify the dosage for any safety reason	For better clarification of titration description of medicinal products
Clinical Trial Summary – End points: pharmacokinetics, 9.3.1 Pharmacokinetics	Sample changed to plasma	For consistency with laboratory methodology
Clinical Trial Summary – Assessment schedule, Statistical considerations, 9.3.1 Pharmacokinetics, 9.3.1.1 Sampling time	Post treatment follow up period added: Week 24- 28 Pharmacokinetic population changed: Up to 18 Hectorol patients (Hectorol® or authorized generic) patients (50% of patients <12 years of age) will undergo serial PK sampling in PK subgroup. Sparse PK schedule changed: At Weeks 2, 4, 6, 8 or 12 and 10 Serial PK schedule changed: at either the Week 8 or 12 visit.	To reinforce patient safety To accommodate change of analysis population To accommodate change of schedule of assessment To accommodate change of schedule of assessments
Clinical Trial Summary – Pharmacokinetics 9.3.1.4 Pharmacokinetics parameters, 11.4.2.3 Analysis of Pharmacokinetic data	Paragraph updated as below: Evaluation of the 1,25-dihydroxyvitamin D2 concentration-time data obtained in this study will be conducted using noncompartmental methods including the following parameters like C_{max} and $AUC_{0\text{-}tau}$ at Week 8 or 12 when Serial PK Samples are collected. If feasible, a model based approach using NONMEM (Icon, Hanover MD USA, Version 7 Level 2 or higher) can be used to derive individual and population mean parameters including absorption rate constant, clearance and volume of distribution will be reported.	To accommodate change in laboratory procedure

Section # and Name	Description of Change	Brief Rationale
Clinical Trial Summary – Sample size determination	Updated to: 30 patients for Hectorol to provide 70% power and 15 patients for Rocaltrol Hectorol: - Early terminations /unevaluable patients adjusted to 20% - Hectorol treated patients adjusted to 38. - The limits for a 95% confidence interval constructed for the proportion of Hectorol® (or authorized generic) treatment group patients achieving the primary endpoint would be ± 0.16 Rocaltrol: - Early terminations /unevaluable patients adjusted to 20% - Rocaltrol treated patients adjusted to 19	To facilitate study recruitment and completion
1.1 Graphical study design	Change of Hectorol arm size to 38 Change of Rocaltrol arm size to 19 Addition of Post-treatment Follow Up period	For consistency of sample size recalculation and change in duration of study
1.2 Study flow chart	Home visits implemented – visit 3, visit 4, visit 5, visit 7, visit 9, visit 11 ECG added at visit 2 and visit 8 Visit 1: Day -14 to -10 Visit 1a Week -6: Day -45 Visit 1b: Day -14 to -10 Respiratory rate is added to vital signs Serum creatinine, blood urea nitrogen, eGFR tests added at Visit 6 and Visit 8 AE monitoring (hypercalciuria) of urinalysis at initial 24-hour and 24-hour urine test implemented at screening Physical examination deleted EOS (Visit 11) at Week 28 added Added footnotes for screening, home-visit, AE monitoring, vital signs, serum pregnancy tests, and PK sampling	To accommodate changes in operational activities and ensure patient safety Added footnotes to the flow-chart for clarity
1.2 Study flow chart, 8.7 Responsibilities, 10.1.4 Visit 3, Week 2 (home visit), Visit 4, Week 4 (home visit), Visit 5, Week 6 (home visit), Visit 6, Week 8 (on-site visit), Visit 7, Week 10 (home visit) and Visit 8, Week 12 (on-site visit), 10.1.5 Visit 9 Week 18 (home visit), 12.2 Informed Consent	Option and description for 'Direct to patient' delivery added for home visits	For better patient follow up flexibility, to reduce patient burden and reinforce patient safety follow up

Section # and Name	Description of Change	Brief Rationale
4.2.1 Study Design Rationale	Screening visit windows updated in Table 1	To accommodate recruitment flexibility
	Updated the Table 1 - Screening Period: additional 1b Visit Scheduling (Week -2)	Clarification on 2 recruitment scenarios for patients requiring or not requiring the washout from previous medication
4.2.2 Dose and regimen	Maximum dose of Hectorol for 5 to <12 years old weighing less than 30 kg body weight updated	To clarify maximum dose
6.1 Description of the protocol	Added text: The Post-treatment follow-up period / end of study (EOS) visit will be at Week 28 Screening period updated to "10 days to 6 weeks" Added the post-treatment follow-up period and specified that it is for 4 weeks	To accommodate EOS at Week 28 For recruitment flexibility To accommodate EOS at Week 28
6.2.1 Duration of study participation for each patient	Number of visits for primary efficacy period updated to 7 visits	To fix typographical error
	Also added below text: The patient will complete the study (EOS) after 4 weeks of post-treatment follow-up period.	Patient safety follow-up
6.2.2 Determination of end of clinical trial (all patients)	Text was updated as follows: The study is finished when the last patient completes the 'end of study' (EOS) visit at Week 28	To accommodate EOS at Week 28
6.3 Interim analysis	Updated as below: Interim analysis can be planned on clinical and/ or pharmacokinetics data to support discussion with Regulatory Authority related to study conduct.	Given the recruitment feasibility challenges, the possibility of an interim analysis for clinical and/or PK data was added, to be performed according to the endpoints and analyses specified in the Amended protocol 03
7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound	Updated as below: Re-screening: Patients who failed screening initially may be re-screened for potential enrollment following investigator's clinical discretion and after discussion with Sponsor. Also, laboratory assessments may be repeated for potential enrollment following investigator's clinical discretion with Sponsor.	To be inclusive for patient eligibility
8.1 Investigational medicinal product	Added Table 2 – Starting Dose by Age Groups	For clarification of starting IMP doses
8.1.1 Dose Titration	Added table for dose adjustment for desired iPTH value	Titration scheme clarification
8.5 Packaging and labeling	Hectorol packaging updated Rocaltrol packaging updated	To ensure trial continuity in case of product supply change /unavailability

Section # and Name	Description of Change	Brief Rationale
8.7.1 Treatment accountability and compliance	Below text added for home visits: When home visit allowed as per local regulations, the Sponsor can arrange to collect the units via authorized services.	To accommodate operational change
	Below text added for home visits: For home visits, the site has to arrange a remote visit (via any digital contact) in order to review phosphate binder use, diet compliance, dosing compliance and patient's diary; dose adjustment evaluation, drug accountability; AE/SAE monitoring and recording of concomitant medication.	To allow home visit activities
8.7.2 Return and/or destruction of treatments	Below text added for home visits: For on-site visits, the patient will return the unused drugs to the site (visit 6, visit 8, visit 10), whereas for home-visits (visit 3, visit 4, visit 5, visit 7, visit 9) Sponsor approved services will collect those from the patient and deliver to the site upon patient's consent. The Investigator will not destroy the unused Investigational Product unless the Sponsor provides written authorization.	To allow home visit activities
8.8 Concomitant Medication	Following added: Box label warning of both drugs for hypersensitivity, contraindication and concomitant medication should be reviewed and followed prior and during the administration.	For patient safety
	The following sentence updated: The use of any vitamin D in any form is prohibited, except as described in this protocol.	For patient safety
	The following deleted: Patients may continue use of a stable regimen of ergocalciferol or multi-vitamins during the study. A stable regimen is one that has been in use for 30 or more days prior to the Screening Visit.	For patient safety
9.2.2.3 Vital Signs, 10.1.2 Screening visit - Visit 1, Week -2 (no wash-out required) or Visit 1b, Week -2, (wash–out required) (on-site visit) Day-16 to Day-10	Blood pressure in supine position and respiratory rate added to vital signs.	For better evaluation of patient status
10 Study procedures	Screening visit period updated to maximum 6 weeks. Visit window updated: For all visits after Day 1/Week 0 (randomization visit), a time frame of a certain number of days will be allowed. The window period for the visit at Week 2 to 12 is ±3 days, for visit at Week 18, 24 and 28 is ±7 days. Home visit description added:	To facilitate screening process To facilitate patient visit flexibility To allow home visit activities

Section # and Name	Description of Change	Brief Rationale
	For home visits, a healthcare technician from Sponsor authorized services will visit the patient at their preferred residence address. This will require a separate consent from the patient. For such visits, the Investigator or delegate will also arrange digital contact with the patient. The detailed activities are mentioned in flow chart Section 1.2 and Section 10.1.	
10.1 Visit schedule	Below paragraphs added: Screening visits, visit 2 (Week 0), Visit 6 (Week 8), Visit 8 (Week 12), Visit 10 (Week 24) will be on-site visits. Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 6), Visit 7 (Week 10), Visit 9 (Week 18), Visit 11 (Week 28) will be home visits. Exceptionally such visits can remain on-site, for example, if the site cannot arrange, not allowed by local regulations, the patient does not consent, etc. Home visits will comprise of a visit to patient's preferred address by a healthcare technician of the Sponsor authorized services and a digital contact with the patient arranged by the Investigator or delegate. At each visit, an appointment will be given for the next visit within allowed visit window period	To allow home visit activities and patient visit flexibility
10.1.1 First Screening visit – Visit 1a, week -6, Day -45: Wash out required (on-site visit)	The washout period in case of patients taking cinacalcet or Vitamin D sterol therapies such as calcitriol, doxercalciferol or paricalcitol at Screening visit is extended from 30 to 45 days prior to baseline.	Patient safety and screening activity flexibility
10.1.2 Screening Visit – Visit 1, Week -2 (no wash-out required) or Visit 1b, Week -2, (wash–out required) (on-site visit) Day-14 to Day-10	Screening visit window updated to Day -14 to Day -10	Screening activity flexibility
10.1.3 Randomization Visit, Visit 2, Week 0, Day 1 (on-site visit)	ECG added	Patient safety follow-up
10.1.4 Visit 3, Week 2 (home visit), Visit 4, Week 4 (home visit), Visit 5, Week 6 (home visit), Visit 6, Week 8 (on-site visit), Visit 7, Week 10 (home visit) and Visit 8, Week 12 (on-site visit):	• Visit 3, Visit 4, Visit 5, Visit 7 made home visit • ECG added at Visit 8 • Serum creatinine, Blood urea nitrogen and GFR calculation added at Visit 6 and Visit 8 • Serial PK sample schedule updated - to be taken at Week 8 or 12	For better patient follow up flexibility, to reduce patient burden and reinforce patient safety follow up
10.1.5 Visit 9 Week 18 (home visit)	• Made home visit	For better patient follow up flexibility and to reduce patient burden

Section # and Name	Description of Change	Brief Rationale
10.1.7 Visit 11, Week 28, End of Study Visit (home visit)	• Added as End of Study home visit • List of activities added: • AE/SAE • Concomitant medication • Vital signs Note added for all visits: *When home visit, data to be collected via digital contact from the patient by the site. **When home visit, blood sampling and/or vital sign measurements to be performed by a healthcare technician Sponsor authorized services.	For better patient follow-up flexibility and to reduce patient burden For operational clarification
10.1.8 Unscheduled visits	Unscheduled visit option added with below paragraph: Unscheduled visit is to be conducted for an unscheduled dispensation of study drug, or if deemed necessary by the investigator for any safety reasons. A regional or national emergency declared by a government agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent routine access to the study site, and may therefore restrict collection of participant data. During such an emergency, if the site is unable to adequately follow the data collection schedule, alternative processes can be proposed and agreed with the Sponsor. All agreed changes will be properly documented in writing.	To accommodate visit flexibility for emergency/crisis
10.2 Definition of Source Data	AESIs were also added along with SAEs for source data filing	Data validation
10.3.2 Permanent treatment discontinuation with investigational medicinal product (s)	Option added for Sponsor decision as well, along with Investigator or patient decision	Patient safety
10.3.3 List of criteria for permanent treatment discontinuation	Added below text: Permanent treatment discontinuation can also be a Sponsor's decision. The list updated: "Major deviation to protocol (any medical event requiring administration of unauthorized medication during the study)" and "Lack of efficacy (treatment failure)" were added as reasons to the treatment discontinuation.	For better patient safety monitoring
10.3.5 Procedure and consequence for patient withdrawal from study	Below paragraph is added: Study withdrawal should be recorded by the Investigator in the appropriate forms of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.	For better study compliance

Section # and Name	Description of Change	Brief Rationale
10.4 Obligation of the investigator regarding safety reporting	• Section 10.4.1.1 updated • Section 10.4.1.2 updated • Section 10.4.1.3 updated • Section 10.4.2 updated • Section 10.4.3 updated • Section 10.4.4 updated • Section 10.4.5 updated • Section 10.4.6 updated • Section 10.4.7 updated	For ensuring patient safety and safety follow up compliance
10.5 Obligations of the sponsor	Below text is added: Investigator safety report must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.	For aligning with Sponsor safety reporting process
10.8 Contraception	Section added for contraception guidance of study participants	For ensuring patient safety
11.1 Determination of Sample Size	Description and calculation updated	To accommodate statistical analysis plan changes
11.3.3 Pharmacokinetic population	Description updated	To accommodate statistical analysis plan changes
11.4.2.3 Analysis of Pharmacokinetic data	Method updated	To accommodate statistical analysis plan changes
12.2 Informed consent	Added below text: The patient needs to consent in writing for the Sponsor authorized services such as direct to patient drug delivery and home visit by healthcare technician.	To ensure patient informed agreement
13.3 Source Document Requirements	Added text for risk-based monitoring	Added in the context of pandemic
17 Appendices	Added new appendices – Appendix B Country-Specific Requirements – Appendix C Protocol Amendment History	
Throughout the document	• Investigational medicinal product updated as: Hectorol® (doxercalciferol) or authorized generic • Non-investigational medicinal product updated as: Rocaltrol® (calcitriol) or authorized generic Updated study age group from 5-18 years to 5-17 years Minor formatting and typographical updates	To ensure consistency in case of clinical supply changes for the products Clarification of the recruitment criteria related to age Editorial updates

CLINICAL TRIAL SUMMARY

COMPOUND:	**STUDY No: LPS14314**
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
INVESTIGATOR/TRIAL LOCATION	United States and South America
PHASE OF DEVELOPMENT	Phase III
STUDY OBJECTIVE(S)	**Primary objective:** Evaluate the effect of Hectorol® (doxercalciferol) capsules in reducing elevated levels of intact parathyroid hormone (iPTH). **Secondary objective(s):** Evaluate the safety profile of Hectorol® capsules versus Rocaltrol® (calcitriol) capsules. Determine the pharmacokinetic profile of 1,25-dihydroxyvitamin D_2 after administration of Hectorol®.
STUDY DESIGN	Randomized, open label, parallel, active comparator study in patients aged 5-17 years with Chronic Kidney Disease (CKD) Stages 3 and 4 and secondary hyperparathyroidism (SHPT) not yet on dialysis. The study will include a Screening Period (10 days to 6 weeks), a Primary Efficacy Period (12 weeks), a Safety Continuation Period (12 weeks) and a post treatment follow up period (4 weeks). Patients will be stratified by age and CKD Stage at baseline with: • At least 30% of patients <12 years of age and at least 30% of patients ≥12 years of age. • At least 30% of patients with Stage 3 (GFR = 30-59 mL/min/1.73m^2) CKD and at least 30% of patients with Stage 4 (GFR = 15-29 mL/min/1.73m^2) CKD. The Rocaltrol® (or authorized generic) active comparator treatment group is included for qualitative comparison purposes only. No formal statistical comparison between the Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) treatment group outcomes will be made. Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) dosing will be titrated to individualized iPTH patient level management. The starting weekly dose and subsequent dose titrations of Hectorol® capsules (or authorized generic) in pediatric patients will not exceed the adult weekly starting dose. See the titration scheme in the Dosing Instructions. The starting dose and titration instructions for Rocaltrol® (or authorized generic) capsules will follow the pediatric pre-dialysis secondary hyperparathyroidism label instructions. In case of product unavailability, Hectorol® and / or Rocaltrol® brand can be substituted by authorized generic forms for use in this trial. Substitute compounds are similar and equivalent as per “Chemistry, Manufacturing and

