

Summary Table of Study Protocol

Title	An Observational Registry Study to Evaluate the use and Safety of Cinacalcet Among Paediatric Patients With Secondary Hyperparathyroidism
Protocol version identifier	Amendment 3
Date of last version of the protocol	20 September 2019
EU Post Authorisation Study (PAS) Register No	EUPAS24954
Active Substance	cinacalcet hydrochloride
Medicinal Product	Mimpara®
Product Reference	EU/1/04/292
Procedure Number	N/A
Joint PASS	No
Research Question and Objectives	<ul style="list-style-type: none"> – What are the characteristics of paediatric patients receiving dialysis using cinacalcet? – How is cinacalcet used in paediatric patients? – How do laboratory values change over time among paediatric cinacalcet users? – What is the incidence of, risk factors for, and management of hypocalcaemia in paediatric patients who initiate cinacalcet? <p><u>Objectives:</u> In a European cohort of paediatric patients with secondary hyperparathyroidism (sHPT) on maintenance dialysis who use cinacalcet:</p> <ol style="list-style-type: none"> 1. To describe patient characteristics 2. To describe how cinacalcet is used 3. To describe laboratory values (parathyroid hormone (PTH), corrected total serum calcium (cCa), phosphate and albumin) over time 4. To describe the incidence of hypocalcaemia 5. To describe risk factors associated with time to hypocalcaemia event 6. To describe management of hypocalcaemia

Country(-ies) of Study	<ul style="list-style-type: none">• Austria, Belgium, Bulgaria, Czech Republic, Denmark,• Finland, France, Germany, Hungary, Italy, The Netherlands, Poland, Portugal, Romania, Spain,• Sweden, and the United Kingdom
Author	PPD [REDACTED] PhD, MSc Observational Research Manager 1 Uxbridge Business Park, Sanderson Road Uxbridge, UB8 1DH, UK

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Europe B.V. Minervum 7061 4817 ZK Breda The Netherlands
MAH Contact	PPD [REDACTED] PhD MSc Manager, Observational Research Amgen Limited 1 Uxbridge Business Park Sanderson Road Uxbridge UB8 1DH The United Kingdom Tel: PPD [REDACTED] Fax: PPD [REDACTED]

Confidentiality Notice

This document contains confidential information of Amgen Inc.

This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number:

Amgen's general number in the US (1-805-447-1000).

Investigator's Agreement

I have read the attached protocol entitled "An observational registry study to evaluate the use and safety of cinacalcet among paediatric patients with secondary hyperparathyroidism", dated **10 February 2020**, and agree to abide by all provisions set forth therein.

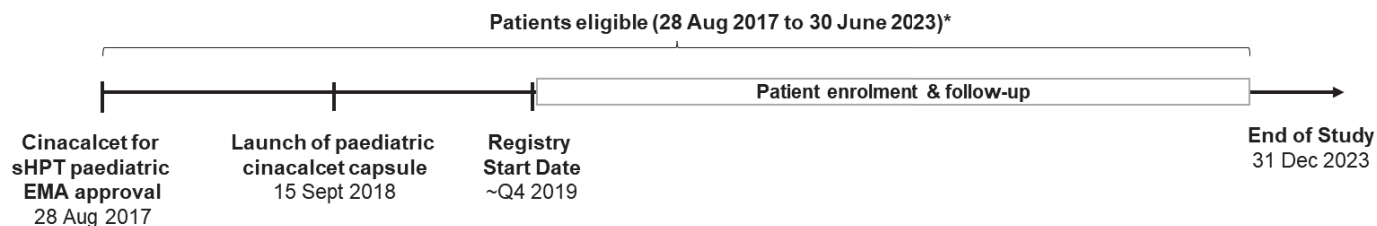
Signature

Name of Investigator

Date (DD Month YYYY)

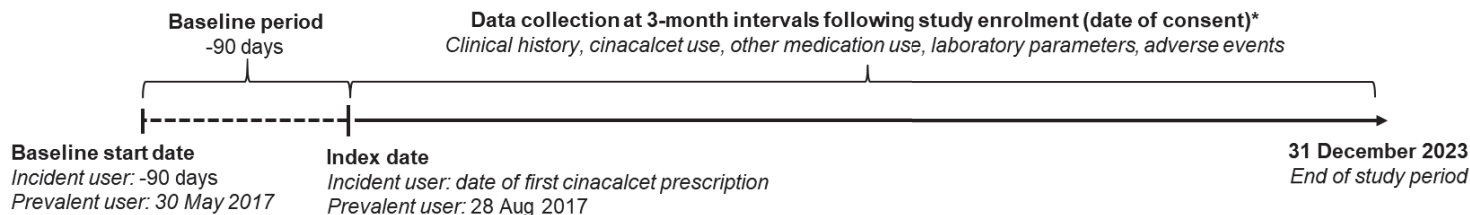
Study Design Schema

SUBJECT ELIGIBILITY



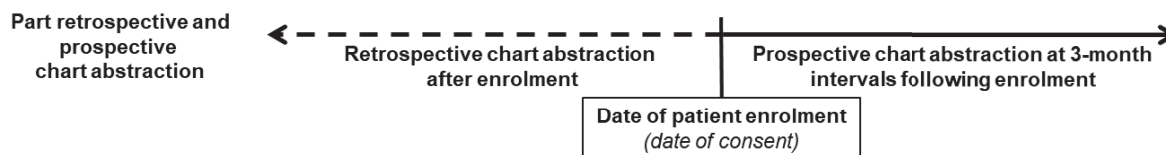
***Patient eligibility:** Patients aged 3 years - <18 years on maintenance dialysis who have a record of cinacalcet use as per EU marketing authorisation from 28 August 2017 to 30 June 2023; and have provided written informed consent or notified participation, according to local requirements will be included. **Patients who have participated in cinacalcet or etelcalcetide clinical trials will be excluded**

PATIENT-LEVEL DATA COLLECTION



***End of follow-up:** death, lost-to-follow-up, transfer to another centre that is not participating in this registry, turns aged 18-years, withdrawal of consent, or end of the study period (i.e., 31 December 2023), whichever comes first.

COMBINED DATA COLLECTION METHODS: retrospective and prospective



*For countries where a combination of retrospective and prospective data collection methods is not possible, all data will be collected retrospectively from 31 December 2023.

1. Table of Contents

Summary Table of Study Protocol	1
Study Design Schema	5
1. Table of Contents	6
2. List of Abbreviations	9
3. Responsible Parties.....	11
4. Abstract	11
5. Amendments and Updates	15
6. Milestones	16
7. Rationale and Background.....	16
7.1 Diseases and Therapeutic Area	16
7.1.1 Therapeutic Options for sHPT	17
7.1.1.1 Product Background.....	18
7.2 Rationale.....	19
7.3 Statistical Inference (Estimation or Hypothesis[es]).....	20
8. Research Question and Objectives.....	20
8.1 Primary	20
9. Research Methods.....	20
9.1 Study Design.....	20
9.2 Setting and Study Population	22
9.2.1 Study Period.....	23
9.2.2 Selection and Number of Sites	23
9.2.3 Patient Eligibility	23
9.2.3.1 Inclusion Criteria	23
9.2.3.2 Exclusion Criteria	24
9.2.4 Baseline Period	24
9.2.5 Study Follow-up.....	24
9.3 Variables.....	24
9.3.1 Exposure Assessment.....	24
9.3.2 Outcome Assessment	25
9.3.3 Covariate Assessment.....	26
9.3.4 Validity and Reliability.....	26
9.4 Data Sources	26
9.5 Study Size.....	26
9.6 Data Management.....	27
9.6.1 Review and Verification of Data Quality.....	27
9.7 Data Analysis	28

9.7.1	Planned Analyses.....	28
9.7.1.1	Interim Analyses/Analyses	28
9.7.1.2	Primary Analysis	28
9.7.2	Planned Method of Analysis	28
9.7.2.1	General Considerations.....	28
9.7.2.2	Missing or Incomplete Data and Lost to Follow-up	28
9.7.2.3	Descriptive Analysis	28
9.7.2.4	Analysis of the Primary Endpoint(s).....	29
9.7.2.5	Sensitivity Analysis.....	30
9.7.3	Analysis of Safety Endpoint(s)/Outcome(s)	30
9.8	Quality Control	30
9.9	Limitations of the Research Methods	31
9.9.1	Internal Validity of Study Design	31
9.9.1.1	Measurement Error(s)/Misclassification(s).....	31
9.9.1.2	Information Bias	32
9.9.1.3	Selection Bias	32
9.9.1.4	Confounding.....	32
9.9.2	External Validity of Study Design.....	33
9.9.3	Analysis Limitations.....	33
9.9.4	Limitations Due to Missing Data and/or Incomplete Data	33
9.10	Other Aspects	33
10.	Protection of Human Subjects.....	33
10.1	Informed Consent.....	34
10.2	Institutional Review Board/Independent Ethics Committee (IRB/IEC).....	34
10.3	Patient Confidentiality	35
10.4	Patients Decision to Withdraw.....	35
11.	Collection, Recording, and Reporting of Safety Information and Product Complaints	36
11.1	Definition of Safety Events	36
11.1.1	Adverse Events	36
11.1.2	Serious Adverse Events	36
11.1.3	Other Safety Findings.....	37
11.1.4	Product Complaints	37
11.2	Safety Collection, Recording and Submission to Amgen Requirements.....	38
11.2.1	Collection of Pregnancy and Lactation Information.....	39
11.2.2	Safety Reporting Requirement to Regulatory Bodies.....	39
12.	Administrative and Legal Obligations	39
12.1	Protocol Amendments and Study Termination	39

13.	Plans for Disseminating and Communicating Study Results	40
13.1	Publication Policy	40
14.	Compensation	40
15.	References	41
16.	Appendices.....	44

List of Tables

Table 1.	Two-sided Confidence Interval Half-widths for Hypothetical Hypocalcaemia Incidence 20%, 25% and 30%, and With Confidence Level at 95%.....	26
----------	--	----

List of Figures

Figure 1.	Data Collection	22
-----------	-----------------------	----

List of Appendices

Appendix A.	List of Stand-alone Documents.....	45
Appendix B.	ENCePP Checklist for Study Protocols.....	46
Appendix C.	Sample Safety Reporting Form(s)	53
Appendix D.	Additional Safety Reporting Information	59
Appendix E.	Pregnancy and Lactation Notification Worksheets.....	60

2. List of Abbreviations

Abbreviations	Full names
ATC	Anatomical Therapeutic Chemical
Ca	Calcium
cCa	Corrected Calcium
Ca-SR	Calcium-sensing receptor
CI	Confidence Interval
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease – Mineral Bone Disorder
eCRF	Electronic Case Report Form
ESCAPE	European Study Consortium for Chronic Kidney Disorders Affecting Pediatric Patients
EMA	European Medicines Agency
ERA/EDTA	European Renal Association/European Dialysis and Transplant Association
EPDWG	European Paediatric Dialysis Working Group (EPDWG)
ESPN	European Society of Paediatric Nephrology
ESRD	End-Stage Renal Disease
EU	European Union
HD	Haemodialysis
HCO ₃	Bicarbonate
HNF1 β	Hepatocyte nuclear factor-1 β
ICJME	International Committee of Medical Journal Editors
IEC	International Ethics Committee
IPDN	International Pediatric Dialysis Network
IQR	Interquartile Range
KM	Kaplan-Meier
KDIGO	Kidney Disease: Improving Global Outcomes
NAPRTCS	North American Paediatric Renal Trials and Collaborative Studies
NKF-K/DOQI™	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
PD	Peritoneal dialysis
pmarp	per million of the age-related population
PSUR	Periodic Safety Update Report
PTH	Parathyroid Hormone
rHGH	Recombinant human growth hormone
RMP	Risk Management Plan
RRT	Renal Replacement Therapy

Abbreviations	Full names
SAP	Statistical Analysis Plan
SCC	Study Coordinating Centre
SD	Standard Deviation
sHPT	Secondary Hyperparathyroidism
SOC	Standard of Care
SOPs	Standard Operation Procedures
SmPC	Summary of Product Characteristics
IPDN	International Paediatric Dialysis Network
US	United States

3. Responsible Parties

Role	Contact Details
Sponsor	Amgen Inc One Amgen Center Drive Thousand Oaks, CA 91320 United States
Principal Investigator	Professor PPD Department of Pediatric Nephrology, Rheumatology, and Dermatology Femme Mère Enfant Hospital, Bron Cedex, France Lyon-Est Medical School, Lyon 1 University Lyon, France

4. Abstract

- **Study Title**

An observational registry study to evaluate the use and safety of cinacalcet among paediatric patients with secondary hyperparathyroidism

- **Study Background and Rationale**

Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) is defined by abnormalities in bone and mineral metabolism that are manifested by abnormal laboratory values, bone lesions and the development of vascular calcification. Secondary hyperparathyroidism (sHPT) in both children and adults with chronic kidney disease (CKD) is an inevitable complication of end-stage renal disease (ESRD) requiring dialysis. Specifically, sHPT is characterised by persistently elevated parathyroid hormone (PTH) concentrations in serum or plasma, and it represents an adaptive response that serves primarily to maintain calcium (Ca) haemostasis systematically as kidney function declines but also to prevent debilitating skeletal complications and achieve normal growth in children (Haffner and Schaefer 2013). The goal of treatment for sHPT in children is similar to adults which is to achieve optimal control of PTH concentrations but there is also an objective for improving growth velocity and ultimately final height (Waller et al. 2003; Loder and Hensinger 1997). Traditional therapies for the management of sHPT in children have included phosphate binders and vitamin D sterols as reviewed in European and international guidelines. Recently, cinacalcet, a calcimimetic agent, was approved in Europe for children undergoing maintenance dialysis, and the

KDIGO 2017 Clinical Practice Guidelines now include calcimimetics as a therapeutic option for managing sHPT ([Ketteler et al. 2017](#)).

