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 **8**
Date of last version of the protocol	**16 May 2023**
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	• 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? Objectives: In a European cohort of paediatric patients with secondary hyperparathyroidism (sHPT) on maintenance dialysis who use cinacalcet: 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
Countries of Study	• Austria, Belgium, Czech Republic, France, Germany, Greece, Italy, Portugal, Spain, and the United Kingdom

Author	PPD Observational Research Manager 4 Uxbridge Business Park, Sanderson Road Uxbridge, UB8 1DH, UK

Marketing Authorisation Holder

Marketing authorisation holder	Amgen Europe B.V. Minervum 7061 4817 ZK Breda The Netherlands
MAH Contact	PPD Senior Manager, Regulatory Affairs Amgen Limited, 4 Uxbridge Business Park, Sanderson Road Uxbridge, UB8 1DH, United Kingdom Tel: PPD

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 **16 November 2023**, and agree to abide by all provisions set forth therein.

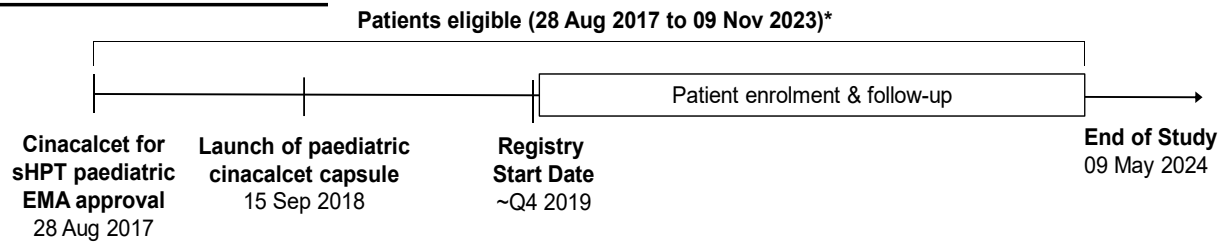
Signature

Name of Investigator

Date (DD Month YYYY)

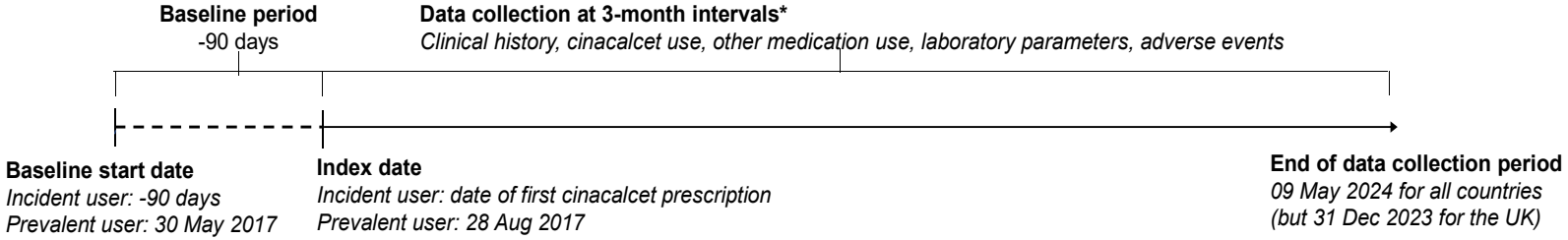
Study Design Schema

SUBJECT ELIGIBILITY



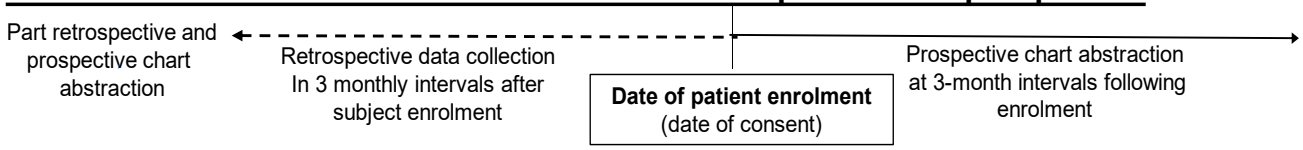
*Patient eligibility: Patients aged 3 years - <18 years on maintenance dialysis who have a record of cinacalcet use as per EU marketing authorization from 28 Aug 2017 to 09 Nov 2023 (Exception: All patients in UK must have initiated cinacalcet use by 30 June 2023); and have provided written informed 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, starts a new clinical trial, withdrawal of consent, or end of the study period (ie, end of data collection period), whichever comes first.