	Controls (CMC) department, therefore posing no changes in the overall efficacy, tolerability or safety.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** I 01. Male or female aged 5 to 17 years old (both inclusive) at the time of randomization. I 02. Weight ≥ 15 kg. I 03. CKD Stage 3 or 4 not on dialysis, defined as GFR between 15 and 59 mL/min/1.73m^2 (established by Schwartz equation) at Week -2 visit. I 04. iPTH value > 75 pg/mL (8.0 pmol/L) for CKD Stage 3 or > 110 pg/mL (11.7 pmol/L) for CKD Stage 4, at Week -2 visit at screening. I 05. Signed informed consent / assent form. **Exclusion criteria:** E 01. The patient has a serum 25-hydroxyvitamin D level <25 ng/ml (62.31 mmol/L) at screening. E 02. The patient has a corrected calcium ≥10.2 mg/dL at the Week -2 visit. E 03. The patient has a serum phosphorus >5.5 mg/dL (1.77mmol/L) for children 13 to 17 years of age; >5.8 mg/dL (1.87mmol/L) for children 5 to 12 years of age at the Week -2 visit. E 04. The patient is anticipated to require maintenance hemodialysis within 3 months. E 05. Deleted in amended protocol 03 E 06. The patient has a history of, or active, symptomatic heart disease within 12 months prior to the baseline (Week 0) visit. E 07. The patient currently has a chronic gastrointestinal disease (ie, malabsorption, severe chronic diarrhea, chronic ulcerative colitis, or ileostomy). E 08. The patient currently has primary hyperparathyroidism or has had a total parathyroidectomy. E 09. The patient has an active malignancy. E 10. The patient is unable to swallow a capsule in size similar to the Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) capsules. E 11. The patient has a history of sensitivity or allergy to doxercalciferol, calcitriol or other vitamin D analogs. E 12. The patient has a history of or active ethanol or drug dependence or abuse, excluding tobacco use. E 13. The patient has taken other investigational drugs within 1 month or 5 half-lives, whichever is longer, prior to screening. E 14. The patient is medically unstable or is not otherwise suitable for study participation, in the opinion of the Investigator. E 15. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study. E 16. Pregnant or breast-feeding female. E 17. Female or male patient who is sexually active and unwilling to abstain from sexual intercourse or is not protected by a highly effective contraceptive method of birth control.

<table>
<tr><td></td><td>E 18. All contraindications of Rocaltrol (or authorized generic) and warning/precaution of Rocaltrol (or authorized generic) use as per the US Rocaltrol (or authorized generic) Labeling (Rocaltrol package insert or authorized generic package insert).
E 19. The patient currently uses aluminum or magnesium-based binders.
E 20. The patient has liver function abnormalities as defined by ALT >3x ULN.</td></tr>
<tr><td>Total expected number of patients</td><td>57</td></tr>
<tr><td>STUDY TREATMENT(s)</td><td></td></tr>
<tr><td>Investigational medicinal product(s)
Formulation:
Route(s) of administration:
Dose regimen:</td><td>Hectorol® (doxercalciferol) or authorized generic
Capsule (0.5 mcg)
Oral
A dose titration scheme is used to individualize the dose to the patient's iPTH management.
<u>Starting Dose</u>:
12 to 17 years old: One 0.5 mcg capsule taken three days a week, at a frequency of every two to three days
5 to < 12 years old: One 0.5 mcg capsule taken two days a week, at a frequency of every three to four days
<table>
<tr><td colspan="3">Starting Dose by Age Groups</td></tr>
<tr><td>Age Group</td><td>Weekly Dose</td><td>Schedule example</td></tr>
<tr><td>12 to 17 years</td><td>3 times weekly</td><td>Monday, Wednesday, Friday</td></tr>
<tr><td>5 to < 12 years</td><td>2 times weekly</td><td>Monday, Thursday</td></tr>
</table>
<u>Dose Titration</u>:
<u>Dose evaluation</u> every 2 weeks, after the study visit's (for on-site or home) iPTH and central laboratory values are received.
The dosage will be increased <u>If</u> iPTH is reduced <30% comparing with the baseline value <u>AND/OR does not</u> reach the physician's clinically desired iPTH range for the patient. Otherwise the actual dosage will be maintained. Physicians can modify the dosage for any safety reason.
<u>Dose titration</u> as outlined in Section 8.1.1 of the protocol. Dose titration is dependent on patient age (5 to <12 years), and (12 to 17 years). For the younger age group (5 to <12 years), patient weight (<30 kg, or <u>≥</u>30 kg) is also taken into consideration.
<u>Decrease the dose</u> by one capsule per day or per week depending on the current dose to a minimum of 1 capsule taken once per week.
The maximum dose is 5 capsules per day taken 7 days per week, and the minimum dose is 1 capsule taken once a week (0.5 mcg/week to 17.5 mcg/weekly dosing range).</td></tr>
</table>

Non investigational medicinal product Formulation:	**Rocaltrol® (calcitriol) or authorized generic**
Formulation:	Capsule (0.25 mcg)
Route(s) of administration:	Oral
Dose regimen:	Note: starting dose and titration recommendations per U.S. PI for Rocaltrol®, or authorized generic. A dose titration scheme is used to individualize the dose to the patient's iPTH management. **Starting Dose**: One 0.25 mcg capsule/day taken seven days a week. **Dose Titration:** Dose evaluation every 2 weeks, after each study visit's iPTH central laboratory value is received. The dosage will be increased **If** iPTH is reduced <30% comparing with the baseline value **AND/OR does not** reach the physician's clinically desired iPTH range for the patient. Otherwise the actual dosage will be maintained. Physicians can modify the dosage for any safety reason. Dose titration: This dosage (starting dose) may be increased if necessary, to 0.5 mcg/day (Two 0.25 mcg capsules seven days a week).
ENDPOINT(S)	**Primary endpoint:** Efficacy: Percentage of patients achieving two consecutive ≥ 30% reductions in iPTH from baseline up to Week 12. **Secondary endpoint(s):** Efficacy: Percentage change in iPTH from baseline to Weeks 12 and 24. Frequency of hypercalcemia, defined as albumin corrected serum calcium >10.2 mg/dL, up to Weeks 12 and 24. Safety: Adverse Events (AEs). Vital signs. Clinical laboratory assessments. Pharmacokinetics: Plasma 1,25-dihydroxyvitamin D_2 concentration-time data.

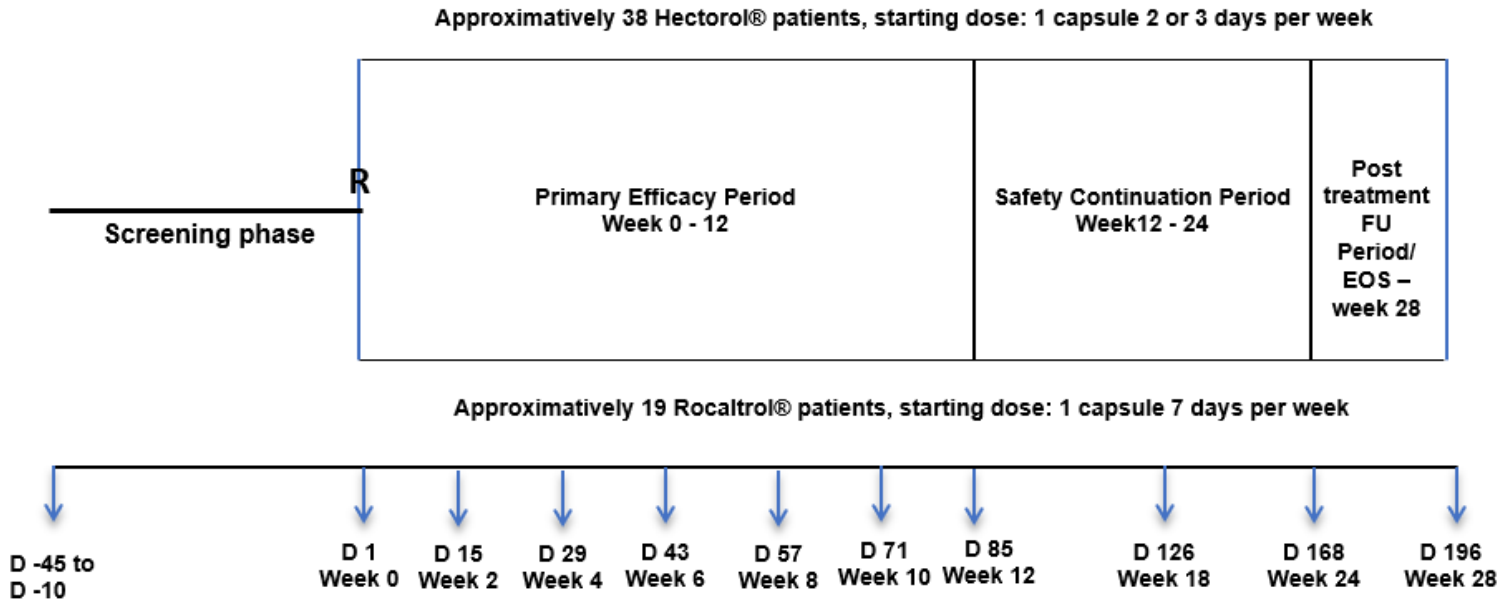
ASSESSMENT SCHEDULE	**Refer to the study flow-chart** **Primary Efficacy Phase (up to Week 12)** **Safety Continuation Phase (between Week 12 to 24)** **Post treatment follow-up Phase (from Week 24 to Week 28)** **Pharmacokinetic parameters:** Upto 18 Hectorol® (or authorized generic) patients (50% of patients <12 years of age) will undergo serial PK sampling in PK subgroup. **SPARSE PK** 1,25-dihydroxyvitamin D_2 will be assessed at Week -2, Baseline, and then within 24 hours of the most recent dose of Hectorol® (or authorized generic) at Weeks 2, 4, 6, 8 or 12 and 10. **SERIAL PK** 1,25-dihydroxyvitamin D_2 will be assessed with serial time point draws (Hours 1 to 3, 4 to 6, 7 to12, and 24 to 36 post-dose in the office/facility) at either the Week 8 or 12 visit. Choice is per the schedule availability of the site and patient.
STATISTICAL CONSIDERATIONS	**Sample size determination:** **Power and Sample Size:** The Rocaltrol (or authorized generic) 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® (or authorized generic) and Rocaltrol treatment group outcomes will be made. Approximately 57 patients will be randomized in a 2:1 ratio to the Hectorol® (or authorized generic) and Rocaltrol (or authorized generic) treatment groups. The study randomization scheme will be stratified by age group (ie, 5 to <12, and 12 to 18, years of age) and CKD stage (ie, 3 and 4). A sample size of 30 patients for the Hectorol® (or authorized generic) treatment group provides 70% power to detect a difference, for the Hectorol® (or authorized generic) treatment group, from a value of <30% for the proportion of patients achieving the primary endpoint, assuming a 2-sided alpha = 0.05, using the normal approximation and that the true proportion for the Hectorol® (or authorized generic) treatment group is 50%. Approximately 38 patients will be randomized to the Hectorol (or authorized generic) treatment group, allowing for 20% early terminations / unevaluable patients. The limits for a 95% confidence interval constructed for the proportion of Hectorol (or authorized generic) treatment group patients achieving the primary endpoint would be ±0.16, assuming 0.50 for the proportion and 38 Hectorol® (or authorized generic) treated patients. The estimate for the proportion of patients achieving the primary endpoint for the Hectorol (or authorized generic) treatment group is extrapolated from the percent changes in plasma iPTH for the doxercalciferol treatment group summarized in Figure 1 of Coburn et al 2004, *Am J Kidney Dis*, (1).

	For the purpose of making a qualitative comparison of the Hectorol® (or authorized generic) safety profile to the active comparator treatment group, a sample size of 15 patients for the Rocaltrol® (or authorized generic) treatment group is based on the 2:1 randomization of patients to the Hectorol® (or authorized generic) treatment group and Rocaltrol® (or authorized generic) treatment group. To allow for 20% early terminations / unevaluable patients, approximately 19 patients will be randomized to the Rocaltrol® (or authorized generic) treatment group. **Analysis population:** **Analysis Sets:** Safety Set: All enrolled patients who are treated with at least 1 dose of study drug. Full Analysis Set: All treated patients with at least 2 assessments of iPTH after use of study drug. Per Protocol Set: All Full Analysis Set-evaluable patients with no significant protocol deviations. **Demographics and Baseline Characteristics:** Demographics and baseline characteristics will be summarized. **Primary analysis:** **Efficacy:** Analyses for efficacy outcomes are descriptive and will be summarized using the Full Analysis Set (primary) and the Per Protocol Set (confirmatory). The percentage of patients meeting the iPTH ≥30% reduction from baseline at 2 consecutive study visits up to Week 12 will be calculated. A 95% confidence interval will be constructed for the proportion of patients achieving the endpoint for the Hectorol® (or authorized generic) treatment group. 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 prior to and including Week 12. The proportion achieving the endpoint for the Rocaltrol (or authorized generic) treatment group will also be summarized. No formal statistical comparison will be made between the Hectorol® (or authorized generic) and Rocaltrol (or authorized generic) treatment groups. **Secondary analysis:** The percentage change in iPTH from baseline to Weeks 12 and 24 will be summarized with descriptive statistics. For the changes from baseline iPTH, the effects over the treatment period time will be explored using a mixed model for repeated measures approach. The complete details, including potential sensitivity analyses for missing data, will be included in the statistical analysis plan. The frequency of hypercalcemia (albumin corrected serum calcium >10.2 mg/mL) up to Weeks 12 and 24 will be summarized descriptively.