In Europe, use of cinacalcet in the paediatric population was granted on 28 August 2017 and is indicated for treatment of sHPT in children aged 3 years and older with ESRD on maintenance dialysis therapy in whom sHPT is not adequately controlled with standard of care therapy ([European Medicines Agency 2017](#)).

Following approval of paediatric cinacalcet for treatment of sHPT in Europe, there is a lack of data on real-world use. In addition, there are uncertainties about the incidence of, risk factors for, and management of hypocalcaemia among paediatrics in routine clinical practice. The rate of hypocalcaemia ranged from 22.7% to 28.0% in the cinacalcet-arm of the paediatric clinical trials ([Schaefer et al. 2017](#); [Sohn et al. 2019](#); [Warady et al. 2019](#)). As part of the agreement with the European Medicines Agency (EMA) following marketing authorization, an observational registry will be conducted to describe real-world utilization of cinacalcet and to describe the incidence of, risk factors for, and management of hypocalcaemia in a cohort of paediatric sHPT patients receiving maintenance dialysis.

- **Research Question and Objective(s)**

- What are the characteristics of paediatric patients receiving dialysis who use cinacalcet?
- How is cinacalcet used in paediatric patients?
- How do laboratory values change over time among paediatric cinacalcet users?
- What is the incidence of, risk factors for, and management of hypocalcaemia in paediatric cinacalcet users?
 - **Primary Objective(s)**

In a European cohort of paediatric patients with sHPT on maintenance dialysis who use cinacalcet:

1. To describe patient characteristics
2. To describe how cinacalcet is used
3. To describe laboratory values (PTH, corrected-calcium (cCa), phosphate, and albumin) over time
4. To describe the incidence of hypocalcaemia
5. To describe risk factors associated with time to hypocalcaemia event
6. To describe management of hypocalcaemia

- **Hypothesis(es)/Estimation**

The objectives of the study are descriptive. No formal hypothesis will be tested.

- **Study Design/Type**

This is a non-interventional observational registry of paediatric patients receiving maintenance dialysis with sHPT and using cinacalcet. A patient will receive standard of care treatment as determined by the patient's physician.

- **Study Population**

The registry will enrol eligible paediatric patients on maintenance dialysis who are prescribed cinacalcet treatment.

- **Summary of Patient Eligibility Criteria**

Inclusion criteria

- **Patients aged ≥ 3 years to < 18 years at the time of cinacalcet initiation**
- **Patients who have provided written informed consent or appropriate parties have been notified of participation (alive or deceased), where required for access to medical charts, according to local laws and regulation requirements.**
- **Patients on maintenance dialysis who are diagnosed with sHPT**
- **Patients that have a record of cinacalcet use (ie prescription) as per European Union (EU) marketing authorisation from 28 August 2017 to 30 June 2023**

Exclusion Criteria

- Patients who have participated in cinacalcet or etelcalcetide clinical trials

- **Follow-up**

The registry will record data abstracted from medical charts. Data will be abstracted from the date the patient had a cinacalcet prescription recorded within the study observation period and will continue until death, lost-to-follow-up, transfer to another centre that is not a participating in this registry, turns age 18-years, withdrawal of consent, or end of the study period (ie, 31 December 2023), whichever comes first. Regardless of whether the patient discontinued cinacalcet, follow-up will continue until one of the events described above occurs.

- **Variables**

- **Baseline**

- Demographics (sex, age at cinacalcet initiation)
 - Medical history (underlying renal disease, presence of comorbidities, HNF1 β mutation, history of parathyroidectomy, history of kidney transplant, and history of hypocalcaemia)

- **Observation period (spans from baseline to end of study follow-up)**

- Cinacalcet use (prevalent or incident user, cinacalcet type (Mimpara or generic), length of cinacalcet use (*prevalent user only*), date of prescription, prescribed dose, dosage forms (tablets or capsules), frequency, length of prescription, date of prescription change, type of prescription change (dose change, drug withheld, drug discontinuation), reason for prescription change (dose titration, non-compliance, adverse event, nausea, vomiting, PTH-low, PTH-high, PTH within target, hypocalcaemia, hypercalcemia, haemodialysis discontinued, parathyroidectomy, kidney transplant, patient refusal, safety finding, product complaint, other)
 - Concomitant medication use (phosphate binders (eg, Calcium carbonate/Calcium acetate, Sevelamer, Lanthanum carbonate, sucroferric oxyhydroxide), oral calcium supplementation, vitamin D (eg, Vitamin D3, active vitamin D analogue), dietary calcium intake, recombinant human growth hormone (rHGH)) in terms of dose, frequency, route of administration, date first taken, and date last taken
 - Laboratory parameters (PTH, cCa, ionized Ca, serum phosphorus, albumin, alkaline phosphatase, bicarbonate (HCO₃), and 25OH-Vitamin D3); and local PTH clinical target and assay range and cCa level definition of hypocalcaemia)
 - Incidence of hypocalcaemia will be identified in two ways: occurrence of laboratory value reporting cCa < 2.1 mmol/L; or reported adverse event due to hypocalcaemia (ie, blood cCa decreased or symptomatic hypocalcaemia).
 - Medical events of parathyroidectomy and kidney transplant (if kidney transplant, additional laboratory parameters (calciuria, urine calcium/creatinine ratio), and renal ultrasounds will be collected)
 - Physical measurements (height, weight before and after dialysis, vital signs (systolic and diastolic blood pressure before dialysis), and Tanner stage)
 - Dialysis treatment (dialysis vintage at time of cinacalcet initiation, dialysis modality, date, dialysis frequency, dialysis dose, duration, dialysate calcium, ionized calcium before dialysis, switched dialysis modality reason, dialysis discontinuation reason; if dialysis modality is peritoneal dialysis, additional parameters (fill volume, number of cycles, duration of cycle, automated or manual)

For physical measurements (except Tanner stage) and dialysis treatment variables, data will only be collected every 90 days (+ 30 days) following index date. For all other variables, all data available will be collected if available in the observation period.

- **Study Sample Size**

Based on the enrolment experience of the IPDN cohort of children and adolescents on maintenance dialysis over the last 10 years, off-label use of cinacalcet was observed among 5 to 10% of the population, or approximately 50 to 100 paediatric patients (IPDN, unpublished). Following EMA approval, use of cinacalcet is expected to double. According to the paediatric cinacalcet clinical trials ([Schaefer et al. 2017](#); [Sohn et al. 2019](#); [Warady et al. 2019](#)), the incidence of hypocalcaemia ranged from 22.7 to 28.0%. Assuming an incidence of 25%, a target sample size of 70 paediatric patients will provide an estimate of hypocalcaemia incidence with a two-sided confidence interval (CI) half-width of 10.1% (ie, two-sided 95% CI: 14.9%, 35.1%) (see [section 9.5](#)).

- **Data Analysis**

There are no formal hypotheses for the study. Descriptive data analyses will be performed. Characteristics of patients who develop and do not develop hypocalcaemia will be described.

Treatment characteristics (cinacalcet and other sHPT medications) will be summarised prior to cinacalcet initiation and after a hypocalcaemia event. PTH, cCa, phosphate and albumin laboratory parameters over time will be summarised.

To describe time-to-event of first hypocalcaemia event, cinacalcet discontinuation and cinacalcet re-initiation, Kaplan-Meier (KM) curves will be calculated.

5. Amendments and Updates

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	8 March 2019		See summary changes	
2	23 August 2019		See summary changes	
Superseding Amendment 2	20 September 2019		See summary changes	
3	10 February 2020		See summary changes	

6. Milestones

Milestone	Planned date
Start of data collection	Q4 2019
End of data collection	December 2023
Study progress report	Annually
Annual Report 1	Q4 2020
Annual Report 2	Q4 2021
Annual Report 3	Q4 2022
Registration in the EU PAS register	Q3 2019
Final report of study results	Q4 2024

** These timelines are subject to receiving timely approvals from national competent authorities and ethics committees which may vary by country.

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Secondary hyperparathyroidism (sHPT) develops in both children and adults with chronic kidney disease (CKD) and is an inevitable complication of end-stage renal disease (ESRD) requiring dialysis. sHPT is characterised by persistently elevated parathyroid hormone (PTH) concentrations in serum or plasma and it represents an adaptive response that serves primarily to maintain calcium (Ca) haemostasis systematically as kidney function declines ([Goodman and Quarles 2008](#)). These biochemical imbalances characterise CKD mineral bone disorder (CKD-MBD) and sHPT is a consequence of CKD-MBD that develops early during the course of progressive renal insufficiency ([Moe 2007](#); [Oh et al. 2002](#)). The pathophysiology of sHPT are similar in children and adults. Worsening of renal function is commonly associated with serious complications, such as increased risk of vascular calcification, fractures, and cardiovascular morbidity and mortality ([Goodman 2004](#)). In children on dialysis, growth retardation and fractures are also prominent findings and sHPT is an important contributor to this disorder ([Kuizon and Salusky 1999](#); [Denburg 2016](#)). The International Paediatric Dialysis Network (IPDN) report the prevalence of bone disease is 15% in the paediatric population ([Borzych et al. 2010](#)); and about 90% of those who receive a bone biopsy show deficient mineralization ([Bakkaloglu et al. 2010](#)) and are at 2-3 times increased risk for fractures compared to healthy children ([Rees et al. 2017](#)).

Globally, the incidence of ESRD in children who require renal replacement therapy (RRT) (ie, haemodialysis (HD) and peritoneal dialysis (PD)) varies widely. The median incidence of ESRD in children < 19 years is 9 (range: 4 to 18) cases per million of the

age-related population (pmarp) and the prevalence ranges from 18 to 100 pmarp (Rees et al. 2017). Specifically, in Europe, the rate of RRT was reported in children (< 20 years) was estimated to be 8.9 (for 2007 to 2011) and 5.5 pmarp for those aged < 15 years (for 2009-11) (Rees et al. 2017). In contrast, the incidence in the US was 14.2 pmarp. Based on 2016 annual report from the European Renal Association/European Dialysis and Transplant Association (ERA/EDTA) Registry, there were 2150 incident RRT paediatric patients aged < 20 in 2011-2016. Of these incident patients, 1616 patients were on maintenance dialysis of whom two-thirds (n = 1080) were on HD with an incidence of 4.0 pmarp and one-third (n = 536) were on PD with an incidence of 2.0 pmarp (ERA-EDTA 2018).

Globally, 44% of the children on chronic dialysis have severe sHPT and this variation varies by region with the highest median PTH found in Latin America (419 pg/mL) followed by North America (290 pg/ml), Asia (208 pg/ml) and Europe (175 pg/ml) (Borzuch et al. 2010). In Europe, the UK Renal Registry reported that among paediatric patients aged < 18 on HD (n = 98) and PD (n = 86), the prevalence of sHPT was 61.2% and 67.4%, respectively. (Hamilton et al. 2016). In contrast, the prevalence of sHPT (> 300 pg/mL (31.8 pmol/L) (Langman et al. 2005)) in the North American Paediatric Renal Trials and Collaborative Studies (NAPRTCS) was 49% among 320 paediatric patients aged 2- < 18 years on maintenance dialysis PTH levels (NAPRTCS, unpublished data).

7.1.1 Therapeutic Options for sHPT

Management of CKD-MBD in children undergoing maintenance dialysis is focussed on correcting all metabolic and clinical abnormalities that could worsen bone and growth. Specifically, the goal of treatment for sHPT in children is similar to adults which is optimal control of PTH concentrations but there is also an objective for improving growth velocity through PTH control and by treatment with recombinant human growth hormone (Waller et al. 2003; Loder and Hensinger 1997). The recommended treatment goals of Kidney Disease: Improving Global Outcomes (KDIGO) are to control serum PTH levels and maintaining normal serum Ca and phosphorus (P) levels (Ketteler et al. 2017). To date, there is no consensus on the PTH target levels in children undergoing maintenance dialysis and international guidelines committees vary (Ketteler et al. 2017; Kidney Disease: Improving Global Outcomes 2009; Klaus et al. 2006). The 2006 European Paediatric Dialysis Working Group suggest targeting PTH levels

between two to three times the upper limit of normal in dialyzed children (ie, 120-180 pg/mL) (Klaus et al. 2006; Haffner and Schaefer 2013).

Therapeutic approaches consist of nutritional calcium intake, phosphate intake control by diet and/or phosphate binders and/or intensification of dialysis, native vitamin D supplementation (Shroff, Wan, Nagler, Bakaloglu, Fischer, et al. 2017), active Vitamin D analogs (Shroff, Wan, Nagler, Bakaloglu, Cozzolino, et al. 2017), and more recently, calcimimetic agents that activate the calcium-sensing receptor (CaSR). Although traditional therapies for sHPT (eg, phosphate binders or vitamin D sterols) are widely used in the paediatric dialysis population, they are sometimes insufficient to manage sHPT due to the potential increase in serum Ca and phosphorus (P). The ability to effectively reduce PTH while simultaneously reducing serum concentrations of Ca and P is widely regarded as a key differentiating attribute of calcimimetics compared with vitamin D analogs, which stimulate Ca and P absorption from the gastrointestinal tract. Cinacalcet acts as an allosteric modulator of the CaSR and regulates PTH secretion by amplifying the sensitivity of the receptor to extracellular calcium, thereby reducing PTH secretion (Nemeth et al. 2004).

The 2017 KDIGO guidelines suggest that dialysis patients can receive cinacalcet as first or second line treatment in combination with vitamin D analogs (Ketteler et al. 2017) although there is no evidence to support giving cinacalcet as first-line in paediatric patients undergoing dialysis. European guidelines are working to define practical approaches to manage paediatric patients with severe sHPT and observational studies could help inform the development of these guidelines.

7.1.1.1 Product Background

Cinacalcet (Mimpara[®]) is a calcimimetic formulated for oral administration. For the adult population, cinacalcet has received marketing authorisation in 75 countries and is indicated for the treatment of sHPT in patients with CKD receiving dialysis. In Europe, use of cinacalcet in the paediatric population was granted on 28 August 2017 and is indicated for treatment of sHPT in children aged 3 years and older with ESRD on maintenance dialysis therapy in whom sHPT is not adequately controlled with standard of care therapy (European Medicines Agency 2017). The posology is a starting dose of ≤ 0.20 mg/kg once daily for children aged ≥ 3 years to < 18 years based on the patient's dry weight. The dose can be increased to achieve a desired target PTH range. The dose should be increased sequentially through available dose levels no more frequently than every 4 weeks. The dose can be increased up to a maximum dose of 2.5 mg/kg/day, not

to exceed a total daily dose of 180 mg. Cinacalcet may be used as part of a therapeutic regimen including phosphate binders and/or Vitamin D sterols, as appropriate.

Life-threatening events and fatal outcomes associated with hypocalcaemia have been reported in both adults and paediatric patients treated with cinacalcet. Since cinacalcet lowers serum Ca, patients should be monitored carefully for the occurrence of hypocalcaemia. Total serum calcium-corrected Ca (cCa) should be in the upper range of, or above, the age-specified reference interval prior to administration of first dose of cinacalcet and closely monitored. The normal cCa range differs depending on methods used by the local laboratory and the age of the child.

7.2 Rationale

The efficacy and safety of cinacalcet for treatment of sHPT in paediatric patients with ESRD receiving dialysis was evaluated in two randomized controlled studies and one single-arm study ([Sohn et al. 2019](#)). Study 1 was a double-blinded, placebo-controlled study in 43 patients aged 6 to < 18 years who were randomized to receive either cinacalcet (n = 22) or placebo (n = 21). The proportion of patients who achieved the primary endpoint ($\geq 30\%$ reduction from baseline in mean plasma PTH) was 55% and 19% in the cinacalcet and placebo groups, respectively. Study 2 was an open-label study of 55 patients aged 6 to < 18 years who were randomized to receive either cinacalcet in addition to standard of care (SOC) (n = 27) or SOC alone (n = 28) ([Schaefer et al. 2017](#)). The study did not meet its primary endpoint ($\geq 30\%$ reduction from baseline in mean plasma PTH). The proportion that achieved the endpoint was 22% of patients in the cinacalcet plus SOC group and 32% of patients in the SOC group. Study 3 was a 26-week open-label, single-arm safety study of 12 patients aged 8 months to < 6 years who received a single dose of cinacalcet orally or by nasogastric or gastric tube ([Sohn et al. 2019](#)). Serum PTH levels reduced by a median 10.8 and 29.6% at 2- and 8-hours post-dose and returned to baseline by 12-72 hours. Single-dose cinacalcet was well-tolerated with no unexpected safety findings.

Among the paediatric subjects exposed to cinacalcet in the three clinical trials, a total of 19 subjects (24%; 64.5 per 100 subject years) had at least one adverse event of hypocalcaemia; and a fatal outcome was also reported in a patient with severe hypocalcaemia ([Schaefer et al. 2017](#); [Sohn et al. 2019](#); [Warady et al. 2019](#)). The Summary of Product Characteristics (SmPC) states that serum cCa levels and patient compliance during treatment with cinacalcet should be closely monitored ([EMA 2016](#)).

Patients should not be initiated on cinacalcet or increase the dose if non-compliance is suspected.

Following approval of paediatric cinacalcet in Europe, there is a lack of data on real-world use. In addition, there are uncertainties about the incidence of, risk factors for and management of hypocalcaemia among paediatrics in routine clinical practice. As part of the agreement with the EMA following marketing authorization, an observational registry will be conducted to describe real-world utilization of cinacalcet and the incidence and risk factors of hypocalcaemia in a cohort of paediatric patients receiving maintenance dialysis with sHPT in order to inform the management of minimizing this risk of hypocalcaemia in clinical practice.

7.3 Statistical Inference (Estimation or Hypothesis[es])

The objectives of the study are descriptive. No formal hypothesis will be tested.

8. Research Question and Objectives

- What are the characteristics of paediatric patients receiving dialysis who use cinacalcet?
- How is cinacalcet used in paediatric patients?
- How do laboratory values change over time among paediatric cinacalcet users?
- What is the incidence of, risk factors for, and management of hypocalcaemia in paediatric cinacalcet users?

8.1 Primary

In a European cohort of paediatric patients with sHPT on maintenance dialysis and using cinacalcet:

1. To describe patient characteristics
2. To describe how cinacalcet is used
3. To describe laboratory values (PTH, cCa, phosphate and albumin) over time
4. To describe the incidence of hypocalcaemia
5. To describe risk factors associated with time to hypocalcaemia event
6. To describe management of hypocalcaemia

9. Research Methods

9.1 Study Design

This is a non-interventional observational registry of paediatric patients receiving maintenance dialysis with sHPT and using cinacalcet. A patient will receive standard of care treatment as determined by the patient's physician. The overall study design is described in the [Study Schema](#).

Patient eligibility

Paediatric patients on maintenance dialysis with sHPT who use cinacalcet are eligible for study inclusion if they meet study eligibility criteria ([section 9.2.3](#)). Patients eligible for participation include those who have a record of cinacalcet use between 28 August 2017 and 30 June 2023.

Potential patients may be identified via paediatric nephrology networks (eg, European Society for Paediatric Nephrology (ESPN) CKD-MBD Working Group, International Pediatric Dialysis Network (IPDN) or European Study Consortium for Chronic Kidney Disorders Affecting Pediatric Patients (ESCAPE)). Those who meet patient eligibility criteria ([section 9.2.3](#)) will be invited to participate in this registry study. **Patients will not be enrolled until all required signatures have been collected on the informed consent form.**

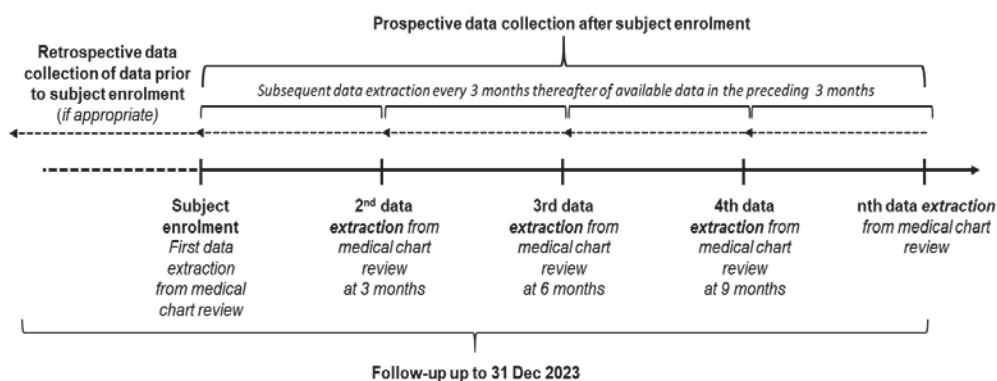
Data collection

Data will be collected from routine medical records and entered into the electronic case report form (eCRF) for the registry database. Baseline data (eg, laboratory parameters PTH, cCa, phosphate, and albumin) in the 90 days prior to index date will be collected. For incident cinacalcet users, this will be 90 days before date of calcimimetic initiation (incident user index date). For prevalent cinacalcet users, this will be from 30 May 2017 to 28 August 2017 (prevalent user index date). Then data will be collected from the index date to the end of the study observational period (31 December 2023) ([section 9.2.5](#)). Chart abstraction will be carried out part retrospectively (ie, data prior to patient enrolment [**enrolment is defined as the date of consent or the date the decision was taken to participate, if consent is not mandated**]) and part prospectively (ie, data **on or** after patient enrolment).

Following enrolment, data will be prospectively collected at 3-month intervals until the end of study follow-up ([Study Schema](#) and [Figure 1](#)). Data available in the preceding 3 months prior to the data collection timepoint will be retrospectively collected. For example, if a patient enrolled on 15 Oct 2019, the next data collection timepoint will be 15 Jan 2020, and all laboratory data values measured between 15 Oct 2019 to 15 Jan 2020 will be collected. If PTH testing was carried out every month, then 3 PTH lab results will be collected. If PTH measurement was carried out only once every three months, then only one value will be collected. The volume of data collected will depend on routine clinical practice at the study site.

However, for countries where a combination of retrospective and prospective data collection methods is not possible, all data will be collected retrospectively before and up to 31 December 2023 (ie, end of study period). Retrospective data will span from 3-months prior to date of cinacalcet initiation (index date) until death, lost-to-follow-up, transfer to another centre that is not participating in this registry, turns age 18-years, withdrawal of consent, or end of the study period (ie, 31 December 2023), whichever comes first.