	Safety: Safety analyses will be summarized using the Safety Set. Adverse events and serious adverse events (SAEs) will be summarized overall, by System Organ Class (SOC) and Preferred Term (PT), using the standardized Medical Dictionary for Regulatory Activities. Adverse events will also be summarized by severity, in which a patient's most severe event within a category (eg, treatment regimen, SOC, PT) will be counted. In addition, treatment-related adverse events will be tabulated. Listings will be provided for all AEs, including those arising before or after treatment, SAEs and AEs leading to discontinuation from the study. Descriptive statistics will be calculated for vital signs and clinical laboratory results at each study time point and for the change from baseline to each post-baseline study time point. **Pharmacokinetics:** Evaluation of the 1,25-dihydroxyvitamin D2 concentration-time data obtained in this study will be conducted using noncompartmental methods including the following parameters like C_{max} and $AUC_{0\text{-}tau}$ at week 8 or 12 when Serial PK Samples are collected. If feasible, a model based approach using NONMEM (Icon, Hanover MD USA, Version 7 Level 2 or higher) can be used to derive individual and population mean parameters including absorption rate constant, clearance and volume of distribution will be reported. If feasible, derived parameters including area under the concentration-time curve will be reported. No formal statistical evaluation of the derived parameters is planned. The pharmacokinetics analyses will be performed separately from the analyses of the other clinical study variables.
DURATION OF STUDY PERIOD (per patient)	10 days to 6 weeks of Screening: • 2-week washout required before inclusion/exclusion laboratory measurements, if patients using exclusion criteria E 05 medications at the time of consent. 24 weeks of Treatment: • Day 1 to Week 12 - Primary Efficacy Period (12 weeks) • Weeks 12 to 24 - Safety Continuation Period (12 weeks) • Post-treatment follow-up period/ End of Study Visit – Week 28

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Detailed information on specific activities at individual visits are shown in the Study Flow Chart 1.2

1.2 STUDY FLOW CHART

	Screening (Washout NOT required)[a]	Screening (Washout Required)[a]		PRIMARY EFFICACY PERIOD							SAFETY CONTINUATION PERIOD		POST-TREATMENT FOLLOW-UP PERIOD/ END OF STUDY
VISIT	1 Week -2[b]	1a Week -6	1b Week -2[b]	2 Week 0	3 Week 2	4 Week 4	5 Week 6	6 Week 8	7 Week 10	8 Week 12	9 Week 18	10 Week 24/ET	11 Week 28/EOS
DAY	Day -14 to -10	Day -45	Day -14 to -10	Day 1	Day 15 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 57 ±3 days	Day 71 ±3 days	Day 85 ±3 days	Day 126 ±7 days	Day 168 ±7 days	Day 196 ±7 days
VISIT TYPE[c, d]	On-site visit	On-site visit	On-site visit	On-site visit	Home-visit	Home-visit	Home-visit	On-site visit	Home-visit	On-site visit	Home-visit	On-site visit	Home-visit
Informed Consent	x	x											
Inclusion Criteria	x	x	x	x									
Exclusion Criteria	x	x	x	x									
Patient Demography	x	x											
Medical/Surgical History	x	x											
Prior Medication	x	x											
Dietary Consult	x	x											
ECG				x						x			
Randomization				x									
Treatment													
Review of phosphate binder use and diet compliance[d]	x	x	x	x	x	x	x	x	x	x	x	x	
Study Treatment(s)													
Hectorol® (or authorized generic) / Rocaltrol® (or authorized generic)				←	—	—	—	—	—	—	—	→	
Review of dosing compliance / patient diary[d]					x	x	x	x	x	x	x	x	
Dose adjustment evaluation[d]					x	x	x	x	x	x	x		
Drug accountability[d]					x	x	x	x	x	x	x	x	
Dispense study drug				x				x		x			
Direct To Patient					x	x	x		x		x		

	Screening (Washout NOT required)[a]	Screening (Washout Required)[a]		PRIMARY EFFICACY PERIOD							SAFETY CONTINUATION PERIOD		POST-TREATMENT FOLLOW-UP PERIOD/ END OF STUDY
VISIT	1 Week -2[b]	1a Week -6	1b Week -2[b]	2 Week 0	3 Week 2	4 Week 4	5 Week 6	6 Week 8	7 Week 10	8 Week 12	9 Week 18	10 Week 24/ET	11 Week 28/EOS
DAY	Day -14 to -10	Day -45	Day -14 to -10	Day 1	Day 15 ±3 days	Day 29 ±3 days	Day 43 ±3 days	Day 57 ±3 days	Day 71 ±3 days	Day 85 ±3 days	Day 126 ±7 days	Day 168 ±7 days	Day 196 ±7 days
VISIT TYPE[c, d]	On-site visit	On-site visit	On-site visit	On-site visit	Home-visit	Home-visit	Home-visit	On-site visit	Home-visit	On-site visit	Home-visit	On-site visit	Home-visit
Efficacy													
iPTH[e]	x		x	x	x	x	x	x	x	x	x	x	
Safety													
AE /SAE monitoring (continuous post-ICF)[d]	x	x	x	x[j]	x	x	x	x	x	x	x	x	x
Concomitant medication[d]	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs[f]	x		x	x								x	x
Height and weight	x		x									x	
Laboratory Testings													
Pregnancy test [e, g]	x		x	x		x		x		x	x	x	
Serum calcium, phosphorus, albumin, calcium-phosphorus product[e]	x		x	x	x	x	x	x	x	x	x	x	
Blood chemistry, hematology[e]	x		x	x				x[e]		x[e]		x	
25-hydroxyvitamin D	x	x										x	
GFR calculation[e]	x		x					x[e]		x[e]		x	
1,25-dihydroxyvitamin D_2 for pharmacokinetic assessment (if randomized to Hectorol® (or authorized generic) [e]	x[h]		x[h]	x[i]	x	x	x	x[k]	x	x[k]			

a In case the patient was taking cinacalcet or Vitamin D sterol therapies such as calciferol, doxercalciferol or paricalcitol within 14 days prior to the screening, these drugs will be discontinued at the first screening visit (visit 1a). An additional screening visit (visit 1b) will be scheduled 4 weeks after visit 1a. he baseline visit will follow 45 days (or 6 weeks) after the first screening visit 1a (wash-out period) and 2 weeks after the visit 1b.

b Week -2 visits can be performed within 14 to 10 days prior to baseline (Week 0 visit).

c If home-visit facility not available for the site or not allowed per local regulation, all visits will remain on-site.

d For home visits, the site has to arrange a remote visit (via any digital contact) in order to review phosphate binder use, diet compliance, dosing compliance and patient's diary; dose adjustment evaluation, drug accountability; AE/SAE monitoring and recording of concomitant medication.

e Hematology (red blood cell count, reticulocyte count [to be performed per local lab where applicable], hemoglobin, hematocrit, platelets, white blood cell count with differential blood count). Blood chemistry (sodium, potassium, bicarbonate, chloride, liver function tests (ALT, AST, total and direct bilirubin, alkaline phosphatase, GGTP), blood glucose, kidney function tests (serum creatinine, blood urea nitrogen) and GFR calculation. Samples to be collected by a healthcare technician from sponsor authorized services for home visits. For on-site visits, the samples to be collected at the site. At visit 6 and visit 8, only serum creatinine, blood urea nitrogen, eGFR samples to be collected and performed.

f Including blood pressure, heart rate, respiratory rate and temperature. For end of study visit, a healthcare technician from sponsor or authorized services will perform these as part of home visits.

g Post-menarchal female patients will have a serum pregnancy test at the Week -2, and Week 12 visits and a urine pregnancy test every 4 weeks (Week 0, 4 and 8), followed by a urine pregnancy test at Week 18, and Week 24.

h Sample to be collected in all patients but analyzed only in patients randomized to Hectorol® (or authorized generic).

i Sample to be collected after randomization (in patient randomized to Hectorol®) (or authorized generic) and prior to the first dose intake.

j AE monitoring (hypercalciuria) of urinalysis at initial 24-hour and 24-hour urine test, to be stored in a sterile container provided during screening.

k Serial PK Samples will be collected from up to 18 Hectorol (or authorized generic) patients' post-dose at hours 1 to 3, 4 to 6, 7-12, and 24-36 hours at either Week 8 or Week 12 – choice is per the schedule availability of the site and patient. At the chosen date, the dose of Hectorol® (or authorized generic) will be administered at the site. A catheter will be used to minimize the number of venipunctures. See Section 9.3.1.1 for additional information.

2 TABLE OF CONTENTS

1 FLOW CHARTS 19
1.1 GRAPHICAL STUDY DESIGN 19
1.2 STUDY FLOW CHART 20
2 TABLE OF CONTENTS 23
3 LIST OF ABBREVIATIONS 28
4 INTRODUCTION AND RATIONALE 29
4.1 INTRODUCTION 29
4.2 RATIONALE 29
4.2.1 STUDY DESIGN RATIONALE 29
4.2.2 Dose and regimen 30
5 STUDY OBJECTIVES 31
5.1 PRIMARY 31
5.2 SECONDARY 31
6 STUDY DESIGN 32
6.1 DESCRIPTION OF THE PROTOCOL 32
6.2 DURATION OF STUDY PARTICIPATION 32
6.2.1 Duration of study participation for each patient 32
6.2.2 Determination of end of clinical trial (all patients) 32
6.3 INTERIM ANALYSIS 33
6.4 STUDY COMMITTEES 33
6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS 33
7 SELECTION OF PATIENTS 34
7.1 INCLUSION CRITERIA 34
7.2 EXCLUSION CRITERIA 34
7.2.1 Exclusion criteria related to study methodology 34
7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies 35
7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound 35

8 STUDY TREATMENTS 36

8.1 INVESTIGATIONAL MEDICINAL PRODUCT 36
8.1.1 Dose Titration 36

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT 40

8.3 BLINDING PROCEDURES 41
8.3.1 Methods of blinding 41

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP 41

8.5 PACKAGING AND LABELING 41

8.6 STORAGE CONDITIONS AND SHELF LIFE 41

8.7 RESPONSIBILITIES 42
8.7.1 Treatment accountability and compliance 42
8.7.2 Return and/or destruction of treatments 43

8.8 CONCOMITANT MEDICATION 43

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT 44

9.1 PRIMARY ENDPOINT 44
9.1.1 Primary efficacy endpoint 44

9.2 SECONDARY ENDPOINTS 44
9.2.1 Secondary efficacy endpoints 44
9.2.2 Safety endpoints 44
9.2.2.1 Adverse events 44
9.2.2.2 Laboratory safety variables 44
9.2.2.3 Vital signs 45

9.3 OTHER ENDPOINTS 45
9.3.1 Pharmacokinetics 45
9.3.1.1 Sampling time 45
9.3.1.2 Pharmacokinetics handling procedure 45
9.3.1.3 Bioanalytical method 46
9.3.1.4 Pharmacokinetics parameters 46
9.3.2 Pharmacogenetic assessment 46

9.4 FUTURE USE OF SAMPLES 46

9.5 APPROPRIATENESS OF MEASUREMENTS 46

10 STUDY PROCEDURES 47

10.1 VISIT SCHEDULE 48

10.1.1 First Screening Visit 1a, Week-6, day-45, Wash-out required (on-site visit) 48
10.1.2 Screening Visit – Visit 1, Week -2 (no wash-out required) or Visit 1b, Week -2, (wash–out required) (on-site visit) Day-14 to Day-10 49
10.1.3 Randomization Visit, Visit 2, Week 0, Day 1 (on-site visit) 49
10.1.4 Visit 3, Week 2 (home visit), Visit 4, Week 4 (home visit), Visit 5, Week 6 (home visit), Visit 6, Week 8 (on-site visit), Visit 7, Week 10 (home visit) and Visit 8, Week 12 (on-site visit): 50
10.1.5 Visit 9, Week 18 (home visit) 51
10.1.6 Visit 10, Week 24, End of Treatment Visit (on-site visit) 51
10.1.7 Visit 11, Week 28, End of Study Visit (home visit) 52
10.1.8 Unscheduled Visits 52
10.2 DEFINITION OF SOURCE DATA 52
10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION 52
10.3.1 Temporary treatment discontinuation with investigational medicinal product 52
10.3.2 Permanent treatment discontinuation with investigational medicinal product(s) 53
10.3.3 List of criteria for permanent treatment discontinuation 53
10.3.4 Handling of patients after permanent treatment discontinuation 53
10.3.5 Procedure and consequence for patient withdrawal from study 54
10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING 55
10.4.1 Definitions of adverse events 55
10.4.1.1 Adverse event 55
10.4.1.2 Serious adverse event 55
10.4.1.3 Adverse event of special interest 56
10.4.2 Evaluation of events, seriousness, severity and causality 57
10.4.3 Documentation of Adverse events 58
10.4.4 General guidelines for reporting adverse events 58
10.4.5 Instructions for reporting serious adverse events 59
10.4.6 Follow up of adverse events 60
10.4.7 Guidelines for management of specific laboratory abnormalities 61
10.5 OBLIGATIONS OF THE SPONSOR 62
10.6 SAFETY INSTRUCTIONS 62
10.6.1 Management of elevated serum albumin corrected calcium > 10.2 mg/dl 62
10.7 ADVERSE EVENTS MONITORING 62
10.8 CONTRACEPTION 63
11 STATISTICAL CONSIDERATIONS 65

11.1 DETERMINATION OF SAMPLE SIZE 65
11.2 DISPOSITION OF PATIENTS 65
11.3 ANALYSIS POPULATIONS 66
11.3.1 Efficacy populations 66
11.3.2 Safety population 66
11.3.3 Pharmacokinetic Population 66
11.4 STATISTICAL METHODS 66
11.4.1 Extent of investigational medicinal product exposure 67
11.4.1.1 Extent of investigational medicinal product exposure 67
11.4.1.2 Compliance 67
11.4.2 Analyses of efficacy endpoints 67
11.4.2.1 Analysis of primary efficacy endpoint(s) 67
11.4.2.2 Analyses of secondary efficacy endpoints 68
11.4.2.3 Analysis of Pharmacokinetic data 68
11.4.3 Analyses of safety data 68
12 ETHICAL AND REGULATORY CONSIDERATIONS 70
12.1 ETHICAL AND REGULATORY STANDARDS 70
12.2 INFORMED CONSENT 70
12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC) 71
13 STUDY MONITORING 72
13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S) 72
13.2 RESPONSIBILITIES OF THE SPONSOR 72
13.3 SOURCE DOCUMENT REQUIREMENTS 72
13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST 73
13.5 USE OF COMPUTERIZED SYSTEMS 73
14 ADDITIONAL REQUIREMENTS 74
14.1 CURRICULUM VITAE 74
14.2 RECORD RETENTION IN STUDY SITES 74
14.3 CONFIDENTIALITY 74
14.4 PROPERTY RIGHTS 75
14.5 DATA PROTECTION 75

14.6 INSURANCE COMPENSATION....75

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES....76

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE....76

14.8.1 By the Sponsor....76

14.8.2 By the Investigator....77

14.9 CLINICAL TRIAL RESULTS....77

14.10 PUBLICATIONS AND COMMUNICATIONS....77

15 CLINICAL TRIAL PROTOCOL AMENDMENTS....78

16 BIBLIOGRAPHIC REFERENCES....79

17 APPENDICES....80

APPENDIX A GENERAL GUIDANCE FOR THE FOLLOW-UP OF LABORATORY ABNORMALITIES BY SANOFI....81

APPENDIX B COUNTRY-SPECIFIC REQUIREMENTS....85

APPENDIX C PROTOCOL AMENDMENT HISTORY....86

3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
AUC:	area under the curve
CKD:	chronic kidney disease
CMC:	Chemistry, Manufacturing and Controls
CRF:	case report form
eCRF:	electronic case report form
GCP:	good clinical practice
GFR:	glomerular filtration rate
GGT:	gamma glutamyl transpeptidase
ICH:	International Conference of Harmonization
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
iPTH:	intact parathyroid hormone
IRB:	investigational review board
IVRS:	Interactive Voice Response System
K/DOQI:	kidney disease outcome quality initiative
mcg:	microgram
PCSA:	potentially clinically significant abnormality
PT:	preferred term
SAE:	serious adverse event
SD:	standard deviation
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
tmax:	time to maximal plasma concentration
ULN:	upper limit of normal
WOCBP:	woman of child bearing potential

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

There are limited clinical data on the use of active vitamin D compounds in children with chronic kidney disease (CKD) and secondary hyperparathyroidism (SHPT) (2). Calcitriol (Rocaltrol® or authorized generic), an active vitamin D3, has been administered in open-label studies to children with CKD Stages 3 and 4. In these studies, calcitriol was found to be generally well tolerated and to improve bone disease (3) A pharmacokinetic study in a small group of pediatric peritoneal dialysis patients found the steady-state pharmacokinetics of calcitriol to be: mean maximum concentration (C_{max}) 116 pmol/L, mean serum half-life 27.4 hours, and mean clearance 15.3 mL/hr/kg (4). Based on this information, the recommended starting dose of calcitriol for children over 3 years of age is 0.25 mcg per day (3). Rocaltrol® (or authorized generic) capsules will be used as a comparator for the safety experience of Hectorol (or authorized generic) capsules.