Figure 1. Data Collection



*For countries where a combination of retrospective and prospective data collection methods is not possible, all data will be collected retrospectively from 31 December 2023.

9.2 Setting and Study Population

The source study population for this study will be comprised of paediatric patients on maintenance dialysis who are prescribed cinacalcet. Potential patients may be identified through paediatric nephrology networks (eg, ESPN CKD-MBD Working Group, IPDN, ESCAPE or other paediatric nephrology networks).

ESPN is a society that promotes research knowledge of paediatric nephrology through teaching, scientific meetings and other methods for the benefit of children with renal disease (<https://espn-online.org/>). The specific CKD-MBD Working Group is focused on providing education and training for management of CKD-MBD in children, perform clinical studies on the topic, and develop appropriate guidelines.

IPDN is a global consortium of paediatric nephrology centres dedicated to the care of children on chronic dialysis (<http://www.pedpd.org/>). Globally, there are 242 institutions in 43 countries participating in the network. In Europe, there are 69 institutions in 18 European Union (EU) countries (Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Ireland, Italy, Lithuania, The Netherlands, Poland, Portugal, Romania, Slovenia, Spain, Sweden and the UK) participating in the IPDN. The network

covers approximately 31% of the paediatric dialysis patients in Europe (Schaefer et al. 2012).

ESCAPE is a consortium of European paediatric nephrologists from 33 nephrology centres in Western Europe (<https://www.escapenet.eu/>) dedicated to improve the care of children with kidney diseases (Furth et al. 2018).

9.2.1 Study Period

The study period is anticipated to include data spanning from 30 May 2017 (ie, 90 days prior to 28 August 2017, date of EU marketing authorisation for paediatric cinacalcet, to capture relevant baseline data for prevalent cinacalcet users) to 31 December 2023 (study end date). Eligible patients are those patients who have initiated cinacalcet by 30 June 2023 in order for all patients to have a minimum of 6-month observation data available. **Patients without a history of prior cinacalcet use should have received at least one dose administration at the time of enrolment.**

However, for countries where prospective data collection is not possible, all data will be retrospectively collected for the period spanning 30 May 2017 (if applicable) to 31 December 2023.

9.2.2 Selection and Number of Sites

Approximately 50 to 70 centres across Europe are expected to participate. Eligible sites are centres who are using cinacalcet among paediatric patients on maintenance dialysis. Approximately 1-2 patients are expected to enrol at each site given this special population.

Site selection will be carried out according to normal site evaluation processes. Selection will be based on interest in study participation, and willingness and capacity to comply with protocol and data entry conventions. Sites will be considered active after fulfilling all legal, regulatory and ethical requirements.

9.2.3 Patient Eligibility

9.2.3.1 Inclusion Criteria

- 101 Patients aged ≥ 3 years to < 18 years **at the time of cinacalcet initiation**
- 102 Patients who have provided written informed consent or **appropriate parties have been notified of participation (alive or deceased), where required for access to medical charts**, according to local **laws and regulation** requirements

103 Patients on maintenance dialysis who are diagnosed with sHPT

104 Patients that have a record of cinacalcet use (ie prescription) as per EU marketing authorisation from 28 August 2017 to 30 June 2023

9.2.3.2 Exclusion Criteria

201 Patients who have participated in cinacalcet or etelcalcetide clinical trials

9.2.4 Baseline Period

For 'prevalent' cinacalcet users, the baseline period spans from 30 May 2017 to 28 August 2017 (index date for prevalent cinacalcet users). For 'incident' cinacalcet users, the baseline period is defined as the 90-day period before the date of cinacalcet initiation (index date for incident cinacalcet users). The most proximal laboratory value available prior to index date will be assessed.

9.2.5 Study Follow-up

The registry will record data abstracted from medical charts. Data will be abstracted from the date the patient had a cinacalcet prescription recorded within the study observation period and will continue until death, lost-to-follow-up, transfer to another centre that is not a participating in this registry, turns age 18-years, withdrawal of consent, or end of the study period (ie, 31 December 2023), whichever comes first. Regardless of whether the patient discontinued cinacalcet, follow-up will continue until one of the events described above occurs.

9.3 Variables

9.3.1 Exposure Assessment

All patients enrolled in the study will have had exposure to cinacalcet. A patient's exposure status will be assessed from the medication history recorded in the patient's medical records (and may be identified by the ATC code for cinacalcet: H05BX01). During the observation period, if a patient discontinues cinacalcet treatment during the study period, the availability of treatment data will end on the date in which cinacalcet was first discontinued. However, data abstraction will continue for other parameters (eg, laboratory parameters, PTH, Ca and P) and will be no different from data collection of patients who are using cinacalcet continuously till the end of the study period or till the occurrence of any event that is described in [section 9.2.5](#). Continuous collection will allow capturing data for patients who may have stopped treatment but re-initiated treatment at a later timepoint. For example, patients who discontinued cinacalcet

because of hypocalcaemia and re-start treatment once Ca levels have returned to normal levels.

9.3.2 Outcome Assessment

Baseline

- Demographics (sex, age at cinacalcet initiation)
- Medical history (underlying renal disease and presence of comorbidities, HNF1 β mutation, history of parathyroidectomy, history of kidney transplant,; and history of hypocalcaemia)

Observation period (spans from baseline to end of study follow-up)

- Dialysis treatment (switch dialysis modality and dialysis discontinuation)
- Cinacalcet use (prevalent or incident user, cinacalcet type (Mimpara or generic), length of cinacalcet use (*prevalent user only*), date of prescription, prescribed dose, dosage forms (tablets or capsules), frequency, length of prescription, date of prescription change, type of prescription change (dose change, drug withheld, drug discontinuation), reason for prescription change (dose titration, non-compliance, adverse event, nausea, vomiting, PTH-low, PTH-high, PTH within target, hypocalcaemia, hypercalcemia, haemodialysis discontinued, parathyroidectomy, kidney transplant, patient refusal, safety finding, product complaint, other)
- Concomitant medication use (phosphate binders (eg, Calcium carbonate/Calcium acetate, Sevelamer, Lanthanum carbonate, sucroferric oxyhydroxide), oral calcium supplementation, vitamin D (eg, Vitamin D3, active vitamin D analogue), dietary calcium intake, rHGH in terms of dose, frequency, route of administration, date first taken, and date last taken)
- Laboratory parameters (PTH, total Ca, ionized Ca, serum phosphorus, albumin, alkaline phosphatase, bicarbonate (HCO₃), 25OH-Vitamin D3 and HNF1 β mutation); and local PTH clinical target and assay range and cCa level definition of hypocalcaemia)
 - Incidence of hypocalcaemia will be identified in two ways: occurrence of laboratory value reporting cCa < 2.1 mmol/L; or reported adverse event due to hypocalcaemia (ie, blood cCa decreased or symptomatic hypocalcaemia)
 - Medical events of parathyroidectomy and kidney transplant(if kidney transplant, additional laboratory parameters, calcinuria, urine calcium/creatinine ratio, and renal ultrasounds will be collected)
 - Physical measurements (height, weight before and after dialysis, vital signs (systolic and diastolic blood pressure before dialysis), Tanner stage)
 - Dialysis treatment (dialysis vintage at time of cinacalcet initiation, dialysis modality, date, dialysis frequency, dialysis dose, duration, dialysate calcium, ionized calcium before dialysis, switched dialysis modality reason, dialysis discontinuation reason; if dialysis modality is peritoneal dialysis, additional parameters (fill volume, number of cycles, duration of cycle, automated or manual)

For physical measurements (except for Tanner stage) and dialysis treatment variables, data will only be collected every 90 days (+ 30 days) following index date. For all other variables, all data available will be collected if available in the observation period.

9.3.3 Covariate Assessment

Baseline covariates (demographics, medical history, concomitant medication use, and laboratory parameters as defined in [section 9.3.2](#)) will be described.

9.3.4 Validity and Reliability

Study variables stated in this protocol are objective and relevant to the question under study. Variables are parameters which are routinely measured as part of clinical management of paediatric CKD HD patients.

9.4 Data Sources

Study variables stated in this protocol are objective and relevant to the question under study. Variables are parameters which are routinely measured as part of clinical management of paediatric CKD HD patients.

9.5 Study Size

Based on the enrolment experience of the IPDN cohort of children and adolescents on maintenance dialysis over the last 10 years, off-label use of cinacalcet was observed among 5 to 10% of the population, or approximately 50 to 100 paediatric patients (IPDN, unpublished). Following EMA approval, use of cinacalcet is expected to double. According to the paediatric cinacalcet clinical trials ([Schaefer et al. 2017](#); [Sohn et al. 2019](#); [Warady et al. 2019](#)), the incidence of hypocalcaemia ranged from 22.7 to 28.0%. Assuming an incidence of 25%, a target sample size of 70 paediatric patients will provide an estimate of hypocalcaemia incidence with a two-sided confidence interval half-width of 10.1% (ie, two-sided 95% CI: 14.9%, 35.1%) (see [Table 1](#)).

Table 1. Two-sided Confidence Interval Half-widths for Hypothetical Hypocalcaemia Incidence 20%, 25% and 30%, and With Confidence Level at 95%

Confidence Interval Half-width	Hypothetical Hypocalcaemia Incidence		
	20.0%	25.0%	30.0%
Sample size			
50	11.1%	12.0%	12.7%
60	10.1%	11.0%	11.6%
70	9.4%	10.1%	10.7%
80	8.8%	9.5%	10.0%
90	8.3%	8.9%	9.5%
100	7.8%	8.5%	9.0%

9.6 Data Management

Data are abstracted by site staff from patient's medical records into an electronic database provided by the sponsor. The sponsor provides protocol-specific training to all staff delegated to abstract patient data. An eCRF Completion Guideline is provided.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, case report forms [CRFs] and other pertinent data) provided that patient confidentiality is respected.

The clinical monitor or designee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data and adherence to local regulations on the conduct of research. The Clinical Monitor or designee is to have access to patient medical records and other study-related records needed to verify the entries on the CRFs in accordance with the local laws and regulations.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and available upon request.
- Updates to eCRFs will be automatically documented through the software's "audit trail."
- To ensure the quality of clinical data across all patients and sites, a clinical data management review is performed on patient data received at Amgen. During this review, patient data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the electronic data capture (EDC) system database for site resolution and closed by Amgen reviewer.

The investigator signs only the Investigator Verification Form for this EDC study. This signature indicates that the investigator inspected or reviewed the data on the eCRF, the data queries, and site notifications, and agrees with the content.

9.6.1 Review and Verification of Data Quality

Automatic edit checks within the database and further manual review by the sponsor will help to ensure quality and completeness of the data. Data queries will be sent to sites for clarification and resolution of discrepancies.

9.7 Data Analysis

A Statistical Analysis Plan (SAP) will be developed and will describe all planned analysis in detail. In addition, specifications of tables, figures and listings (TFLs) will be specified.

9.7.1 Planned Analyses

9.7.1.1 Interim Analyses/Analyses

Analyses will be conducted to provide data annually to the EMA **as requested**.

9.7.1.2 Primary Analysis

The primary analysis will be performed at a single time point at the end of the study period (ie, end of data collection 31 December 2023) (see timeline in [section 6](#)).

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

There are no formal hypotheses for the study. Descriptive data analyses will be performed. Continuous data will be described using mean, standard deviation (SD), median, interquartile range (IQR) and minimum and maximum values; and categorical variables will be described using counts and frequencies.

Analyses will be performed overall and for two cohorts, incident and prevalent cinacalcet users.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Missing or incomplete data will be reviewed. No imputation of missing data will be performed. When applicable, for continuous variables, the number of nonmissing observations will be presented; and for categorical variables, missing responses will be presented as a separate category.

Patients lost to follow-up will be summarised and censored from analyses, where appropriate.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

The number of enrolled patients will be summarised overall and by country.

9.7.2.3.2 Description of Patient Characteristics

Demographics and baseline characteristics (specified in [Section 9.3.2](#)) of patients who initiate cinacalcet and patients who develop and do not develop hypocalcaemia will be summarised.

Treatment characteristics (sHPT medications) at time of first cinacalcet use (*'incident cohort'*) or on 28 August 2017 (*'prevalent cohort'*) will be summarised.

PTH, Ca, P and other relevant laboratory parameters will be described by plotting the median and IQR values every month (30 days) or three months (90 days) following index date and following hypocalcaemia event. Data will be presented overall and stratified by levels of control (eg, low, medium or high of Ca values or mild, moderate or severe PTH levels) at baseline or following hypocalcaemia event (mild, moderate and severe hypocalcaemia) to show the longitudinal trajectory of laboratory values.

To describe time-to-event of first hypocalcaemia event (*incident cinacalcet cohort only*), cinacalcet discontinuation (*incident cinacalcet cohort only*) and cinacalcet re-initiation, KM curves will be plotted, and KM estimates will be calculated. Patients will be censored if they had a kidney transplant, parathyroidectomy or experienced one of the follow-up events ([section 9.2.5](#)), whichever comes first. In the time to hypocalcaemia event analysis, patients will also be censored if they discontinued cinacalcet.

To describe risk factors associated with time to first hypocalcaemia event (*incident cinacalcet cohort only*) after cinacalcet initiation, a multivariate Cox model will be used.

9.7.2.4 Analysis of the Primary Endpoint(s)

Demographics and baseline characteristics (specified in [Section 9.3.2](#)) of patients who initiate cinacalcet and patients who develop and do not develop hypocalcaemia will be summarised.

Treatment characteristics (sHPT medications) at time of first cinacalcet use (*'incident cohort'*) or on 28 August 2017 (*'prevalent cohort'*) will be summarised.

PTH, Ca, P and other relevant laboratory parameters will be described by plotting the median and IQR values every month (30 days) or three months (90 days) following index date and following hypocalcaemia event. Data will be presented overall and stratified by levels of control (eg, low, medium or high of Ca values or mild, moderate or severe PTH levels) at baseline or following hypocalcaemia event (mild, moderate and severe hypocalcaemia) to show the longitudinal trajectory of laboratory values.

To describe time-to-event of first hypocalcaemia event (*incident cinacalcet cohort only*), cinacalcet discontinuation (*incident cinacalcet cohort only*) and cinacalcet re-initiation, KM curves will be plotted, and KM estimates will be calculated. Patients will be censored if they had a kidney transplant, parathyroidectomy or experienced one of the follow-up

events ([section 9.2.5](#)), whichever comes first. In the time to hypocalcaemia event analysis, patients will also be censored if they discontinued cinacalcet.

To describe risk factors associated with time to first hypocalcaemia event (*incident cinacalcet cohort only*) after cinacalcet initiation, a multivariate Cox model will be used.

9.7.2.5 Sensitivity Analysis

The analysis of hypocalcaemia may be repeated using total serum Ca thresholds. In addition, the analysis of hypocalcaemia may be repeated by each of the following definitions of hypocalcaemia: 1) according to cCa levels only 2) as a reported adverse event (ie, blood decreased cCa or symptomatic hypocalcaemia) or 3) according local site cCa definition of hypocalcaemia

9.7.2.5.1 Subgroup Analysis

Not applicable

9.7.2.5.2 Stratified Analysis

The following stratified analyses may be performed:

- Hypocalcaemia will be grouped by low (2.1- < 2.5 mmol/L), medium (2.5- < 2.75 mmol/L) and high (\geq 2.75 mmol/L) normal cCa levels at baseline cinacalcet
- Hypocalcaemia may be stratified by severity, mild, moderate and severe (as defined in [section 9.7.2.4](#))
- Incidence of hypocalcaemia will be stratified by cinacalcet dosage forms: tablet < 30mg (ie, crushed tablet), tablet \geq 30 mg or capsules.
- Incidence of hypocalcaemia will be stratified by occurrence in retrospective vs. prospective data collection

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

9.7.2.5.4 Other Sensitivity Analysis

Other sensitivity analyses may be conducted to meet country-specific regulatory requirements. Details will be specified in the SAP.

9.7.3 Analysis of Safety Endpoint(s)/Outcome(s)

The incidence of hypocalcaemia will be summarised as described in [section 9.7.2.4](#).

9.8 Quality Control

Source data verification will be performed at the study site, in accordance with Amgen standard operating procedures (SOPs).

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities. Documents to be maintained for the study are as follows:

- patient files containing the completed eCRF, informed consent forms, as applicable, and patient identification list
- study files containing the protocol with all amendments, copies of prestudy documentation, and all correspondence to and from the Independent Ethics Committee (IEC) or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available. Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs, and outputs generated for the study. At study close, data are uploaded from the Medidata Rave database and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

9.9.1.1 Measurement Error(s)/Misclassification(s)

Persistence of medications is quantified by the number of days the medication is available to the patient. This represents a simplified measure, since the definition does not access if the patient takes the medication (ie, compliance/adherence). Nonetheless, in the absence of a valid measure and to maintain consistency and comparability between studies of persistence, the number of days the medication was prescribed to the patient during his/her observation period in this study will be used as a proxy to define persistence.

Hypocalcaemia event is defined by cCa laboratory value and reporting of adverse event due to hypocalcaemia (ie, blood cCa decreased or symptomatic hypocalcaemia). It is possible that hypocalcaemia may be under-reported if a patient did not have both albumin and total serum Ca measured on the same day to calculate cCa. However, we may assume that for those circumstances, hypocalcaemia events (if any occurred) are likely to be asymptomatic. For symptomatic hypocalcaemia events, which result in hospitalisation or medical interventions, these events will be captured as an adverse event.

9.9.1.2 Information Bias

Information bias is unlikely to affect the findings of this study unless participating sites record exposures and/or outcomes more diligently for patients treated with cinacalcet compared to nephrology centres not participating in the study. It is possible that hospitalised patients may artificially appear to be non-persistent (ie, discontinued) as new prescriptions may not be issued until they return to their nephrology centre. If this is the case, then time-varying analyses would identify hospitalisation as a risk factor, although it should be acknowledged that it would be impossible to determine if this is a true (worsening clinical condition) or artificial effect. However, we anticipate this occurrence to be low as most acute complications are managed in the paediatric nephrology unit where they are normally cared for.

9.9.1.3 Selection Bias

Patients included in the study represent paediatric patients who receive maintenance dialysis and are treated at nephrology centres participating in the IPDN or ESCAPE networks. The study may not be representative of the paediatric population receiving cinacalcet at nephrology centres that are not participating in these paediatric nephrology networks.

9.9.1.4 Confounding

As with all observational studies, residual confounding is plausible if relevant confounding factors (eg, data known to inform treatment decisions) were not collected and cannot be considered in adjusted analyses. In addition, confounding by indication is also plausible if patients who are treated with other sHPT medications (eg, vitamin D) are inherently different from those who are treated with cinacalcet, eg, if one group is more likely to have severe sHPT (high PTH levels) than the other.

9.9.2 External Validity of Study Design

As with all observational studies, residual confounding is plausible if relevant confounding factors (eg, data known to inform treatment decisions) were not collected and cannot be considered in adjusted analyses. In addition, confounding by indication is also plausible if patients who are treated with other sHPT medications (eg, vitamin D) are inherently different from those who are treated with cinacalcet., eg, if one group is more likely to have severe sHPT (high PTH levels) than the other.

9.9.3 Analysis Limitations

The precision of estimates will depend on the number of sHPT patients treated with cinacalcet.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Key variables are those expected to be recorded in routine clinical care of paediatric CKD dialysis patients and missing/incomplete data recorded in the patient's medical records is therefore not anticipated or limited.

9.10 Other Aspects

Not applicable.

10. Protection of Human Subjects

This study will comply with all relevant ethical and regulatory requirements in each country and will not be used for the conduct of marketing surveys or other marketing purposes. The study will comply with Amgen adverse event reporting SOPs. This study and data collection will be conducted in accordance with the relevant local laws.

The responsible physician is also responsible for sending the following documents to Amgen or its representative for review before study initiation occurs:

- Signed and dated protocol signature page (Responsible Physician's Agreement)
- Copy of the Central Ethics Board approval of the protocol, waiver for requirement of informed consent where applicable
- Patient or patient's legally acceptable representative has provided informed consent (for countries where required per local regulations)
- Up-to-date curriculum vitae of responsible physician and all co/sub-physicians
- Signed confidentiality agreement
- Signed study contract

The responsible physician will be charged with maintaining correct and comprehensive documentation, while the Amgen monitor/designee is tasked to ensure that the responsible physician is following the correct study protocol.

10.1 Informed Consent

Where an informed consent is required per local regulations, an initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. **Where required by local laws and regulations, agreement to participate will be sought from appropriate parties for the inclusion of deceased subject's data.** Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

Before a patient's participation in the study, the investigator will explain to the patient, or his/her legally authorized representative, the aims, methods, anticipated benefits, and potential hazards of the study, and answer all questions regarding the study.

The acquisition of informed consent is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the subject **and/or parent** or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the patient or the patient's legally authorized representative.

If local regulations do not require an informed consent to be signed but mandate that the patient is notified about the study, the investigator should document the notification process in the patient's medical record.

10.2 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB/IEC or relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before study can be executed.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The Investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or

serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval/renewal throughout the duration of the study. Copies of the Investigator's reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

10.3 Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained for documents submitted to Amgen.

- Patients are to be identified by a unique patient identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- Documents that are not for submission to Amgen (eg, signed informed consent forms, as applicable) are to be kept in confidence by the Investigator, except as described below.

Subject to compliance with local country regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the Sponsor, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the patient's original medical records for verification of study-related activities and data. Direct access includes examining, analysing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obliged to inform and obtain the consent of the patient to permit such individuals to have access to his/her study-related records, including personal information.

10.4 Patients Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The investigator is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

11. Collection, Recording, and Reporting of Safety Information and Product Complaints

The study is an observational registry that will collect data from patient's routine medical records. Data collection will use a combination of retrospective and prospective methods (see [section 9.1](#)). For countries, where a combination of retrospective and prospective methods is not possible, all data will be collected retrospectively from 31 December 2023. Data available prior to enrolment into the registry will be retrospectively collected (if appropriate). Data after enrolment (ie, defined as date of consent) will be prospectively collected at 3-month intervals until death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, withdrawal of consent, or end of the study period (ie, 31 December 2023), whichever comes first. **For deceased patients, all data will be collected retrospectively.**

11.1 Definition of Safety Events

11.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient administered a pharmaceutical product(s) irrespective of a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s).

The definition of an adverse event includes:

- Worsening of a pre-existing condition or underlying disease
- Events associated with the discontinuation of the use of a product(s), (eg, appearance of new symptoms)

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen.

11.1.2 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least one of the following serious criteria:

- is fatal
- is life threatening (places the patient at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity

- is a congenital anomaly/birth defect
- is an “other medically important serious event” that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for “serious” is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

“Other medically important serious events” refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

Other Safety Findings (regardless of association with an adverse event) include:

- Medication errors, overdose, whether accidental or intentional, misuse, or abuse involving an Amgen product,
- Pregnancy and lactation exposure,
- Transmission of infectious agents,
- Reports of uses outside the terms for authorized use of the product including off-label use,
- Occupational exposure,
- Any lack or loss of intended effect of the product(s).

11.1.4 Product Complaints

Product Complaints include any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

- Cinacalcet

11.2 Safety Collection, Recording and Submission to Amgen Requirements

The study is using a combination of retrospective and prospective data collection methods.

Retrospective data includes data spanning from date of first cinacalcet prescription to date of enrolment (ie, date of consent) or 31 December 2023, whichever comes first.

This study is collecting data from patient medical records. The safety outcomes that are listed in [section 9.3.2](#) will be documented on the medical history eCRF and analysed in this study. Safety events considered to have occurred following patient exposure to cinacalcet and occurred prior to enrolment into the study will be reported in aggregate in the final study report as rates. See [section 9.3.2](#) for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

Prospective data includes data spanning from date of enrolment and will continue until death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, withdrawal of consent, or end of the study period (ie, 31 December 2023), whichever comes first.