Doxercalciferol (Hectorol®or authorized generic) is a vitamin D_2 prodrug (1α-hydroxyvitamin D_2) that is converted by the liver to active 1,25-dihydroxycalciferol D_2, a naturally occurring, biologically active form of vitamin D_2. Doxercalciferol has been shown to lower intact parathyroid hormone levels (iPTH) in adult patients with CKD Stages 3 to 5 with moderate to severe SHPT (1, 5, 6). The pharmacokinetics of 1,25-dihydroxyvitamin D_2 following oral dosing of doxercalciferol has also been investigated in adult CKD patients. In a study of 11 CKD Stage 5 patients who received 10 mcg oral doxercalciferol every 48 hours for 5 doses followed by 5 mcg oral doxercalciferol every 48 hours for an additional 5 doses, the mean pharmacokinetic parameters for 1,25-dihydroxyvitamin D_2 were: C_{max} = 38.0 ±21.1 pg/mL; time of maximum drug concentration (tmax) = 12.4 ±2.8 hrs; area under the concentration-time curve (AUC) = 1232 ±731 hr x pg/mL (7). The risk/benefit of doxercalciferol in pediatric CKD patients, however, has not been established.

The purpose of this study is to evaluate the efficacy, safety, and pharmacokinetics of doxercalciferol in pediatric Stages 3 and 4 CKD patients with moderate to severe SHPT not yet on dialysis. For further information about Hectorol®, please refer to the current Investigational Brochure (8).

4.2 RATIONALE

4.2.1 STUDY DESIGN RATIONALE

This is a Phase III, multicenter, randomized, open label, parallel group, active control study in pediatric patients with Stages 3 and 4 CKD not yet on dialysis and elevated iPTH levels indicative of SHPT. Patients will be stratified at enrollment by age (5 to <12 and 12 to 17 years of age) and CKD severity (Stages 3 and 4), with at least 30% of patients in each age group and at least 30% of patients in each CKD Stage.

An active control study will support the interpretation of safety information in a medically complex patient population with multiple comorbidities and concomitant medications such as pediatric patients with chronic kidney disease Stages 3 and 4 with SHPT not yet on dialysis.

No formal statistical comparisons will be made between the Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) treatment groups for either efficacy or safety outcomes, and the study is not powered for such comparisons.

Table 1 - Screening Period: additional 1b Visit Scheduling (Week -2)

If Vitamin D Sterol or Calcimimetic (calcitriol/paricalcitol/doxercalciferol/cinacalcet) was taken by patient within 14 days prior to the first Screening Visit:
1a Screening Visit (Week – 6) à **1b Screening Visit** (**Week – 2)** à Week 0 Visit (in 10 to 14 days, after reviewing) Week - 2 Visit (laboratory results)
Diet & Phosphate Binder Adjustment Identified at Screening Visit
1a Screening Visit (Week – 6) à **1b Visit (Week – 2)** à Week 0 Visit (in 10 to 14 days, after reviewing) Week - 2 Visit (laboratory results)
• **If Vitamin D Sterol or Calcimimetic (calcitriol/paricalcitol/doxercalciferol/cinacalcet) was NOT taken by patient within 14 days prior to the first Screening Visit** **and** • **If no diet and no phosphate binder adjustment is required:** ➔ **No Washout** ➔Single **Screening Visit = Visit 1 (Week -2)**
Week – 2 Visit à Week 0 Visit (in 10 to 14 days, after reviewing Week - 2 Visit laboratory results)

4.2.2 Dose and regimen

The starting dose of Hectorol® (or authorized generic) per the package insert (9) for adult patients with SHPT and CKD Stages 3 or 4 is 1 mcg every day for a total weekly dose of 7 mcg. For this pediatric study, the starting dose of Hectorol (or authorized generic) and all potential titration increases are less than those used in adults and have been modeled to provide weekly exposures comparable to those observed in adults. The pediatric starting doses are: for 12 to 17 year-old patients, 0.5 mcg every 2 to 3 days for a total weekly dose of 1.5 mcg; and for 5 to <12 year-old patients, 0.5 mcg every 3 to 4 days for a total weekly dose of 1.0 mcg. The lower starting doses in this pediatric study may require multiple dose increases in order to decrease the elevated iPTH. However, the intent of the gradual dose titration is to minimize the potential for hypercalcemia, hyperphosphatemia, and /or other biochemical fluctuations in this complex pediatric patient disease.

The dose titrations and maximum doses used in this pediatric study have been modeled to provide comparable maximum exposures to those predicted for adult patients. After a series of dose titrations, the maximum dose in adults is 3.5 mcg every day for a total weekly dose of 24.5 mcg; the maximum dose in pediatric patients 12 to 17 years old is 2.5 mcg every day for a total weekly dose of 17.5 mcg; the maximum dose in pediatric patients 5 to <12 years old and ≥30 kg body weight is 2.0 mcg every day for a total weekly dose of 14.0 mcg; and the maximum dose in pediatric patients 5 to <12 years old and <30 kg body weight is 1.0 mcg every day for a total weekly dose of 7.0 mcg.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to evaluate the effect of Hectorol® (doxercalciferol) capsules in reducing elevated levels of intact parathyroid hormone (iPTH).

5.2 SECONDARY

The secondary objectives are:

- 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®.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This is a Phase III, randomized, multinational, open-label, parallel group, active comparator study in patients aged 5-17 years with CKD Stages 3 and 4 and SHPT not yet on dialysis. The study will include a Screening Period (10 days to 6 weeks), a Primary Efficacy Period (12 weeks), a Safety Continuation Period (12 weeks) and a Post-Treatment Follow up Period (4 weeks). Eligible patients will be randomized either to the Hectorol® (or authorized generic) or Rocaltrol® (or authorized generic) treatment groups in a 2:1 ratio and will be stratified by age and CKD Stage at baseline as follows:

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

All patients will be treated with either Hectorol® (or authorized generic) or Rocaltrol® (or authorized generic) from randomization until Week 24, which represents the end of treatment visit. The Post-treatment follow-up period / end of study (EOS) visit will be at Week 28.

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

Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) dosing will be adjusted to the iPTH plasma levels measured bi-weekly in all patients. For this pediatric study, the starting dose of Hectorol (or authorized generic) 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® (or authorized generic) capsules will follow the pediatric pre-dialysis SHPT label instructions (3).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

Following the Screening Period, which can last up to 6 weeks with 2 visits, eligible patients will be randomized and followed for 28 weeks. Twelve weeks after randomization, the Primary Efficacy Period ends. During that Period, 7 visits are planned. The subsequent Safety Continuation Period will last for another 12 weeks with additional 2 visits. The patient will complete the study (EOS) after 4 weeks of post-treatment follow-up period.

6.2.2 Determination of end of clinical trial (all patients)

The study is finished when the last patient completes the ‘end of study’ (EOS) visit at Week 28.

6.3 INTERIM ANALYSIS

Interim analysis can be planned on clinical and/ or pharmacokinetics data to support discussion with Regulatory Authority related to study conduct.

6.4 STUDY COMMITTEES

This is an open-label, active controlled study. No Study Committees are planned.

6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

Key study design elements are based on a regulatory post-marketing requirement for Hectorol® issued by the Food and Drug Administration (FDA) in the United States, as well as subsequent discussions with FDA. An appropriately designed active control study (ie, with Rocaltrol®) may be able to provide adequate information with regard to safety and efficacy of Hectorol® in this pediatric patient population.

In case of product unavailability, Hectorol® and / or Rocaltrol® brand can be substituted by authorized generic forms for use in this trial. Substitute compounds are similar and equivalent as per CMC, therefore posing no changes in the overall efficacy, tolerability or safety.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Male or female aged 5 to 17 years old (both inclusive) at the time of randomization.

I 02. Weight ≥15 kg.

I 03. CKD Stage 3 or 4 not yet on dialysis, defined as GFR between 15 and 59 mL/min/1.73 m^2 (established by Schwartz equation) at the Week -2 visit.

I 04. iPTH value >75 pg/mL (8.0 pmol/L) for CKD Stage 3 or > 110 pg/mL (11.7 pmol/L) for CKD Stage 4, at the Week -2 visit at screening*.

I 05. Written informed consent, signed by the patient's parent / legal guardian.

I 06. Written assent, for patients capable of understanding the purpose of the study.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. The patient has a serum 25-hydroxyvitamin D level < 25ng/ml (62.31 mmol/L) at screening*.

E 02. The patient has a corrected calcium ≥10.2 mg/dL at the Week -2 visit.

E 03. A serum phosphorus >5.5 mg/dL (1.77 mmol/L) for children 13 to 17 years of age; >5.8 mg/dL (1.87 mmol/L) for children 5 to 12 years of age at the Week -2 visit*.

E 04. The patient is anticipated to require maintenance hemodialysis within 3 months.

E 05. Deleted in amended protocol 03.

E 06. The patient has a history of, or active symptomatic heart disease within 12 months prior to the baseline (Week 0) visit.

E 07. The patient currently has a chronic gastrointestinal disease (ie, malabsorption, severe chronic diarrhea, chronic ulcerative colitis, or ileostomy).

E 08. The patient currently has primary hyperparathyroidism or has had a total parathyroidectomy.

E 09. The patient has an active malignancy.

E 10. The patient is unable to swallow a capsule in size similar to the Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) capsules.

E 11. The patient has a history of sensitivity or allergy to doxercalciferol, calcitriol or other vitamin D analogs.

E 12. The patient has a history of or active ethanol or drug dependence or abuse, excluding tobacco use.

E 13. The patient has taken other investigational drugs within 1 month or 5 half-lives, whichever is longer, prior to screening.

E 14. The patient is medically unstable or is not otherwise suitable for study participation, in the opinion of the Investigator.

E 15. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study.

E 16. Pregnant or breast-feeding female.

E 17. Female or male patient who is sexually active and unwilling to abstain from sexual intercourse or is not protected by a highly effective contraceptive method of birth control.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 18. All contraindications of Rocaltrol® (or authorized generic) and warning/precaution of Rocaltrol® (or authorized generic) use as per the US Rocaltrol® (or authorized generic) Labeling *(Rocaltrol® or authorized generic package insert)* (3).

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 19. The patient currently uses aluminum or magnesium-based binders.

E 20. The patient has liver function abnormalities as defined by ALT >3x ULN.

*Re-screening: Patients who failed screening initially may be re-screened for potential enrollment following investigator's clinical discretion and after discussion with Sponsor. Also, laboratory assessments may be repeated for potential enrollment following investigator's clinical discretion with Sponsor. Treatment considerations may be made at the investigator's discretion with possible reference to K/DOQI Clinical Practice Guidance for Bone Metabolism and Disease in Children with Chronic Kidney Disease; 2005 (2).

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT

The active ingredient in Hectorol® or authorized generic is doxercalciferol, a synthetic vitamin D_2 analog that undergoes metabolic activation *in vivo* to form 1α, 25-dihydroxyvitamin D_2, a naturally occurring, biologically active form of vitamin D_2.

Hectorol® (doxercalciferol capsules) or authorized generic is a soft gelatin capsule, containing 0.5 mcg doxercalciferol.

A dose titration scheme will be used to adjust the dose to the patients' iPTH plasma level. The **starting dose** depends on the patients' age as follows:

- 12 – 17 years old: one 0.5 mcg capsule taken three days a week, *at a frequency of every two to three days.*
- 5 to < 12 years old: one 0.5 mcg capsule taken two days a week, *at a frequency of every three to four days.*

Table 2 - Starting Dose by Age Groups

Starting Dose by Age Groups		
Age Group	**Weekly Dose**	**Schedule example**
12 to 17 years	0.5 mcg 3 times weekly	Monday, Wednesday, Friday
5 to <12 years	0.5 mcg 2 times weekly	Monday, Thursday

The **titration scheme** depends on the iPTH and central laboratory values (corrected total serum calcium and phosphorus) measured every two weeks. The dosage will be increased if iPTH is reduced <30% comparing with the baseline value AND/OR does not reach the physician's clinically desired iPTH range for the patient. Otherwise the actual dosage will be maintained. Physicians can modify the dosage for any safety reason. The target iPTH ranges are 35-70 pg/ml for Stage 3 CKD and 70-110 pg/mL for Stage 4 CKD in patients not receiving growth hormone. In patients receiving growth hormone, the target iPTH ranges may be higher.

8.1.1 Dose Titration

Dose evaluation every 2 weeks, after the study visit's iPTH and central laboratory values are received at the site.

The dosage will be increased **If** iPTH is reduced <30% comparing with the baseline value **AND/OR does not** reach the physician's clinically desired iPTH range for the patient. Otherwise the actual dosage will be maintained. Physicians can modify the dosage for any safety reason.

Dose adjustment		**iPTH value reaches desired range**	
		Yes	**No**
iPTH reduction from baseline >=30%	**Yes**	maintained	maintained
	No	maintained	Increase

Dose titration – the tables below outline the proposed dose increases for the younger and older age groups respectively. Dose titration is dependent on patient age (5 to <12 years), and (12 to 17 years). For the younger age group (5 to <12 years), patient weight (<30 kg, or ≥30 kg) is also taken into consideration.

Table 3 - Dose Titration for Patients 5 to <12 Years of Age (<30 kg)

	Total # Capsules / Week	# Days Dosed	Example Schedule
Starting Dose	2	Two days per week	1 capsule Monday 1 capsule Thursday
Titration 1	4	Four days per week	1 capsule Monday 1 capsule Thursday 1 capsule Friday 1 capsule Sunday
Titration 2	7	Seven days per week	1 capsule Monday 1 capsule Tuesday 1 capsule Wednesday 1 capsule Thursday 1 capsule Friday 1 capsule Saturday 1 capsule Sunday
Titration 3	9	Seven days per week	2 capsules Monday 1 capsule Tuesday 1 capsule Wednesday 1 capsule Thursday 2 capsules Friday 1 capsule Saturday 1 capsule Sunday
Titration 4	11	Seven days per week	2 capsules Monday 1 capsule Tuesday 1 capsule Wednesday 2 capsules Thursday 2 capsules Friday 1 capsule Saturday 2 capsules Sunday
Titration 5[a]	14	Seven days per week	2 capsules Monday 2 capsules Tuesday 2 capsules Wednesday 2 capsules Thursday 2 capsules Friday 2 capsules Saturday 2 capsules Sunday

a There is a total of 5 possible dose titrations (dose titrations occur at Week 2, 4, 6, 8, 10, 12, and 18).

Table 4 - Dose Titration for Patients 5 to <12 Years of Age (≥30 kg)

	Total # Capsules / Week	# Days Dosed	Example Schedule
Starting Dose	2	Two days per week	1 capsule Monday
			1 capsule Thursday
Titration 1	4	Four days per week	1 capsule Monday
			1 capsule Thursday
			1 capsule Friday
			1 capsule Sunday
Titration 2	7	Seven days per week	1 capsule Monday
			1 capsule Tuesday
			1 capsule Wednesday
			1 capsule Thursday
			1 capsule Friday
			1 capsule Saturday
			1 capsule Sunday
Titration 3	14	Seven days per week	2 capsules Monday
			2 capsules Tuesday
			2 capsules Wednesday
			2 capsules Thursday
			2 capsules Friday
			2 capsules Saturday
			2 capsules Sunday
Titration 4	21	Seven days per week	3 capsules Monday
			3 capsules Tuesday
			3 capsules Wednesday
			3 capsules Thursday
			3 capsules Friday
			3 capsules Saturday
			3 capsules Sunday
Titration 5[a]	28	Seven days per week	4 capsules Monday
			4 capsules Tuesday
			4 capsules Wednesday
			4 capsules Thursday
			4 capsules Friday
			4 capsules Saturday
			4 capsules Sunday

a There is a total of 5 possible dose titrations (dose titrations occur at Week 2, 4, 6, 8, 10, 12, and 18).