This study is collecting information from patient's medical records. All safety events (adverse events, product complaints, and other safety findings) considered to have occurred following patient exposure to cinacalcet will be collected from enrolment. The Investigator is responsible for ensuring that all safety events they become aware of during study period, are recorded in the patient's appropriate study documentation. Those safety events which are considered serious must also be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness. Non-serious Adverse Events (AEs) must be reported in an expeditious manner, not to exceed 15 calendar days of Investigator awareness.

If the electronic data capture (EDC) system is unavailable to the site staff, the adverse event which is considered serious must still be reported to Amgen within 1 business day of the Investigator's awareness, using the paper Adverse Event Contingency Report Form. Non-serious Adverse Events (AEs) must be reported in an expeditious manner, not to exceed 15 calendar days of Investigator awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event

Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See [Appendix C](#) for sample Safety Report Form(s), [Appendix D](#) for Additional Safety Reporting Information regarding the adverse event grading scale used in this study, and [Appendix E](#) for sample Pregnancy and Lactation Notification Worksheets. The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded in the study documentation where safety data may also be recorded.

11.2.1 Collection of Pregnancy and Lactation Information

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

11.2.2 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs/IECs, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of serious adverse events in accordance with local procedures and statutes.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify the IRB/IEC or

other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

13. Plans for Disseminating and Communicating Study Results

The protocol and an abstract of results will be posted as per guidelines for studies meeting the criteria for PASS. Results may also be submitted to any local/competent authorities as requested. Results of this study are also to be submitted for publication.

13.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

14. Compensation

Not applicable.

15. References

- Bakkaloglu, S. A., K. Wesseling-Perry, R. C. Pereira, B. Gales, H. J. Wang, R. M. Elashoff, and I. B. Salusky. 2010. 'Value of the new bone classification system in pediatric renal osteodystrophy', *Clin J Am Soc Nephrol*, 5: 1860-6.
- Borzych, D., L. Rees, I. S. Ha, A. Chua, P. G. Valles, M. Lipka, P. Zambrano, T. Ahlenstiel, S. A. Bakkaloglu, A. P. Spizzirri, L. Lopez, F. Ozaltin, N. Printza, P. Hari, G. Klaus, M. Bak, A. Vogel, G. Ariceta, H. K. Yap, B. A. Warady, F. Schaefer, and P. D. Network International Pediatric. 2010. 'The bone and mineral disorder of children undergoing chronic peritoneal dialysis', *Kidney Int*, 78: 1295-304.
- Denburg, M. R. 2016. 'Skeletal manifestations of renal disease in childhood', *Curr Opin Nephrol Hypertens*, 25: 292-300.
- EMA. 2016. 'European Medicines Agency: Parsabiv: EPAR product information : Summary of product characteristics. Available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003995/WC500217100.pdf . Accessed November 16, 2018.'
- ERA-EDTA. 2018. 'ERA-EDTA Registry: ERA-EDTA Registry Annual Report 2016. Amsterdam UMC, location AMC, Department of Medical Informatics, Amsterdam, the Netherlands, 2018. Accessed on 14 November: <https://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2016.pdf>'.
- European Medicines Agency. 2017. 'Mimpara Summary of Product Characteristics; Available at: https://www.ema.europa.eu/documents/product-information/mimpara-epar-product-information_en.pdf. Accessed 14 November 2018'.
- Furth, S. L., C. Pierce, W. F. Hui, C. A. White, C. S. Wong, F. Schaefer, E. Wuhl, A. G. Abraham, B. A. Warady, Children Chronic Kidney Disease in, Control Effect of Strict Blood Pressure, and A. C. E. Inhibition on the Progression of CRF in Pediatric Patients Study Investigators. 2018. 'Estimating Time to ESRD in Children With CKD', *Am J Kidney Dis*, 71: 783-92.
- Goodman, W. G. 2004. 'The consequences of uncontrolled secondary hyperparathyroidism and its treatment in chronic kidney disease', *Semin Dial*, 17: 209-16.
- Goodman, W. G., and L. D. Quarles. 2008. 'Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics', *Kidney Int*, 74: 276-88.
- Haffner, D., and F. Schaefer. 2013. 'Searching the optimal PTH target range in children undergoing peritoneal dialysis: new insights from international cohort studies', *Pediatr Nephrol*, 28: 537-45.
- Hamilton, A. J., F. Braddon, A. Casula, C. Inward, M. Lewis, T. Mallett, H. Maxwell, C. O'Brien, Y. Tse, and M. D. Sinha. 2016. 'UK Renal Registry 18th Annual Report: Chapter 10 Clinical, Haematological and Biochemical Parameters in Patients Receiving Renal Replacement Therapy in Paediatric Centres in the UK in 2014: National and Centre-specific Analyses', *Nephron*, 132 Suppl 1: 237-52.

- Ketteler, M., G. A. Block, P. Evenepoel, M. Fukagawa, C. A. Herzog, L. McCann, S. M. Moe, R. Shroff, M. A. Tonelli, N. D. Toussaint, M. G. Vervloet, and M. B. Leonard. 2017. 'Executive summary of the 2017 KDIGO Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) Guideline Update: what's changed and why it matters', *Kidney Int*, 92: 26-36.
- Kidney Disease: Improving Global Outcomes, C. K. D. M. B. D. Work Group. 2009. 'KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)', *Kidney Int Suppl*: S1-130.
- Klaus, G., A. Watson, A. Edefonti, M. Fischbach, K. Ronnholm, F. Schaefer, E. Simkova, C. J. Stefanidis, V. Strazdins, J. Vande Walle, C. Schroder, A. Zurowska, M. Ekim, and Group European Pediatric Dialysis Working. 2006. 'Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines', *Pediatr Nephrol*, 21: 151-9.
- Kuizon, B. D., and I. B. Salusky. 1999. 'Growth retardation in children with chronic renal failure', *J Bone Miner Res*, 14: 1680-90.
- Langman, CB, IB Salusky, L Greenbaum, H Jueppner, M Leonard, P Nelson, A Portale, BA Warady, RE Bowen, WL Oppenheim, A Levin, M Rocco, G Eknoyan, N Levin, G Bailie, B Becker, PG Blake, A Collins, PW Crooks, WE Haley, AR Hull, L Hunsicker, BL Jaber, CA Johnson, GA Kaysen, K King, M Klag, D Latos, D Mapes, L McCann, RL Mehta, M Michael, W Mitch, JV Nally, G Obrador, RS Parekh, TG Patel, BJG Pereira, NR Powe, C Ronco, AC Schoolwerth, R Vanholder, NK Wenger, D Wheeler, WW Williams, SL Yang, J Briggs, D Warnock, D Fingerhut, M Fiorarancio, A Gucciardo, L Mormino, and K Willis. 2005. 'K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease: Work group membership', *American Journal of Kidney Diseases*, 46.
- Loder, R. T., and R. N. Hensinger. 1997. 'Slipped capital femoral epiphysis associated with renal failure osteodystrophy', *J Pediatr Orthop*, 17: 205-11.
- Moe, S. M. 2007. 'Vitamin D, cardiovascular disease, and survival in dialysis patients', *J Bone Miner Res*, 22 Suppl 2: V95-9.
- Nemeth, E. F., W. H. Heaton, M. Miller, J. Fox, M. F. Balandrin, B. C. Van Wagenen, M. Colloton, W. Karbon, J. Scherrer, E. Shatzen, G. Rishton, S. Scully, M. Qi, R. Harris, D. Lacey, and D. Martin. 2004. 'Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl', *J Pharmacol Exp Ther*, 308: 627-35.
- Oh, J., R. Wunsch, M. Turzer, M. Bahner, P. Raggi, U. Querfeld, O. Mehls, and F. Schaefer. 2002. 'Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure', *Circulation*, 106: 100-5.
- Rees, L., F. Schaefer, C. P. Schmitt, R. Shroff, and B. A. Warady. 2017. 'Chronic dialysis in children and adolescents: challenges and outcomes', *Lancet Child Adolesc Health*, 1: 68-77.
- Schaefer, F., D. Borzych-Duzalka, M. Azocar, R. L. Munarriz, L. Sever, N. Aksu, L. S. Barbosa, Y. S. Galan, H. Xu, P. A. Coccia, A. Szabo, W. Wong, R. Salim, E. Vidal, S. Pottoore, B. A. Warady, and Ippn investigators. 2012. 'Impact of global economic disparities on practices and outcomes of chronic peritoneal dialysis in children: insights from the International Pediatric Peritoneal Dialysis Network Registry', *Perit Dial Int*, 32: 399-409.

Schaefer, F., D. Drozd, B. Fouqueray, J. Iles, X. Ma, M.N. Rheault, C. J. Stefanidis, N.M. Rodig, and B.A. Warady. 2017. 'A Phase 3, Multicenter, Randomized, Open-Label, Controlled Study to Assess the Efficacy, Safety, and Tolerability of Cinacalcet in Addition to Standard of Care in Pediatric Subjects Ages 6 to 17 Years', *J Am Soc Nephrol*: 475.

Shroff, R., M. Wan, E. V. Nagler, S. Bakkaloglu, M. Cozzolino, J. Bacchetta, A. Edefonti, C. J. Stefanidis, J. Vande Walle, G. Ariceta, G. Klaus, D. Haffner, C. P. Schmitt, Mineral European Society for Paediatric Nephrology Chronic Kidney Disease, Disorders Bone, and Groups Dialysis Working. 2017. 'Clinical practice recommendations for treatment with active vitamin D analogues in children with chronic kidney disease Stages 2-5 and on dialysis', *Nephrol Dial Transplant*, 32: 1114-27.

Shroff, R., M. Wan, E. V. Nagler, S. Bakkaloglu, D. C. Fischer, N. Bishop, M. Cozzolino, J. Bacchetta, A. Edefonti, C. J. Stefanidis, J. Vande Walle, D. Haffner, G. Klaus, C. P. Schmitt, Mineral European Society for Paediatric Nephrology Chronic Kidney Disease, Disorders Bone, and Groups Dialysis Working. 2017. 'Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease Stages 2-5 and on dialysis', *Nephrol Dial Transplant*, 32: 1098-113.

Sohn, W.Y., A.A. Portale, I. B. Salusky, H. Zhang, L.L. Yan, B. Ertik, S. Shahinfar, E. Lee, B. Dehmel, and B. A. Warady. 2019. 'An open-label, single-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of cinacalcet in pediatric subjects aged 28 days to < 6 years with chronic kidney disease receiving dialysis', *Pediatr Nephrol*, 34: 145-54.

Waller, S., S. Ledermann, R. Trompeter, W. van't Hoff, D. Ridout, and L. Rees. 2003. 'Catch-up growth with normal parathyroid hormone levels in chronic renal failure', *Pediatr Nephrol*, 18: 1236-41.

Warady, B. A., J. N. Iles, G. Ariceta, B. Dehmel, G. Hidalgo, X. Jiang, B. Laskin, S. Shahinfar, J. Vande Walle, and F. Schaefer. 2019. 'A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet in pediatric patients with chronic kidney disease and secondary hyperparathyroidism receiving dialysis', *Pediatr Nephrol*, 34: 475-86.

16. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference Number	Date	Title
1	1	23 August 2019	20180204 German Country-Specific Supplement 1

Appendix B. ENCePP Checklist for Study Protocols



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH



Doc.Ref. EMA/540136/2009

European Network of Centres for
Pharmacoepidemiology and
Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The [European Network of Centres for Pharmacoepidemiology and Pharmacovigilance \(ENCePP\)](#) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the [ENCePP Guide on Methodological Standards in Pharmacoepidemiology](#), which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the [Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies](#)). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

A prospective observational registry study to evaluate the use and safety of cinacalcet among paediatric patients with secondary hyperparathyroidism

Study reference number:

20180204

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.2 End of data collection ²	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.3 Study progress report(s)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.4 Interim progress report(s)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
1.1.5 Registration in the EU PAS register	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6
1.1.6 Final report of study results.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	6

Comments:

¹ Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

² Date from which the analytical dataset is completely available.