Table 5 - Dose Titration for Patients 12 to 17 Years of Age

	Total # Capsules / Week	# Days Dosed	Example Schedule
Starting Dose	3	Three days per week	1 capsule Monday 1 capsule Wednesday 1 capsule Friday
Titration 1	7	Seven days per week	1 capsule Monday 1 capsule Tuesday 1 capsule Wednesday 1 capsule Thursday 1 capsule Friday 1 capsule Saturday 1 capsule Sunday
Titration 2	14	Seven days per week	2 capsules Monday 2 capsules Tuesday 2 capsules Wednesday 2 capsules Thursday 2 capsules Friday 2 capsules Saturday 2 capsules Sunday
Titration 3	21	Seven days per week	3 capsules Monday 3 capsules Tuesday 3 capsules Wednesday 3 capsules Thursday 3 capsules Friday 3 capsules Saturday 3 capsules Sunday
Titration 4	28	Seven days per week	4 capsules Monday 4 capsules Tuesday 4 capsules Wednesday 4 capsules Thursday 4 capsules Friday 4 capsules Saturday 4 capsules Sunday
Titration 5[a]	35	Seven days per week	5 capsules Monday 5 capsules Tuesday 5 capsules Wednesday 5 capsules Thursday 5 capsules Friday 5 capsules Saturday 5 capsules Sunday

a There is a total of 5 possible dose titrations (dose titrations occur at Week 2, 4, 6, 8, 10, 12, and 18).

Decrease the dose by one capsule per day or per week depending on current dose to a minimum of 1 capsule once per week. The maximum dose is 5 capsules per day taken 7 days per week, and the minimum dose is 1 capsule taken once a week (0.5 mcg/week to 17.5 mcg/weekly dosage range).

Under certain circumstances, Hectorol® (or authorized generic) dosing should be suspended or reduced as follows:

1. If the iPTH level falls below the target range (<35 pg/mL for Stage 3 CKD and <70 pg/mL for Stage 4 CKD), suspend Hectorol® (or authorized generic) dosing for 1 week and then resume at a reduced dose.
2. If the corrected total serum calcium level is >10.2 mg/dL, the following measures should be taken until the value is <9.8 mg/dL: suspend or reduce Hectorol® (or authorized generic) dosing; stop or reduce calcium-based phosphate binders; reduce calcium supplements; or restrict dietary calcium.
3. If the serum phosphorus level exceeds the ULN (>6.5 mg/dL for age 5 years; >5.8 mg/dL for ages >5 to 12 years; >4.5 mg/dL for ages >12 to 17 years), the following measures should be taken until the value normalizes: restrict dietary phosphate; increase calcium-based or non-metal-based phosphate binders; or suspend Hectorol® (or authorized generic) dose for 1 week and then resume at a lower dose.

8.2 NON-INVESTIGATIONAL MEDICINAL PRODUCT

The active ingredient for Rocaltrol® or authorized generic capsules is 1α, 25-dihydroxycholecalciferol, a synthetic vitamin D_3 analog. It is available as 0.25 mcg or 0.5 mcg capsules. For detailed information please refer to the Rocaltrol® US package insert.

Starting Dose:

The starting dose is one 0.25 mcg capsule/day, taken seven days a week.

Dose Titration:

For dose titration, dose evaluation is to be performed every 2 weeks when the iPTH value from the central laboratory is received.

The dosage will be increased **if** iPTH is reduced <30% comparing with the baseline value **AND/OR does not** reach the physician's clinically desired iPTH range for the patient. Otherwise the actual dosage will be maintained. Physicians can modify the dosage for any safety reason.

Dose titration: The starting dose may be increased if necessary to 0.5 mcg/day (= two 0.25 mcg capsules, seven days a week).

8.3 BLINDING PROCEDURES

This is an open-label design with no blinding of the study medication.

8.3.1 Methods of blinding

NA.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

- The treatment kit number list is generated centrally by Sanofi.
- Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) are packaged in accordance with this list.
- Randomization and treatment allocation are performed centrally by an Interactive Voice Response System (IVRS); the IVRS generates the patient randomization list and allocates the treatment number and the corresponding treatment kits to the patients according to it.
- The randomization will be stratified by age (5 to <12 years, 12 to 17 years) and CKD stage (Stage 3 [GFR = 30-59 mL/min/1.73m^2], Stage 4 [GFR = 15-29 mL/min/1.73m^2]).
- The patient number is a unique identifier assigned at study inclusion.
- A patient is defined as randomized, if a randomized treatment has been allocated regardless whether the treatment kit was used or not.
- A patient cannot be randomized more than once. Patients will be assigned new treatment kits at every dispensation per IVRS but the arm assignment at randomization does not change.

8.5 PACKAGING AND LABELING

- Hectorol® /authorized generic will be supplied in 50 count bottles or commercially available bottle counts.
- Rocaltrol® / authorized generic will be supplied in commercially packaged 30 count bottles or commercially available bottle counts.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the Hectorol®(or authorized generic) & Rocaltrol® (or authorized generic) in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures.

Control of Hectorol® (or authorized generic) & Rocaltrol® (or authorized generic) storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) will be responsible for ensuring that the Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) capsules will be dispensed to the patient from site during on-site visits or via Sponsor approved services (direct to patient) for home-visits in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) issued and returned is maintained. Any quality issue noticed with the receipt or use of an Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) and eliminate potential hazards.

Under no circumstances will the Investigator supply Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) to a third party, allows the Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) to be used other than as directed by this clinical trial protocol, or dispose of Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) in any other manner.

8.7.1 Treatment accountability and compliance

- Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) accountability:
  - Treatment units are returned by the patient at each site visit. When home visit allowed as per local regulations, the Sponsor can arrange to collect the units via authorized services.
  - The Investigator counts the number of capsules remaining in the returned bottles, fills in the Treatment Log Form.
  - The Investigator records the dosing information on the appropriate page(s) of the electronic Case Report Form (eCRF).
  - The monitor in charge of the study then checks the eCRF data by comparing them with the Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) which he/she has retrieved and treatment log forms.

- For home visits, the site has to arrange a remote visit (via any digital contact) in order to review phosphate binder use, diet compliance, dosing compliance and patient's diary; dose adjustment evaluation, drug accountability; AE/SAE monitoring and recording of concomitant medication.

8.7.2 Return and/or destruction of treatments

All Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) used, partially-used or unused treatments will be retrieved by the Sponsor. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

For on-site visits, the patient will return the unused drugs to the site (Visit 6, Visit 8, Visit 10), whereas for home-visits (Visit 3, Visit 4, Visit 5, Visit 7, Visit 9) Sponsor approved services will collect those from the patient and deliver to the site upon patient's consent.

The Investigator will not destroy the unused Investigational Product unless the Sponsor provides written authorization.

8.8 CONCOMITANT MEDICATION

Box label warning of both drugs for hypersensitivity, contraindication and concomitant medication should be reviewed and followed prior and during the administration. The use of any vitamin D in any form is prohibited, except as described in this protocol. If, in the opinion of the investigator, treatment with vitamin D sterol therapy is necessary, the patient is to be withdrawn from the study.

Patients should be maintained on a clinically appropriate phosphate binder regimen for the duration of the study. Serum phosphorus and calcium should be monitored to manage each patient's levels to the appropriate Kidney Disease Outcome Quality Initiative target ranges.

Aluminum and magnesium-containing antacids and doxercalciferol are not to be used concomitantly.

The patient and the parents/legal representative are to be counseled to maintain a stable dietary intake of protein, phosphorus, and calcium (if indicated for the patient's stage of renal disease) throughout the study. The progress is documented in an individual patient diary.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary efficacy endpoint

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

iPTH is measured at screening, at baseline (Day 1), and at visits (Weeks 2, 4, 6, 8, 10, 12, 18, and 24).

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

The following secondary endpoints have been selected:

- 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.

9.2.2 Safety endpoints

9.2.2.1 Adverse events

Refer to Section 10.4, Section 10.6, Section 10.7 for details.

9.2.2.2 Laboratory safety variables

The clinical laboratory data are collected in accordance with the study schedule in Section 1.2 and consist of:

- Hematology (red blood cell count, reticulocyte count, hemoglobin, hematocrit, platelets, white blood cell count with differential blood count),
- Clinical chemistry (sodium, potassium, albumin, calcium, albumin-corrected serum calcium, bicarbonate, chloride, phosphorus, calcium-phosphorus product),
- Liver function tests (ALT, AST, total and direct bilirubin, alkaline phosphatase, GGTP),
- Blood glucose, 25-hydroxyvitamin D,
- Kidney function test (serum creatinine, blood urea nitrogen and GFR calculation, according to the Schwartz equation: GFR (mL/min/1.73 m^2) = (0.41 × Height in cm) / Creatinine in mg/dL),

- Central laboratory results will be provided to sites. An alert will be provided by the Central laboratory to sites in case of 2 consecutive significant elevations of corrected calcium >10.2 mg/dl.

All tests are performed by a Central Laboratory.

Post-menarchal female patients will have a serum pregnancy test at week -2 and week 12 (visit 8) and a urine pregnancy test starting at visit 2 (week 0), visit 4 (week 4), visit 6 (week 8), followed by a urine pregnancy test at visit 9 (week 18) and visit 10 (week 24).

9.2.2.3 Vital signs

Vital signs include: blood pressure in supine position, heart rate, respiratory rate and temperature.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

Pharmacokinetics will be assessed in Hectorol® (or authorized generic) patients. Serial PK samples will be collected from up to18 Hectorol® (or authorized generic) patients (50% of patients < 12 years of age).

9.3.1.1 Sampling time

Blood samples will be collected for determination of plasma 1, 25 hydroxyvitamin D_2, the active and measurable metabolite of doxercalciferol, according to the study flow chart (see Section 1.2). The parent drug (1α-hydroxyvitamin D_2) will also be measured pending assay availability.

For the sparse PK samples, 1, 25 hydroxyvitamin D_2 will be assessed at Week -2, baseline and then within 24 hours of the most recent dose of Hectorol® (or authorized generic) at Weeks 2, 4, 6, 8 or 12 and 10.

For the serial PK samples, 1, 25 hydroxyvitamin D_2 will be assessed 1 to 3 hours, 4 to 6 hours, 7 to 12 hours and 24 to 36 hours after dosing in the office at either the week 8 or 12 site visit. Choice is up to the patient and site availability. The dose of Hectorol® (or authorized generic) will be administered at the site that day.

A minimum of 3 ml of blood is needed for each PK sample; for each patient that will undergo PK sampling, a total volume of 33 ml of blood is needed.

9.3.1.2 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipping of plasma are described in separate lab manuals.

9.3.1.3 Bioanalytical method

Plasma samples will be assayed using LC-MS/MS method.

9.3.1.4 Pharmacokinetics parameters

1, 25 hydroxyvitamin D_2 plasma concentration data will be used in a separate population PK analysis. Evaluation of the 1,25-dihydroxyvitamin D2 concentration-time data obtained in this study will be conducted using noncompartmental methods including the following parameters like C_{max} and $AUC_{0\text{-}tau}$ at week 8 or 12 when Serial PK Samples are collected. If feasible, a model based approach using NONMEM (Icon, Hanover MD USA, Version 7 Level 2 or higher) can be used to derive individual and population mean parameters including absorption rate constant, clearance and volume of distribution will be reported. If feasible, derived parameters including area under the concentration-time curve will be reported. No formal statistical evaluation of the derived parameters is planned.

9.3.2 Pharmacogenetic assessment

NA.

9.4 FUTURE USE OF SAMPLES

NA.

9.5 APPROPRIATENESS OF MEASUREMENTS

The activation of parathyroid hormone (PTH) occurs in the kidney and results in an up-regulation of the 25-OH vitamin D_3 1-α-hydroxylase, the enzyme, which facilitates the formation and activation of 1α, 25-dihydroxyvitamin D_2, and 1α, 25 dihydroxyvitamin D_3 . Chronic kidney failure is the most common cause for secondary hyperparathyroidism due to the reduced synthesis of 1, 25 dihydroxyvitamin D_2.

Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) and its active vitamin D metabolites control the intestinal absorption of dietary calcium, the tubular reabsorption of calcium by the kidney and, in conjunction with PTH, the mobilization of calcium from the skeleton.

From that, the measurement of iPTH is an ideal candidate to evaluate the effect of Hectorol® (or authorized generic) on the PTH activity in patients with CKD, Stages 3 and 4.

10 STUDY PROCEDURES

The study consists of a Washout/Screening Period of a maximum of 6 weeks, a Primary Efficacy period of 12 weeks, a Safety Continuation Period of another 12 weeks, and a Post Treatment Follow- Up period (EOS) of 4 weeks.

For all visits after Day 1/Week 0 (randomization visit), a time frame of a certain number of days will be allowed. The window period for the visit at week 2 to 12 is ±3 days, for visit at week 18, 24 and 28 is ±7 days.

For all visits after Day 1/randomization visit, if one visit date is changed, then the next visit should take place according to the initial schedule as outlined in Section 1.2 (Study Flow Chart).

Ideally, all the visits should take place in the morning approximately at the same time. However, after randomization in case there is no other possibility for the patient, visits can be arranged later in the day.

For home visits, a healthcare technician from Sponsor authorized services will visit the patient at their preferred residence address. This will require a separate consent from the patient. For such visits, the Investigator or delegate will also arrange digital contact with the patient. The detail activities are mentioned in flow chart Section 1.2 and Section 10.1.

10.1 VISIT SCHEDULE

Screening visits, Visit 2 (Week 0), Visit 6 (Week 8), Visit 8 (Week 12), Visit 10 (Week 24) will be on-site visits.

Visit 3 (Week 2), visit 4 (Week 4), Visit 5 (Week 6), Visit 7 (Week 10), Visit 9 (Week 18), Visit 11 (Week 28) will be home visits. Exceptionally such visits can remain on-site, for example, if the site cannot arrange, not allowed by local regulations, the patient does not consent, etc. Home visits will comprise of a visit to patient's preferred address by a healthcare technician of the Sponsor authorized services and a digital contact with the patient arranged by the Investigator or delegate.

At each visit, an appointment will be given for the next visit within allowed visit window. The patient should be seen in the morning, if possible.

10.1.1 First Screening Visit 1a, Week-6, day-45, Wash-out required (on-site visit)

In case the patient was taking cinacalcet or Vitamin D sterol therapies such as calciferol, doxercalciferol or paricalcitol within 14 days **prior to the screening**, these drugs will be discontinued at the first screening visit (visit 1a). An additional screening visit (visit 1b) will be scheduled in 4 weeks after visit 1a. The baseline visit will follow 45 days (or 6 weeks) after the first screening visit 1a (wash-out period) and 2 weeks after the visit 1b.