--

<u>Section 2: Research question</u>	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.2 The objective(s) of the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Comments:

No hypothesis testing for this observational study
--

<u>Section 3: Study design</u>	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2.1
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	11

Comments:

--

<u>Section 4: Source and study populations</u>	Yes	No	N/A	Section Number
4.1 Is the source population described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.1
4.2.2 Age and sex?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.3
4.2.3 Country of origin?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Pg3
4.2.4 Disease/indication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.3
4.2.5 Duration of follow-up?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.5
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.2.3

Section 4: Source and study populations	Yes	No	N/A	Section Number
event or inclusion/exclusion criteria)				

Comments:

--

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

Biological mechanism of action is not an objective of the study.
--

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

The objective of the study is not being evaluated for HTA endpoints.
--

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol describe how confounding will be addressed in the study?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1.4
7.1.1. Does the protocol address confounding by indication if applicable?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1.4
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1.3

Section 7: Bias	Yes	No	N/A	Section Number
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1.2
7.3 Does the protocol address the validity of the study covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9

Comments:

--

Section 8: Effect modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2.4

Comments:

--

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2
9.1.3 Covariates?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.2
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
9.3.3 Covariates?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

No data linkage is required for this study.

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.2 Are descriptive analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.3 Are stratified analyses included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7.2.5.2
10.4 Does the plan describe methods for adjusting for confounding?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.7
10.5 Does the plan describe methods for handling missing data?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.4
10.6 Is sample size and/or statistical power estimated?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Comments:

--

<u>Section 11: Data management and quality control</u>	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
11.2 Are methods of quality assurance described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6
11.3 Is there a system in place for independent review of study results?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

Comments:

Independent review of study results when there is a plan to submit results for publication.

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1.3
12.1.2 Information bias?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.9.1.4
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.5

Comments:

--

<u>Section 13: Ethical issues</u>	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	10
13.2 Has any outcome of an ethical review procedure been addressed?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
13.3 Have data protection requirements been described?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	9.6

<u>Section 13: Ethical issues</u>	Yes	No	N/A	Section Number

Comments:

At this time point, the protocol has not been submitted for ethical review pending CHMP opinion of the protocol.

<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	5

Comments:

<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	13
15.2 Are plans described for disseminating study results externally, including publication?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	13

Comments:

Name of the main author of the protocol: PPD [redacted] PhD MSc

Date: 11/02/2019

Signature: _____ PPD [redacted] Digitally signed by PP [redacted]
Date: 2019.02.11 13:17:58 Z

Appendix C. Sample Safety Reporting Form(s)

ATTENTION: CONTACT PVOPs CSL PRODUCT REPRESENTATIVE FOR STUDY SPECIFIC FORM

Completion Instructions - Electronic Adverse Event Contingency Report Form **(For use for Observational Research Studies using Electronic Data Capture [EDC])**

NOTE: This form is to be used under restricted conditions outlined on page 1 below. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

General Instructions

The protocol will provide instruction on what types of events to report for the study. This form is to be used **ONLY** to report events that must be captured in the Amgen safety database. *Indicates a mandatory field.

What to report on this form:

- All adverse events associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol
- The following safety findings are to be reported on this form as events regardless of association with an adverse event
 - Medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product
 - Transmission of infectious agents
 - Reports of uses outside the terms for authorized use of the product including off label use
 - Occupational exposure
 - Any lack or loss of intended effect of the product(s)
 - Product complaint **ONLY IF ASSOCIATED WITH AN ADVERSE EVENT**

The following should not be reported on this form and should be reported via the normal process set up for the study

- Pregnancy and lactation reports
- Product complaints without association with an AE

1. Site Information

Site Number* – Enter your assigned site number for this study

Investigator*, Country*, Reporter*, Phone No., and Fax No. – Enter information requested

2. Subject Information

Subject ID Number* – Enter the entire number assigned to the subject

Age at event onset, Sex, and Race – Enter the subject's demographic information

End of Study date – If the subject has already completed the study or terminated the study early, enter the End of Study date

If you are submitting follow-up information to a previous report, provide the adverse event term for the previous report as well as the start date for the initial event.

3. Adverse Event

Provide the date the Investigator became aware of this Information

Adverse Event Diagnosis or Syndrome* –

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Date Started* – Enter date the adverse event first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

Date Ended – Enter date the adverse event ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Is event serious?* – Indicate **Yes** or **No**. **This is a mandatory field.**

Serious Criteria Code* – **This is a mandatory field for serious events.** Enter all reasons why the reported event has met serious criteria:

Immediately life-threatening: Use only if the subject was at immediate risk of death from the event as it occurred.

Emergency treatment is often required to sustain life in this situation. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

Completion Instructions - Electronic Adverse Event Contingency Report Form
(for use for Studies using Electronic Data Capture [EDC])

Note, this form is to be used under restricted conditions outlined on page 1 of the form. If you must fax an event report to Amgen, you must also enter that event into the EDC system (eg, Rave) when it becomes available.

4. IP Administration including Lot # and Serial # when known / available.

- If the investigator decides an event should be reported in an expedited manner, but it does not meet other serious criteria, "Other Medically Important Serious Event" may be the appropriate serious criterion.

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported. **This is a mandatory field.**

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g. prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g. heating pads, infusion pumps)**

Outcome of Event – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Resolved – End date is known

- Not resolved / Unknown – End date is unknown
- Fatal – Event led to death

5. Hospitalization

If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an adverse event. Protocol specified hospitalizations are exempt.

At the top of Page 2, provide your Site Number and the Subject ID Number in the designated section.

6. Amgen drug Under Study Administration including Lot # and Serial # when known / available.

Initial Start Date – Enter date the product was first administered, regardless of dose.

Date of Dose Prior to or at the time of the Event – Enter date the product was last administered prior to, or at the time of, the onset of the event.

Dose, Route, and Frequency at or prior to the event – Enter the appropriate information for the dose, route and frequency at, or prior to, the onset of the event.

Action Taken with Product – Enter the status of the product administration.

7. Concomitant Medications

Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in [section 5](#) (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event

Continuing – Indicate if the subject is still taking the medication

Event Treatment – Indicate if the medication was used to treat the event

8. Relevant Medical History

Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event allergies and any relevant prior therapy, such as radiation. Include dates if available.

9. Relevant Laboratory Tests

Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

10. Other Relevant Tests

Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results and units (if applicable).

At the top of Page 3, provide your Site Number and the Subject ID Number in the designated section.

11. Case Description

Describe Event – Enter summary of the event. Provide narrative details of the events listed in [section 3](#). Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in [section 6](#)). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of page 3 and fax the form to Amgen. *If the reporter is not the investigator, designee must be identified on the Delegation of Authority form.*

AMGEN
Study # 20180204
Sensipar

Electronic Adverse Event Contingency Report Form
For Restricted Use

Reason for reporting this event via fax

The Clinical Trial Database (eg. Rave):

- Is not available due to internet outage at my site
 Is not yet available for this study
 Has been closed for this study

<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number 	Investigator	Country
Reporter	Phone Number ()	Fax Number ()

2. SUBJECT INFORMATION

Subject ID Number 	Age at event onset	Sex <input type="checkbox"/> F <input type="checkbox"/> M	Race	If applicable, provide End of Study date
-----------------------	--------------------	--	------	--

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day ____ Month ____ Year _____

3. ADVERSE EVENT

Provide the date the Investigator became aware of this information: Day ____ Month ____ Year ____

Adverse Event <u>diagnosis</u> or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report <i>List one event per line. If event is fatal, enter the cause of death. Entry of "death" is not acceptable, as this is an outcome.</i>	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of drug under study	Is event serious?	If serious, enter Serious Criteria code (see codes below)	Relationship		Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
						Is there a reasonable possibility that the Event may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study?			
						Sensipar			
				<input type="checkbox"/> Yes <input type="checkbox"/> No					
				<input type="checkbox"/> Yes <input type="checkbox"/> No					
				<input type="checkbox"/> Yes <input type="checkbox"/> No					

Serious Criteria: 01 Fatal 02 Immediately life-threatening 03 Required/prolonged hospitalization 04 Persistent or significant disability /incapacity 05 Congenital anomaly / birth defect 06 Other medically important serious event

4. Was subject hospitalized or was a hospitalization prolonged due this event? No Yes If yes, please complete all of [Section 4](#)

Date Admitted Day Month Year	Date Discharged Day Month Year

Appendix D. Additional Safety Reporting Information

The Investigator will make an assessment of severity for adverse event and serious adverse event reported during the study. The assessment of severity will be based on:

Adverse Event Severity Scoring System

Grade	Amgen Standard Adverse Event Severity Scoring System
1	MILD: Aware of sign or symptom, but easily tolerated
2	MODERATE: Discomfort enough to cause interference with usual activity
3	SEVERE: Incapacitating with inability to work or do usual activity

Appendix E. Pregnancy and Lactation Notification Worksheets

AMGEN[®] Pregnancy Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180204

Study Design: Interventional Observational (If Observational: Prospective Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject Gender: Female Male Subject age (at onset): _____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? Yes No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? Yes No

5. Pregnancy Information

Pregnant female's last menstrual period (LMP) mm____/ dd____/ yyyy____ Unknown N/A

Estimated date of delivery mm____/ dd____/ yyyy____
If N/A, date of termination (actual or planned) mm____/ dd____/ yyyy____

Has the pregnant female already delivered? Yes No Unknown N/A

If yes, provide date of delivery: mm____/ dd____/ yyyy____

Was the infant healthy? Yes No Unknown N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

Form Completed by:

Print Name: _____

Title: _____

Signature: _____

Date: _____

AMGEN[®] Lactation Notification Form

Report to Amgen at: USTO fax: +1-888-814-8653, Non-US fax: +44 (0)207-136-1046 or email (worldwide): svc-ags-in-us@amgen.com

1. Case Administrative Information

Protocol/Study Number: 20180204

Study Design: Interventional Observational (If Observational: Prospective Retrospective)

2. Contact Information

Investigator Name _____ Site # _____

Phone (____) _____ Fax (____) _____ Email _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ Subject age (at onset): _____ (in years)

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm____/dd____/yyyy____

Was the Amgen product (or study drug) discontinued? Yes No

If yes, provide product (or study drug) stop date: mm ____/dd ____/yyyy ____

Did the subject withdraw from the study? Yes No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? Yes No

If No, provide stop date: mm ____/dd ____/yyyy ____

Infant date of birth: mm ____/dd ____/yyyy ____

Infant gender: Female Male

Is the infant healthy? Yes No Unknown N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details: _____

Form Completed by:

Print Name: _____

Title: _____

Signature: _____

Date: _____

Protocol Amendment 3

Protocol Title: An Observational Registry Study to Evaluate the use and Safety of Cinacalcet Among Paediatric Patients With Secondary Hyperparathyroidism

Amgen Protocol Number Mimpara® (cinacalcet) 20180204
EU Post Authorisation Study (PAS) Register No. EUPAS24954

Amendment 3 Date: 10 February 2020

Rationale:

- This protocol is being amended to correct a typographical error in [Section 9.2.5](#), where the event of having a parathyroidectomy was mistakenly added as a reason to discontinue follow-up.
- [Section 9.1](#). Study Design updated to ensure that sites know not to enrol a subject until all signatures (as opposed to just the subject's) have been collected on the informed consent form.
- [Section 9.2.1](#). Study Design, Data Collection updated to specify that subjects without a history of prior cinacalcet use should have received at least one dose administration at the time of enrolment.
- [Section 9.2.3.1](#). Inclusion Criteria 101 updated to clarify that age is not at enrolment but at initiation of Cinacalcet.
- [Section 9.2.3.1](#). Inclusion Criteria 102 updated to clarify inclusion criteria wherein patients who have provided written informed consent or notified of participation **(alive or deceased), where required for access to medical charts**, according to local **laws and regulation** requirements.
- [Section 9.7.1.1](#). Interim Analyses/Analyses updated to clarify that analyses will be conducted to provide data annually to the EMA **if requested**, since the European Medicines Agency (EMA) has agreed to have less frequent reports.
- [Section 10.1](#). Informed Consent, Paragraph 1 updated to specify that patient data can be collected retrospectively although the patient is deceased given consent from appropriate parties where required by local regulations.
- [Section 10.1](#). Informed Consent, Paragraph 3 updated to reflect that a parent's signature may be provided given that this is a paediatric study.