- Informed consent/ Assent: The patient and/or the parents/legal representative will be informed about the aim and methods of the study, its constraints and risk and the study duration. The written informed consent must be signed by the parents or legal representative. In case the patient is old enough to comprehend the aim and methods of the study as well as the risk, the patient needs to consent verbally as well. In accordance with local regulations, minor participants with capacity for writing could sign off on an assent form. Only patients who meet the inclusion criteria as noted in Section 7 may be screened.
- Inclusion/Exclusion criteria.
- Patients' Demography.
- Medical/Surgical history.
- Prior medications (within 3 months prior to screening).
- Dietary consult.
- Review of phosphate binder intake and diet compliance.
- Continuous AE/SAE monitoring after Informed consent has been signed.
- Concomitant medication.
- 25-hydroxyvitamin D.

10.1.2 Screening Visit – Visit 1, Week -2 (no wash-out required) or Visit 1b, Week -2, (wash–out required) (on-site visit) Day-14 to Day-10

- Informed consent/ Assent for Visit 1 only (refer to Section 10.1.1).
- Inclusion and exclusion criteria.
- Patients' Demography for Visit 1 only.
- Medical/Surgical history for Visit 1 only.
- Prior medications (within 3 months prior screening) for Visit 1 only.
- Dietary consult for Visit 1 only.
- Review of phosphate binder use and diet compliance.
- Continuous AE/SAE monitoring after Informed consent has been signed.
- Concomitant medication.
- Vital signs (blood pressure in supine position, heart rate, respiratory rate and temperature).
- Height and weight.
- Laboratory testings:
  - iPTH,
  - Serum pregnancy test (for WOCBP),
  - Albumin-corrected serum calcium, calcium, phosphorus, albumin, calcium-phosphorus product,
  - Blood chemistry, hematology,
  - 25-hydroxyvitamin D for Visit 1 only,
  - GFR calculation,
  - 1, 25 dihydroxyvitamin D_2.

10.1.3 Randomization Visit, Visit 2, Week 0, Day 1 (on-site visit)

The following checks/ tasks will be performed:

- Inclusion and exclusion criteria.
- The patient will be randomized to either Hectorol® (or authorized generic) or Rocaltrol® (or authorized generic) in a 2:1 scheme.
- Dispense study drug, please refer to Section 8.1 for details. A diary will be provided to the patient to record doses intakes.
- Review of phosphate binder use and diet compliance.
- iPTH.
- Continuous AE/SAE monitoring.

- Concomitant medication.
- Vital sign.
- ECG.
- Urine pregnancy test (for WOCBA).
- Laboratory testings: albumin-corrected serum calcium, calcium, phosphorus, albumin, calcium-phosphorus product, blood chemistry, hematology.
- 1, 25 dihydroxyvitamin D_2 (sample to be collected after randomization (in patient randomized to Hectorol® or authorized generic) and prior to the first dose intake).
- Parents/Patient to be trained to complete patient diary: Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) dosing and diet and phosphate binder.

10.1.4 Visit 3, Week 2 (home visit), Visit 4, Week 4 (home visit), Visit 5, Week 6 (home visit), Visit 6, Week 8 (on-site visit), Visit 7, Week 10 (home visit) and Visit 8, Week 12 (on-site visit):

At each visit, the following checks/ tasks will be performed:

- Direct to patient (when home visit at Visit 3, Visit 4, Visit 5, Visit 7) OR dispense study drug (for on-site visit 6, visit 8), please refer to Section 8.1 for details
- Review of phosphate binder use and diet compliance*.
- Review of dosing compliance and patient's diary review*.
- Dose adjustment evaluation*.
- Drug accountability*.
- iPTH.**
- Continuous AE/SAE monitoring*.
- Concomitant medication*.
- ECG, only at Visit 8 (Week 12)
- Urine pregnancy test only on Visit 4 (Week 4)*, 6 (Week 8), and serum pregnancy test at Visit 8 (Week 12).
- Albumin-corrected serum calcium, calcium, phosphorus, albumin, calcium-phosphorus product.**
- Serum Creatinine and Blood Urea nitrogen, at Visit 6 (Week 8) and Visit 8 (Week 12)
- GFR calculation, at Visit 6 (Week 8) and Visit 8 (Week 12)
- 1, 25 dihydroxyvitamin D_2 (sample to be collected in patient randomized to Hectorol® [or authorized generic]).**

At Week 8 or 12, additional blood samples will be taken for serial PK measurements (see Section 9.3.1).

10.1.5 Visit 9, Week 18 (home visit)

The following checks/tasks will be performed:

- Direct to patient , please refer to Section 8.1 for details
- Review of phosphate binder use and diet compliance*.
- Review of dosing compliance and the patient's diary review*
- Dose adjustment evaluation*.
- Drug accountability*.
- iPTH**.
- Continuous AE/SAE monitoring*.
- Concomitant medication*.
- Urine pregnancy test.**
- Albumin-corrected serum calcium, calcium, phosphorus, albumin, calcium-phosphorus product.**

10.1.6 Visit 10, Week 24, End of Treatment Visit (on-site visit)

The following checks/tasks will be performed at the end of treatment visit:

- Review of phosphate binder use and diet compliance.
- Review of dosing compliance through drug return accountability and patient's diary review.
- Drug accountability.
- iPTH.
- Continuous AE/SAE monitoring.
- Concomitant medication.
- Vital sign.
- Height and weight.
- Urine pregnancy test.
- Laboratory testings: albumin-corrected serum calcium, calcium, phosphorus, albumin, calcium-phosphorus product, blood chemistry, hematology.
- GFR calculation.
- 25-hydroxyvitamin D.

10.1.7 Visit 11, Week 28, End of Study Visit (home visit)

The following checks/tasks will be performed at the final visit:

- AE/SAE*.
- Concomitant medications*.
- Vital signs**.

Note:

*When home visit, data to be collected via digital contact from the patient by the site.

**When home visit, blood sampling and/or vital sign measurements to be performed by a healthcare technician Sponsor authorized services.

10.1.8 Unscheduled Visits

Unscheduled visit is to be conducted for an unscheduled dispensation of study drug, or if deemed necessary by the investigator for any safety reasons.

A regional or national emergency declared by a government agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent routine access to the study site, and may therefore restrict collection of participant data. During such an emergency, if the site is unable to adequately follow the data collection schedule, alternative processes can be proposed and agreed with the Sponsor. All agreed changes will be properly documented in writing.

10.2 DEFINITION OF SOURCE DATA

All data collected in the CRF come from source documents that are part of the patient dossier.

Adverse events and follow-up; in case of a SAE or of an AESI, the site should file in the source document at least copies of the hospitalization and any relevant examination reports documenting the follow up of the SAE or the AESI.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The study treatment should be continued whenever possible. In case the study treatment is stopped, it should be determined whether the stop can be made temporarily; permanent study treatment discontinuation should be a last resort. Any study treatment discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Re-initiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best

medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

If the iPTH value falls below 35 pg/mL (Stage 3 CKD) or 70 pg/mL (Stage 4 CKD), Hectorol® (or authorized generic) dosing should be suspended for 1 week and then resumed at a reduced dose.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator, or the Sponsor or the patient/parent not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the study treatment if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. Permanent treatment discontinuation can also be a Sponsor's decision. All efforts should be made to document the reasons for treatment discontinuation, and this should be documented in the e-CRF.

- The patient experiences an intolerable or unacceptable adverse event as per physician's clinical judgement.
- Major deviation to protocol (any medical event requiring administration of unauthorized medication during the study).
- Lack of efficacy (treatment failure).
- If, in the Investigator's opinion, continuation with the administration of the study treatment would be detrimental to the patient's safety or well-being.
- Pregnancy, intention for pregnancy, or no longer with effective contraceptive method for birth control, applicable for both male and female participants.
- At patient request, ie, withdrawal of the consent for treatment.

Discontinuation of treatment does not imply withdrawal from study; refer also to Section 10.3.5.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the study treatment including a pharmacokinetics sample, if appropriate.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF, when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a pharmacokinetics sample, if appropriate.

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records checks. Subjects requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study. If possible, the patients should be assessed using the procedures defined above.

Subjects who withdraw should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.

Preferably the subject should withdraw consent in writing and, if the subject or the subject's representative refuses or is physically unavailable, the site should document and sign the reason for the subject's failure to withdraw consent in writing. The informed consent for the study should note that although a subject is free to leave the study and stop taking study medication, the investigators hope the patient will remain for follow up status evaluations.

Study withdrawal should be recorded by the Investigator in the appropriate forms of the e-CRF and in the patient's medical records when considered as confirmed. In the medical record, at least the date of the withdrawal and the reason should be documented.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment, occurring or detected from the date the participant signs the informed consent form, irrespective of the period of the study (periods without administration of the IMP (eg run-in period or defined FU period after study drug withdrawal) are also concerned).

Based on the study design, patients may experience variation above or below the range given for iPTH during the study. These variations in iPTH are expected based on the study design and will not be considered as an Adverse Event. If, based on investigator judgment, serum iPTH values are beyond what would be expected based on the study design, these values should be recorded as Adverse Events.

10.4.1.2 Serious adverse event

Seriousness is done in accordance with ICH Topic E2A and DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001.

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

- Results in death,
- Is life-threatening [(1)],
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Is medically significant [(2)],
- Results in persistent or significant disability/incapacity [(3)],
- Is a congenital anomaly/birth defect [(4)].

[(1)] Life-threatening in this context refers to an event in which the participant 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.

[(2)] Any event that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the participant or might require intervention to prevent one of these outcomes.

[(3)] Disability/incapacity in this context refers to any event that seriously disrupts the ability of the participant to lead a normal life, in other words leads to a persistent or permanent significant change, deterioration, injury or perturbation of the participant's body functions or structure, physical activity and/or quality of life.

[(4)] Congenital anomaly or birth defect refers to the exposure to the IMP before conception (in men or women) or during pregnancy that resulted in an adverse outcome in the child.

The investigator should exercise his/her scientific and medical judgement to decide whether or not such an event requires expedited reporting to sponsor, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm,
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse,
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN,
- Suicide attempt or any event suggestive of suicidality,
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
- Bullous cutaneous eruptions,
- Cancers diagnosed during the study,
- Chronic neurodegenerative diseases (newly diagnosed).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (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 (CIOMS VII definitions).

In addition, some known ADRs may be different by type and severity in children compared to adults. Specific ADRs may be unique to pediatrics such as effects on growth and development and effects on organ maturation (CNS, organs).

The AESI list is based on the evaluation of available safety data mentioned in the current reference documents for doxercalciferol (Hectorol® or authorized generic), IB dated Dec 2015 and CCDS for oral doxercalciferol dated 30 Sep 2011), as well as on the characteristics of the treated population (children from 5-17 year-old).

The following events should be immediately documented and reported as AESIs within 24h:

- Hypercalcemia: monitoring should include: (i) detection of association of serum hypercalcemia and hyperphosphatemia (serum Ca x P ≥55 mg2/dL2) with baseline, Albumin corrected serum calcium >10.2 mg/dl, EOT, EOS assessments as well as for cause during the study; (ii) Abdominal and chest X-Rays/Body CT scan focusing on kidneys, heart, with baseline and EOS assessments.

- *In case of hypercalcemia immediate suspension of doxercalciferol therapy, institution of a low calcium diet, and withdrawal of calcium supplements is required. Serum calcium levels should be determined at least weekly until normocalcemia ensues.*

- Hypercalciuria.
- Any suspicion of calcification of soft tissues including blood vessels (prolonged hypercalcemia may lead to calcification of soft tissues. Target organs: kidney, heart, and blood vessels).
- Acute worsening of renal failure.
- Any cardiac rhythm disorders (documented ECG).
- Growth arrest: any relevant changes in the growth and development parameters of the treated children (weight loss, abnormal growth parameters) that are not matching known impairment in the target population (Stage 3-4 non dialyzed CKD).

In addition, the following AEs should be immediately documented and reported:

- Pregnancy of a female patient entered into the study. It will qualify as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
- If a female participant becomes pregnant, the investigator must stop immediately Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) and follow-up of the pregnancy (mandatory) until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic):

  An overdose (accidental or intentional) with the Hectorol® (or authorized generic) /Rocalatrol® (or authorized generic) is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval.

  Of note, asymptomatic overdose has to be reported as a standard AE.
- 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.

Adverse events of special interest may be added or removed during a study by protocol amendment.

10.4.2 Evaluation of events, seriousness, severity and causality

This evaluation must be assessed by the investigator and reported in the AE form. The investigator gives his/her own opinion regarding the **seriousness**, the **severity** of the event as well as the **cause-effect (causality) relationship** between an adverse event and the test drugs Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic).

The Seriousness should be evaluated according to international guidelines (see definition Section 10.4.1.2).

The severity/intensity should be evaluated according to the following rule: mild, moderate and severe.

The causal relationship to Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) must be assessed and should be reported in the AE form. In general, the expression reasonable causal relationship means to convey that there is evidence or arguments to suggest a causal relationship.

10.4.3 Documentation of Adverse events

The investigator must ensure that all events are well documented. In particular for SAEs and AESIs, the investigator should provide to the Sponsor, as they become available, with anonymized copies of the documents which provide additional useful information, such as hospital admission reports, reports of further consultations, laboratory test reports, reports of other examinations aiding diagnosis *(where possible, the results from pre-test drug assessments should be appended for comparison with the results obtained under* Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic), or the autopsy report, if autopsy is performed. The Investigator must be ready for providing additional medical documentation upon request of pharmacovigilance requirements.

This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team, up to as noticed by the Sponsor.
If the adverse event has not resolved at the participant's final visit in the study, the participant must be followed up suitably and any information on the final outcome of the event will be reported.

When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study as defined by the protocol for that patient.

If the follow-up of the participant is not done by the investigator him/herself (hospitalization, followed by a specialist or the participant's general practitioner, etc), all efforts should be made to establish/maintain contact with the person/department in charge of follow-up of the participant.

The data should be obtained through observation of the patient and from any information volunteered by the patient and/or the parents.

10.4.4 General guidelines for reporting adverse events

The investigator should:

- Report all AEs, regardless of seriousness or relationship to Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic), spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient. These AEs are to be recorded with all appropriate and relevant information on the corresponding page(s) or screen(s) of the CRF.

- Report the seriousness, severity and causality and specify the date of onset, intensity, action taken with respect to Hectorol® (or authorized generic) /Rocaltrol®(or authorized generic), corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the Hectorol® (or authorized generic) /Rocaltrol® or by the study procedure(s). Whenever possible, diagnosis or single syndrome should be reported instead of symptoms.
  - Take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients.
  - This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team, up to as noticed by the Sponsor. Continue the patient's observations until the end of the study as defined by the protocol, when treatment is prematurely discontinued.
  - Report AESIs (serious or not) within 24h following the same reporting scheme as the SAEs, even if not fulfilling a seriousness criterion, using the corresponding screens in the e-CRF.
  - Report any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported.
- Report laboratory or vital signs abnormalities as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
  - Fulfil his/her regulatory obligations to the Competent Authorities and/or to the IRB/IEC in accordance with local regulations

Instructions for AE reporting are summarized in Table 6.

10.4.5 Instructions for reporting serious adverse events

Any SAE and/or AESI meeting the definition mentioned in Section 10.4.1.2 and Section 10.4.1.3 must be reported and recorded by the sponsor on the corresponding page(s) or screen(s) of the e-CRF:

- From the signature of the informed consent up to the end of the study as defined by the protocol OR participant's last study visit for all events regardless of seriousness or relationship to Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic).
- After the participant's last study visit.