- [Section 11](#). Collection, Recording, and Reporting of Safety Information and Product Complaints updated to clarify that for deceased patients, all data will be collected retrospectively so that it may be available for extraction although the patient is deceased.

Description of Changes:

Section: Global

Change: Updated version date throughout document from 20 September 2019 to **10 February 2020**

Section: Global

Change: Updated Protocol version identifier from Amendment 2 to Amendment **3**

Section: Global

Delete:

turns aged 18-years

Section: 4. Abstract, Summary of Patient Eligibility Criteria, Inclusion Criteria

Replace:

- Patients aged ≥ 3 years to < 18 years on maintenance dialysis who are diagnosed with sHPT and have a record of cinacalcet use (ie, prescription) as per EU marketing authorisation from 28 August 2017 to 30 June 2023;
- Provided written informed consent or notified of participation, according to local requirements.

With:

- **Patients aged ≥ 3 years to < 18 years at the time of cinacalcet initiation**
- **Patients who have provided written informed consent or appropriate parties have been notified of participation (alive or deceased), where required for access to medical charts, according to local laws and regulation requirements.**
- **Patients on maintenance dialysis who are diagnosed with sHPT**
- **Patients that have a record of cinacalcet use (ie prescription) as per European Union (EU) marketing authorisation from 28 August 2017 to 30 June 2023**

Section: 5. Amendments and Updates

Replace:

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	8 March 2019		See summary changes	
2	23 August 2019		See summary changes	
3	20 September 2019		See summary changes	

With:

Amendment or Update No.	Date	Section of Study Protocol	Amendment or Update	Reason
1	8 March 2019		See summary changes	
2	23 August 2019		See summary changes	
Superseding Amendment 2	20 September 2019		See summary changes	
3	10 February 2020		See summary changes	

Section: 9.1. Study Design, Patient eligibility, paragraph 2

Add:

Potential patients may be identified via paediatric nephrology networks (eg, European Society for Paediatric Nephrology (ESPN) CKD-MBD Working Group, International Pediatric Dialysis Network (IPDN) or European Study Consortium for Chronic Kidney Disorders Affecting Pediatric Patients (ESCAPE)). Those who meet patient eligibility criteria (section 9.2.3) will be invited to participate in this registry study. **Patients will not be enrolled until all required signatures have been collected on the informed consent form.**

Section: 9.1. Study Design, Data Collection, paragraph 1

Replace:

Chart abstraction will be carried out part retrospectively (ie, data prior to patient enrolment (date of consent)) and part prospectively (ie, data after patient enrolment).

With:

Chart abstraction will be carried out part retrospectively (ie, data prior to patient enrolment [**enrolment is defined as the date of consent or the date the decision**

was taken to participate, if consent is not mandated]) and part prospectively (ie, data on or after patient enrolment).

Section: 9.2.1. Study Period, Data Collection, paragraph 1

Add:

Eligible patients are those patients who have initiated cinacalcet by 30 June 2023 in order for all patients to have a minimum of 6-month observation data available. **Patients without a history of prior cinacalcet use should have received at least one dose administration at the time of enrolment.**

Section: 9.2.3.1. Inclusion Criteria, number 101 and 102

Replace:

- 101 Patients aged ≥ 3 years to < 18 years on maintenance dialysis who are diagnosed with sHPT and have a record of cinacalcet use (ie, prescription) as per EU marketing authorisation from 28 August 2017 to 30 June 2023;
- 102 Patients who have provided written informed consent or notified of participation, according to local requirements.

With:

- 101 Patients aged ≥ 3 years to < 18 years **at the time of cinacalcet initiation**
- 102 Patients who have provided written informed consent or **appropriate parties have been** notified of participation (**alive or deceased**), where **required for access to medical charts**, according to local **laws and regulation** requirements
- 103 **Patients on maintenance dialysis who are diagnosed with sHPT**
- 104 **Patients that have a record of cinacalcet use (ie prescription) as per EU marketing authorisation from 28 August 2017 to 30 June 2023**

Section: 9.2.5. Study Follow-up

Delete:

The registry will record data abstracted from medical charts. Data will be abstracted from the date the patient had a cinacalcet prescription recorded within the study observation

period and will continue until death, ~~parathyroidectomy~~, lost-to-follow-up, transfer to another centre that is not a participating in this registry, turns aged 18-years, withdrawal of consent, or end of the study period (ie, 31 December 2023), whichever comes first. Regardless of whether the patient discontinued cinacalcet, follow-up will continue until one of the events described above occurs.

Section: 9.7.1.1 Interim Analyses/Analyses

Add:

Analyses will be conducted to provide data annually to the EMA **as requested**.

Section: 10.1 Informed Consent, Paragraph 1

Add:

Where an informed consent is required per local regulations, an initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. **Where required by local laws and regulations, consent will be sought from appropriate parties for the inclusion of deceased subject's data.** Updates to the sample informed consent form are to be communicated formally in writing from the Amgen Study Manager to the investigator. The written informed consent form is to be prepared in the language(s) of the potential patient population.

Section: 10.1 Informed Consent, Paragraph 3

Add:

The acquisition of informed consent is to be documented in the patient's medical records, and the informed consent form is to be signed and personally dated by the subject **and/or parent** or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the informed consent form(s) must be provided to the patient or the patient's legally authorized representative.

Section: 11. Collection, Recording, and Reporting of Safety Information and Product Complaints

Add:

The study is an observational registry that will collect data from patient's routine medical records. Data collection will use a combination of retrospective and prospective methods

(see section 9.1). For countries, where a combination of retrospective and prospective methods is not possible, all data will be collected retrospectively from 31 December 2023. Data available prior to enrolment into the registry will be retrospectively collected (if appropriate). Data after enrolment (ie, defined as date of consent) will be prospectively collected at 3-month intervals until death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, withdrawal of consent, or end of the study period (ie, 31 December 2023), whichever comes first. **For deceased patients, all data will be collected retrospectively.**

Superseding Amendment 2

Protocol Title: An Observational Registry Study To Evaluate The Use And Safety Of Cinacalcet Among Paediatric Patients With Secondary Hyperparathyroidism

Amgen Protocol Number Cinacalcet 20180204

Amendment Date: 20 September 2019

Rationale

20180204 Protocol Amendment 2, superseding amendment 1 is being submitted to correct for minor administrative changes.

Summary of Changes

- Specifically, there was an error in the text for [section 9.2.4](#) and [9.2.5](#) which are identical. For consistency, the text in [section 9.2.5](#) Study Follow-up has been corrected to reflect the defined study follow-up period as defined in the Abstract and in [section 9.1](#) Study design.
- To correct administration, typographical and formatting changes throughout the protocol; as well as correct for consistency of text (eg, inclusion criteria in abstract matches with inclusion criteria in [section 9.2.3.1](#))

Amendment 2

Protocol Title: An Observational Registry Study To Evaluate The Use And Safety Of Cinacalcet Among Paediatric Patients With Secondary Hyperparathyroidism

Amgen Protocol Number Cinacalcet 20180204

Amendment Date: 23 August 2019

Rationale:

The Final PRAC Assessment Report for Post-Authorisation Measure Mimpara MEA 035.1 received on the 5 June 2019 based on Amendment 1 of the original PASS protocol (20180204) concludes that the amended protocol proposal is adequate to meet the objective specified in the EU Risk Management Plan. The Post-Authorisation Measure is considered fulfilled.

The following non-substantial amendments are made to address the PRAC Rapporteur comments as well as clarify sections that were unclear.

Summary of Changes

- Hypocalcemia definition: hypocalcemia will be defined according to corrected calcium (cCa) levels as well as by frequency of reported **adverse event (ie, blood decreased Ca or symptomatic hypocalcemia)**. The initial protocol was limited to hospitalization events of hypocalcaemia. This revised definition will increase the sensitivity of detecting hypocalcaemia if hypocalcaemia occurs and the patient is not hospitalised.
- Section 7.2 Rationale: As per EMA feedback, the rationale has been updated to state the following “As part of an agreement with the EMA following marketing authorization , an observational registry will be conducted to describe real-world utilization of cinacalcet and the incidence and risk factors of hypocalcaemia in a cohort of paediatric patients receiving maintenance dialysis with sHPT **in order to inform the management of minimizing this hypocalcaemia risk in clinical practice**”
- Study period includes eligible patients who have initiated or have a record of cinacalcet between 28 August 2017 and 30 June 2023. The observation period ends on 31 December 2023. Patients will have at least 6 months of observation data. For patient eligibility, patient inclusion criteria has been worded more explicitly that we want to include “patients who are aged ≥ 3 - < 18 years on maintenance dialysis **who are diagnosed with sHPT and** have a record of cinacalcet use as per EU marketing authorisation from 28 Aug 2017 to 30 Jun 2023.” This was a suggestion from the EMA feedback. For the exclusion criteria, we have added the following exclusion criteria that states “**Patients who have participated in cinacalcet or etelcalcetide clinical trials**” will be excluded as these patients would not reflect patients who are being treated in routine clinical practice

- For the follow-up and observation period, patients will continue to be followed-up regardless of whether they had a parathyroidectomy event as they may have recurrent disease because of residual parathyroid tissue that was not completely removed and may have recurrent sHPT disease, start on maintenance dialysis and may re-start treatment with cinacalcet.
- Based on UK country-specific feedback, only a retrospective design may be feasible. We have included the following language throughout the protocol, where applicable. "For countries where combination of retrospective and prospective data collection methods is not possible, all data will be collected retrospectively from 31 December 2023."
- Variables have been updated to be clearly defined and reflect the specific data definitions that we require for the development of the eCRF
- Analyses will be carried out report to the EMA on an annual basis. This has been clarified in the section interim analyses/analyses
- In response to an EMA comment, we have added an additional sensitivity analysis that may be performed which is to examine the incidence of hypocalcaemia according by the two different definitions: laboratory cCa levels and adverse event (ie, blood decreased cCa or symptomatic hypocalcaemia)
- As per the EMA comment, stratified analyses for the incidence of hypocalcaemia events will also be analysed by occurrence in retrospective vs. prospective data collection
- Additional sensitivity analyses may be country-specific regulatory requirements (eg, Germany).
- A country-specific protocol supplement for Germany is included as a stand-alone document (as listed in Appendix A) to meet local regulatory requirements.

Minor amendments

- Objective 4 revised wording as suggested by EMA: Instead of "What is the incidence of, risk factors for, and treatment responses following hypocalcaemia in paediatric patients who initiate cinacalcet", *modified*, "What is the incidence of, risk factors for, **and management of hypocalcaemia in paediatric patients who initiate cinacalcet?**" This has been revised throughout the protocol.
- The Medinfo General number for multi-country studies is given using the US contact info rather than country-specific med-info number to align with updated guidance in FORM-023668
- Section 3. Amgen Sponsor details have been updated from Amgen Limited to Amgen Inc
- Section 10.1 Informed consent language has been updated to reflect updated Amgen boilerplate language as outlined in protocol template FORM-023669 v14.0.
- Appendix D: Adverse Event Severity Scoring System has been added for clarity for reporting
- To correct administration, typographical and formatting changes throughout the protocol

Amendment 1

Protocol Title: An Observational Registry Study to Evaluate the Use and Safety of Cinacalcet Among Paediatric Patients With Secondary Hyperparathyroidism

Amgen Protocol Number 20180204

Amendment Date: 08 March 2019

Rationale:

The 20180204 International Pediatric Dialysis Network (IPDN) prospective registry study was submitted to the Pharmacovigilance Risk Assessment Committee (PRAC) for review. Following comments received from PRAC, it was determined that the IPDN registry did not have the operational capacity to conduct the study and instead a separate paediatric Mimpara registry will be designed to capture the required data. The study protocol has been updated to reflect the proposal agreed upon with the PRAC and to address the PRAC's comments.

The revised study is a non-interventional observational registry study to evaluate the use and safety of cinacalcet among paediatric patients with secondary hyperparathyroidism. Subjects will receive standard of care treatment as determined by their physician(s). Data will be collected from routine medical records and entered in the registry database.