- Irrespective of the time to onset after the end of the study in case of serious adverse event related to the search Hectorol® (or authorized generic) /Rocaltrol® (or authorized generic) or experimental procedure.

In the case of occurrence of an SAE, the Investigator or any designees must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.

A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any hospitalization for social reasons, educational purpose or routine check-up should not be considered as an adverse event and should not be reported in the e-CRF.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by Hectorol® (or authorized generic) or Rocaltrol® (or authorized generic) with a reasonable possibility, should be reported to the monitoring team.

10.4.6 Follow up of adverse events

The Investigator must take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, in order to ensure the safety of the patients, or until death.

This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team, up to as noticed by the Sponsor.
Any change in terms of diagnosis, intensity, seriousness, measures taken, causality or outcome regarding an adverse event already reported must be reported.

If the adverse event has not resolved at the participant's final visit in the study, the participant must be followed up suitably and any information on the final outcome of the event will be reported.

When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
If the follow-up of the participant is not done by the investigator him/herself (hospitalization, followed by a specialist or the participant's general practitioner, etc), all efforts should be made to establish/maintain contact with the person/department in charge of follow-up of the participant.

10.4.7 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix A.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia,
- Thrombocytopenia,
- Acute renal insufficiency,
- ALT.

NOTE: In some clinical trials these laboratory abnormalities can be considered as AESIs (see Section 10.4.1.3).

Table 6 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Comple-mentary Form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	Hypercalcemia	Yes	Yes	No
		Hypercalciuria	Yes	Yes	No
		Albumin corrected serum calcium > 10.2 mg/dl	Yes	Yes	No
		Calcification of soft tissues including blood vessels	Yes	Yes	No
		Acute worsening of renal failure	Yes	Yes	No
		Cardiac rhythm disorders	Yes	Yes	No
		Growth arrest (signs and symptoms)	Yes	Yes	No

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Comple-mentary Form	Other specific forms
Other Adverse Events		Pregnancy	Yes	Yes	Yes
		Symptomatic overdose	Yes	Yes	No
		ALT≥3 ULN (if baseline ALT<ULN) and ALT≥2 x baseline (if baseline ALT≥ULN).	Yes	Yes	Yes

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs, that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs, that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.
- Investigator safety report must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

For Hectorol® (or authorized generic), any AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Management of elevated serum albumin corrected calcium > 10.2 mg/dl

In the event that the serum albumin corrected calcium level exceeds 10.2 mg/dl, therapies that increase serum calcium should be adjusted according to the Guideline 7 of the K/DOQI Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease (9).

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

10.8 CONTRACEPTION

Birth control requirements for females are to be implemented as follows:

Female subjects must not be breast feeding or pregnant (as confirmed by serum pregnancy test) at the time of study entry and must agree to undergo serum pregnancy testing. In addition, pregnancy test should be conducted in case of an unexpected delay of menorrhea or if the WOCBP experiences unexpected delay in routine menstruation.

A woman of child bearing potential (WOCBP) is any female who has experienced menarche and does not meet the criteria for "woman not of child bearing potential".

WOCBP must agree that they will take means to reduce reproductive risk by agreeing to use a double method of contraception. Acceptable methods of contraception are defined for this protocol as:

For male:

1. True abstinence: agree to remain abstinent from penile-vaginal intercourse on a long-term and persistent basis, when this is in line with the preferred and usual lifestyle of the subject.
2. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods), and withdrawal are not acceptable methods of contraception.
3. Agree to use male condom plus an additional contraceptive method with a failure rate of <1% per year.
4. Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

For WOCBP:

1. True abstinence: agree to remain abstinent from penile-vaginal intercourse on a long-term and persistent basis, when this is in line with the preferred and usual lifestyle of the subject.
2. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
3. Highly effective oral contraceptives, such as biphasic and triphasic oral contraceptives are considered adequate. Progestogene only pills or "mini pills" which have demonstrated lower efficacy will not be acceptable.
4. Injectable hormones (ie, Depo-Provera), hormonal implants, transdermal patches or intrauterine device (IUD) or intrauterine systems (IUS) which have demonstrated efficacy comparable to high efficacy oral contraceptives are adequate.

Therefore:

For female subjects participating in the study:

If the subject is a "Woman not of Child Bearing Potential, then no method is required.

If the subject is a WOCBP and meets criteria for "true abstinence" (as defined above) then no method is required. These subjects must agree that they will use acceptable double methods of contraception before becoming sexually active.

If the subject is a WOCBP and sexually active with a male partner who is sterilized (as defined above), then an additional method of contraception is recommended but not required. These subjects must agree that they will use acceptable double methods of contraception before becoming sexually active with another male partner.

Otherwise both the female subject participating to the study and the male partner must use an acceptable method of contraception as defined above.

For male subjects participating to the study:

If the subject is sterilized (as defined above) then no method is required.

If the subject meets criteria for "true abstinence" (as defined above) then no method is required. These subjects must agree that they will use acceptable double methods of contraception before becoming sexually active.

If the subject is sexually active with a female partner who is a "Woman not of Child Bearing Potential", then no other method is required. These subjects must agree that they will use acceptable double methods of contraception before becoming sexually active with another female partner.

Otherwise both the male subject participating to the study and the female partner must use an acceptable method of contraception as defined above.

Female subjects must continue to use a medically acceptable form of birth control for at least 4 weeks after the last dose of study drug.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The Rocaltrol® or authorized generic 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® (or authorized generic) and Rocaltrol® (or authorized generic) treatment group outcomes will be made.

Approximately 57 patients will be randomized in a 2:1 ratio to the Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) treatment groups. The study randomization scheme will be stratified by age group (ie, 5 to <12, and 12 to 17, years of age) and CKD stage (ie, 3 and 4).

A sample size of 30 patients for the Hectorol® (or authorized generic) treatment group provides 70% power to detect a difference, for the Hectorol® (or authorized generic) treatment group, from a value of <30% for the proportion of patients achieving the primary endpoint (Section 9.1.1), assuming a 2-sided alpha = 0.05, using the normal approximation and that the true proportion for the Hectorol® (or authorized generic) treatment group is 50%. Approximately 38 patients will be randomized to the Hectorol® (or authorized generic) treatment group, allowing for 20% early terminations / unevaluable patients. The limits for a 95% confidence interval constructed for the proportion of Hectorol® (or authorized generic) treatment group patients achieving the primary endpoint would be ± 0.16, assuming 0.50 for the proportion and 38 Hectorol® (or authorized generic) treated patients. The estimate for the proportion of patients achieving the primary endpoint for the Hectorol® (or authorized generic) 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® (or authorized generic) safety profile to the active comparator treatment group, a sample size of 15 patients for the Rocaltrol® (or authorized generic) treatment group is based on the 2:1 randomization of patients to the Hectorol® (or authorized generic) treatment group and Rocaltrol® (or authorized generic) treatment group. To allow for 20% early terminations / unevaluable patients, approximately 19 patients will be randomized to the Rocaltrol® (or authorized generic) treatment group.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients with the first treatment kit number allocated and recorded in the IVRS/IWRS database, and regardless of whether the treatment kit was used or not.

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

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.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

- The randomized population comprises all patients randomized either into the Hectorol® (or authorized generic) or Rocaltrol® (or authorized generic) group.
- The Full Analysis Set (FAS) comprises all treated patients with at least 2 assessments of iPTH after use of study drug.
- The Per Protocol Set (PPS) comprises all full analysis set-evaluable patients with no significant protocol deviations.

11.3.2 Safety population

- The Safety Population comprises all randomized patients who have taken at least one Hectorol® (or authorized generic) or Rocaltrol® (or authorized generic) dose.

11.3.3 Pharmacokinetic Population

The pharmacokinetic population comprises patients randomized to Hectorol® (or authorized generic) who have at least one measurable post dose 1, 25 hydroxyvitamin D_2 concentration. For up to 18 patients of the Hectorol® (or authorized generic) group who will undergo serial sampling, half of these patients will be under the age of 12 years.

11.4 STATISTICAL METHODS

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

For continuous variables, descriptive statistics (n, mean, median, standard deviation, minimum and maximum) will be presented. For categorical variables, frequencies and percentages will be presented.

11.4.1 Extent of investigational medicinal product exposure

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

- Note: the exposure and compliance of all IMPs will also be summarized.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date +1 day, regardless of unplanned intermittent discontinuations.

- Dose information will be assessed by the following variable:
- Starting dose and dose titration, including dose increase, dose reduction, dose halt and the reasons for these changes will be collected.

11.4.1.2 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.

Treatment compliance, above-planned and under-planned dosing percentages will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance greater 100%, 100 – 80%, and less than 80% compliance will be summarized.

11.4.2 Analyses of efficacy endpoints

Analyses for efficacy outcomes are descriptive, and will be summarized using the Full Analysis Set (primary) and the Per Protocol Set (confirmatory).

11.4.2.1 Analysis of primary efficacy endpoint(s)

The percentage of patients meeting the iPTH ≥30% reduction from baseline at 2 consecutive study visits up to Week 12 will be calculated. A 95% confidence interval will be constructed for the proportion of patients achieving the endpoint for the Hectorol® (or authorized generic) treatment group. 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 prior to and including Week 12. The proportion achieving the endpoint for the Rocaltrol® (or authorized generic) treatment group will also be summarized. No formal statistical comparison will be made between the Hectorol® (or authorized generic) and Rocaltrol® (or authorized generic) treatment groups.

11.4.2.2 Analyses of secondary efficacy endpoints

The percentage change in iPTH from baseline to Weeks 12 and 24 will be summarized with descriptive statistics. For the changes from baseline iPTH, the effects over the treatment period time will be explored using a mixed model for repeated measures approach. The complete details, including potential sensitivity analyses for missing data, will be included in the statistical analysis plan.

The frequency of hypercalcemia (Albumin corrected serum calcium >10.2 mg/mL) up to Weeks 12 and 24 will be summarized descriptively.

11.4.2.3 Analysis of Pharmacokinetic data

Evaluation of the 1,25-dihydroxyvitamin D2 concentration-time data obtained in this study will be conducted using noncompartmental methods including the following parameters like C_{max} and $AUC_{0\text{-}tau}$ at week 8 or 12 when Serial PK Samples are collected. If feasible, a model-based approach using NONMEM (Icon, Hanover MD USA, Version 7 Level 2 or higher) can be used to derive individual and population mean parameters including absorption rate constant, clearance and volume of distribution will be reported. If feasible, derived parameters including area under the concentration-time curve will be reported. No formal statistical evaluation of the derived parameters is planned. The pharmacokinetics analyses will be performed separately from the analyses of the other clinical study variables.

11.4.3 Analyses of safety data

All safety analyses will be performed on the Safety population using the following common rules:

- The baseline value is defined generally as the last available value before randomization.

Adverse events and serious adverse events (SAEs) will be summarized overall, by System Organ Class (SOC) and Preferred Term (PT), using the standardized Medical Dictionary for Regulatory Activities. Adverse events will also be summarized by severity, in which a patient's most severe event within a category (eg, treatment regimen, SOC, PT) will be counted. In addition, treatment-related adverse events will be tabulated. Listings will be provided for all AEs, including those arising before or after treatment, SAEs and AEs leading to discontinuation from the study.

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. 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.

Descriptive statistics will be calculated for vital signs and clinical laboratory results at each study time point and for the change from baseline to each post-baseline study time point. The following definitions will be applied to laboratory parameters and vital signs:

- 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.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Sub-investigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient (and the parent[s] or guardian[s]) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the ethics committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the informed consent form should be signed, name filled in and personally dated by the patient's parent(s) or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. Local law must be observed in deciding whether 1 or both parents/guardians consent is required. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian's signature.

In addition, participants will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

Participants who can read the assent form will do so before writing their name and dating or signing and dating the form.

Participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent form used by the Investigator for obtaining the Patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

The patient needs to consent in writing for the Sponsor authorized services such as direct to patient drug delivery and home visit by healthcare technician.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Sub-investigators shall be appointed and listed in a timely manner. The Sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file,

appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document, which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Sub-investigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Sub-investigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Sub-investigators of the confidential nature of the clinical trial.

The Investigator and the Sub-investigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Sub-investigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Sub-investigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity (Caucasian/White, Black, Asian/ Oriental, Others) will be collected in this study because these data are required by several regulatory authorities (eg, on Afro American population for FDA).

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.
- Non-compliance of the Investigator or Sub-investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

16 BIBLIOGRAPHIC REFERENCES

1. Coburn JW, Maung HM, Elangovan L, Germain MJ, Lindberg JS, Sprague SM, 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 May;43(5):877-90.

2. K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease. Am J kidney Dis. 2005;46:Suppl 1:S1-121.

3. Rocatrol® (calcitriol) Package Insert. Available at: http://www.rocatrol.us/rocatrol. Accessed October 27, 2015.

4. Jones CL, Vieth R, Spino M, Ledermann S, Kooh SW, Balfe J, et al. Comparisons between oral and intraperitoneal 1,25-dihydroxyvitamin D3 therapy in children treated with peritoneal dialysis. Clin Nephrol. 1994 Jul;42(1):44-9.

5. Maung HM, Elangovan L, Frazao J, Bower JD, Kelley BJ, Acchiardo SR, et al. Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1alpha-hyroxyvitamin D2) in dialysis patients with secondary hyperparathyroidism: A sequential comparison. Am J Kidney Dis. 2001 Mar;37(3):532-43.

6. Frazao J, Elangovan L, Maung HM, Chesney RW, Acchiardo SR, Bower JD, et al. Intermittent doxercalciferol (1alpha-hyroxyvitamin D2) therapy for secondary hyperparathyroidism. Am J Kidney Dis. 2000 Sep;36(3):550-61.

7. Upton RA, Knutson JC, Bishop CW, LeVan LW. Pharmacokinetics of doxercalciferol, a new vitamin D analogue that lowers parathyroid hormone. Nephrol Dial Transplant. 2003 Apr;18(4):750-8.

8. Sanofi. Hectorol® Investigator's Brochure, current version.

9. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Children with Chronic Kidney Disease. Am J Kidney Dis. 2005;46(2):Suppl 1:S39-48.

17 APPENDICES

Appendix A General Guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

Neutrophils < 1500/mm^3 or according to ethnic group

Repeat immediately a full blood count if value close to 1500/mm^3

Neutrophils < 1500/mm^3 confirmed with signs of infection	Neutrophils < 1500/mm^3 confirmed with no signs of infection
1. **DISCONTINUE** Investigational Medicinal Product, hospitalization should be considered 2. **PERFORM** biological investigations for infection	1. **DISCONTINUE** Investigational Medicinal Product 2. **INVESTIGATE** for infection

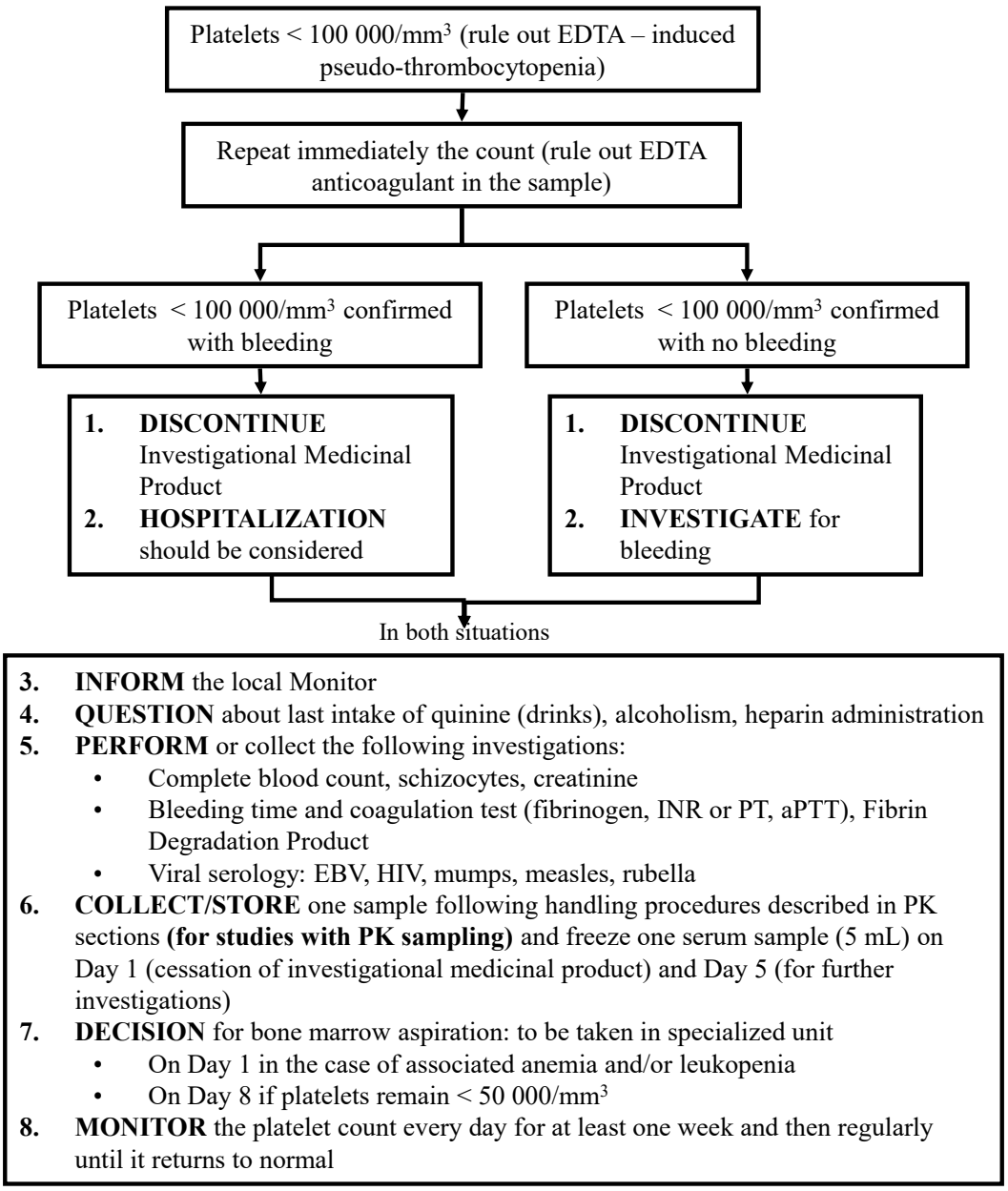
In both situations

3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

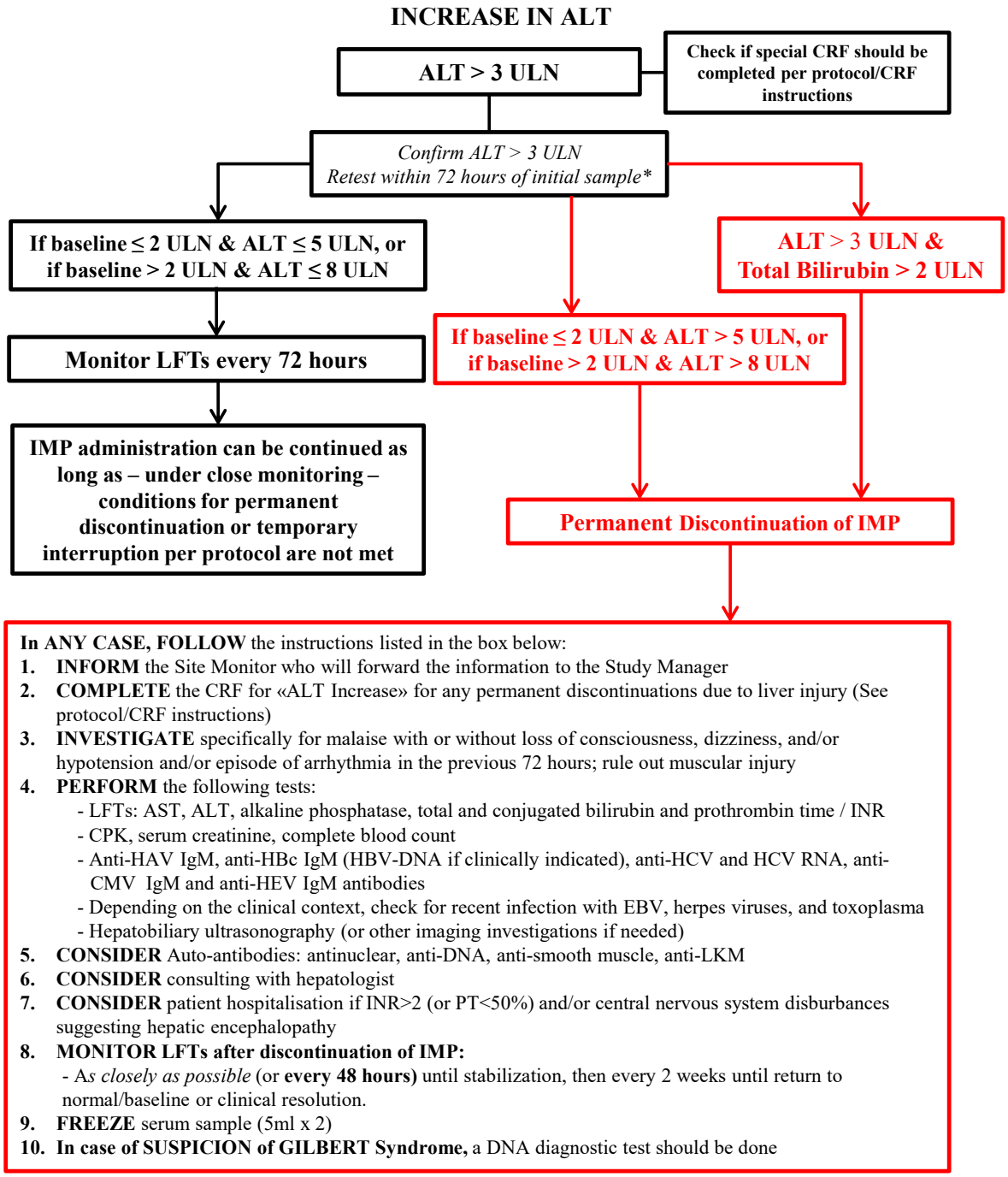
Neutropenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

THROMBOCYTOPENIA



Note:
The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.



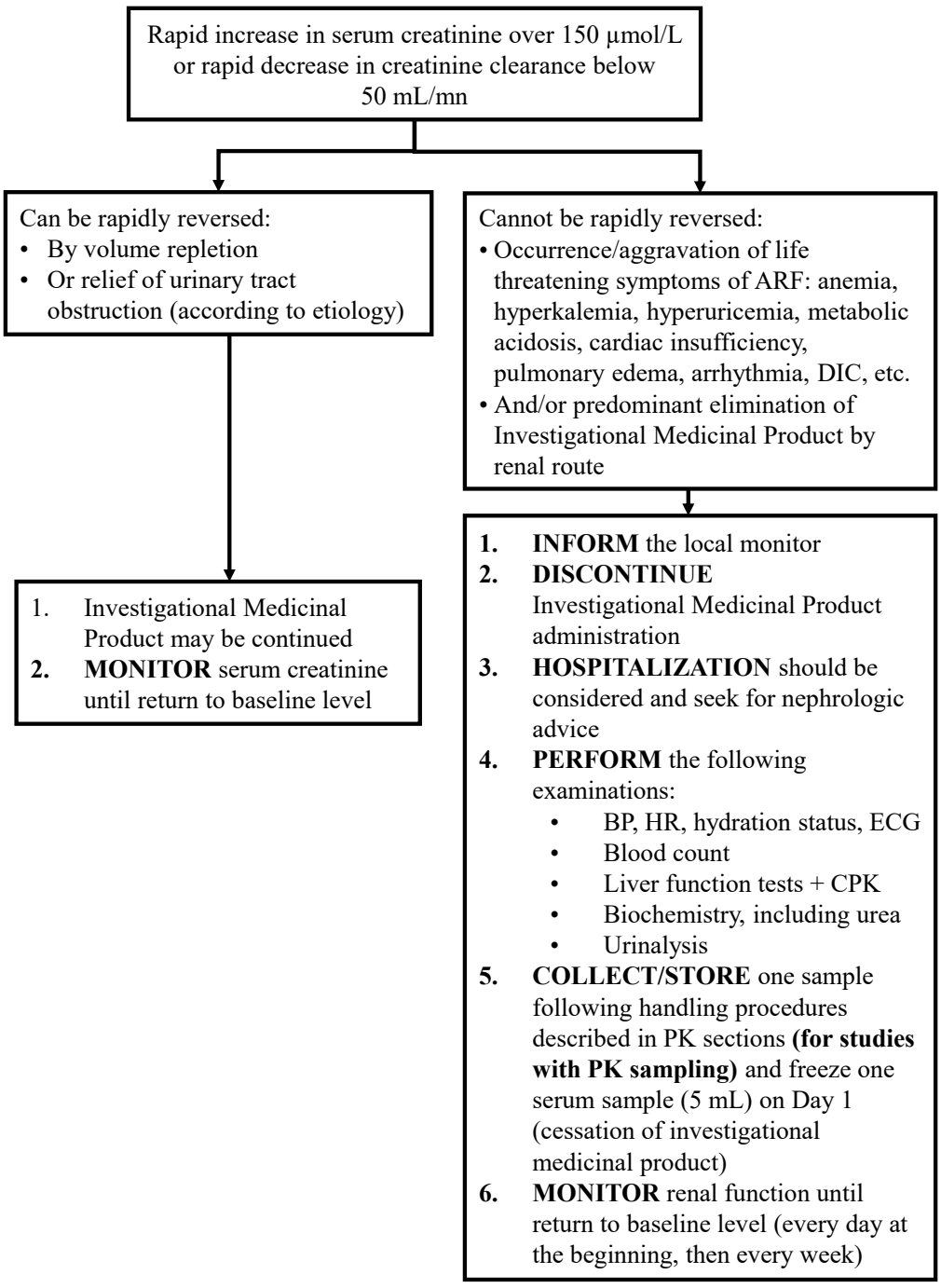
In ANY CASE, FOLLOW the instructions listed in the box below:

1. **INFORM** the Site Monitor who will forward the information to the Study Manager
2. **COMPLETE** the CRF for «ALT Increase» for any permanent discontinuations due to liver injury (See protocol/CRF instructions)
3. **INVESTIGATE** specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia in the previous 72 hours; rule out muscular injury
4. **PERFORM** the following tests:
   - LFTs: AST, ALT, alkaline phosphatase, total and conjugated bilirubin and prothrombin time / INR
   - CPK, serum creatinine, complete blood count
   - Anti-HAV IgM, anti-HBc IgM (HBV-DNA if clinically indicated), anti-HCV and HCV RNA, anti-CMV IgM and anti-HEV IgM antibodies
   - Depending on the clinical context, check for recent infection with EBV, herpes viruses, and toxoplasma
   - Hepatobiliary ultrasonography (or other imaging investigations if needed)
5. **CONSIDER** Auto-antibodies: antinuclear, anti-DNA, anti-smooth muscle, anti-LKM
6. **CONSIDER** consulting with hepatologist
7. **CONSIDER** patient hospitalisation if INR>2 (or PT<50%) and/or central nervous system disburbances suggesting hepatic encephalopathy
8. **MONITOR LFTs after discontinuation of IMP:**
   - As *closely as possible* (or **every 48 hours)** until stabilization, then every 2 weeks until return to normal/baseline or clinical resolution.
9. **FREEZE** serum sample (5ml x 2)
10. **In case of SUSPICION of GILBERT Syndrome,** a DNA diagnostic test should be done

Note:
Normalization is defined as < ULN or baseline value if baseline value is >ULN.
As soon as seriousness criterion is met or the event leads to permanent treatment discontinuation, the monitoring team should be notified within 24 hours.
*If unable to retest in 72 hours, use original lab results to decide on further monitoring/ discontinuation .

Note: ALT ≥ 3 ULN (if baseline ALT < ULN) or ALT ≥ 2 times the baseline value (if baseline ALT ≥ ULN) should be notified within 24 hours to the monitoring team (see Sections 10.4.1.3, 10.4.6, and 10.4.5). In addition, if ALT < 3 ULN meets a seriousness criterion, the event should be notified within 24 hours to the monitoring team.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as AE only if at least one of the criteria listed in the General guidelines for reporting adverse events in Section 10.4.2 is met.

Appendix B COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

Appendix C PROTOCOL AMENDMENT HISTORY

Amendment 01 – 10 February 2016

Reason for amendment:

- **Change to the dose titration scheme for Hectorol**

  Rationale: The change is being implemented following a request from the Food and Drug Administration (FDA) that the same titration scheme be implemented for both Hectorol® and Rocaltrol® treatment arms, in other words, the decision to hold, increase, or lower the dose should be based on whether the iPTH is reduced by ≥30% and/or reaches the physician's clinical desired iPTH range for the patient.

- **Addition of measurement of estimate GFR at Week 24**

  Rationale: The change is being implemented following a request from the FDA that measurement of estimate GFR be scheduled at Week 24 or the end of the study to determine if there is a significant change from baseline in response to treatment.

- **Update of IND number**

  Rationale: Update of previous typographic error of IND number.

Amendment 02 – 29 March 2016

Reason for amendment:

- **Change to the dose titration scheme and maximum dose for Hectorol**

  Rationale: The change is being implemented to address a comment from the Food and Drug Administration (FDA) that limiting the maximum daily dose of Hectorol® to 1 mcg may not achieve systemic exposures comparable to the maximum recommended daily dose in pre-dialysis adults (3.5 mcg). For this reason, the dose titration schemes and maximum daily doses have been modified so that predicted systemic exposures in pediatric subjects are comparable to the systemic exposures observed at the maximum recommended daily dose in pre-dialysis adults. The modified dose titration schemes and maximum daily doses are supported by population pharmacokinetic simulations.

- **Change to the target PTH level in patients receiving growth hormone**

  Rationale: Qualify that patients with Stage 3 and Stage 4 CKD receiving growth hormone may have higher target iPTH ranges, as growth hormone increases the iPTH level and aggressively managing iPTH levels in this population may blunt the growth response.

- **Change to the description for the patient identification number**

  Rationale: The statement regarding the number of digits in the patient identification number is being modified as it is not in line with the numbering system currently in use by the Sponsor.

- **Change to the description of the PK assays planned for the study**

  Rationale: Clarify that the PK of the parent drug (1α-hydroxyvitamin D_2) will also be measured pending assay availability to address a comment from the FDA.

- **Update to withdrawal of consent language following FDA recommendation**

  Rationale: Update to withdrawal of consent language following general comments from the FDA to be implemented across all Sponsor programs.

- **Study title wording edit in the Clinical Trial Summary**

  Rationale: A minor update of the wording for the title of the study has been implemented to be consistent with the study title as it appears on the cover page.

Signature Page for VV-CLIN-0210862 v4.0
lps14314-16-1-1-amended-protocol03

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]