COMBINED DATA COLLECTION METHODS: retrospective and prospective



*For countries where prospective data collection is not possible, all data will be collected retrospectively before and up to the end of data collection period.

1. Table of Contents

List of Tables

List of Figures

List of Appendices

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
ESPN	European Society of Paediatric Nephrology
ESRD	end-stage renal disease
EU	European Union
HD	haemodialysis
HCO3	bicarbonate
HNF1ß	hepatocyte nuclear factor-1ß
ICJME	International Committee of Medical Journal Editors
IEC	Independent 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
Q3M	every three-month
rHGH	recombinant human growth hormone
RMP	risk management plan

Abbreviations	Full names
RRT	renal replacement therapy
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
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 children 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 authori**s**ation, an observational registry is being 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 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?

- **Primary Objectives**

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/guardians and/or patients who have provided written informed consent/assent 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 who used cinacalcet for sHPT on or after the date of dialysis initiation.
- Patients who have a record of cinacalcet use (ie, prescription) as per European Union (EU) marketing authorisation from 28 August 2017 to 09 November 2023. Exception: All **patient**s in the United Kingdom (UK) must have initiated cinacalcet use by 30 June 2023.

Exclusion Criteria

- Patients who have participated in cinacalcet or etelcalcetide clinical trials at the time of cinacalcet initiation.
- If a **patient** took cinacalcet prior to initiation of dialysis, they must have at least 90 days between the cinacalcet stop date (before starting dialysis) and restart date (after starting dialysis).

- **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 patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, or end of the study period (ie, end of data collection period), 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).
- Any known medical history that is present before the date of enrolment (underlying renal disease, presence of comorbidities, hepatocyte nuclear factor-1ß (HNF1ß) 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], recombinant human grown hormone [rHGH]) in terms of dose, frequency, route of administration, date first taken, and date last taken.
- Laboratory parameters (PTH, cCa, ionised Ca, serum phosphorus, albumin, alkaline phosphatase, bicarbonate [HCO3], and 25OH-Vitamin D3, **and HN1Fß 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; and/or reported adverse event due to hypocalcaemia (eg, 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 if available at 3 months and 1 year after the kidney transplant).
- 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 of dialysis, dialysis frequency, dialysis dose, duration, dialysate calcium, ionised 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.

All laboratory data that is taken as a standard of care will be collected if available in the observation period.

- Every three-month (Q3M) collection for all labs: If the analyte measurement was carried out only once in the three-month period, then only one value will be collected within the month "X" folder. There is no need to open an unscheduled laboratory folder.
- PTH: Any PTH values deemed clinically significant by the **investigator**.
- Total or ionised calcium: Monthly collection between the Q3M visits, and collection of any low calcium values or calcium values deemed clinically significant by the **investigator** until resolution.
- cCa (albumin & total calcium): Monthly collection between the Q3M visits, and collection of any low corrected calcium values or corrected calcium values deemed clinically significant by the **investigator** until resolution.
- Phosphorus: Monthly collection between the Q3M visits and any values deemed clinically significant by the **investigator**.

- **Study Sample Size**

Based on the enrolment experience of the International Pediatric Dialysis Network (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 **was** expected to double. **However, based on more recent enrolment experience of the IPDN cohort aged 3 to < 18 years of age on maintenance dialysis, use of cinacalcet since August 2017 (month of the EU paediatric marketing authorisation) was observed in approximately 65 paediatric patients (IPDN, unpublished)**. 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 **45** paediatric patients will provide an estimate of hypocalcaemia incidence with a two-sided confidence interval (CI) half-width of **12.7**% (ie, two-sided 95% CI: **12.3**%, **37.7**%) (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		
4	02 October 2020	See summary changes		
5	26 May 2022	See summary changes		
6	03 November 2022	See summary changes		
7	16 May 2023	See summary of changes		
8	**16 November 2023**	**See summary of changes**		

6. Milestones

Milestone	Planned date
Start of data collection	Q4 2019
End of data collection	May 2024
Study progress report	Annually
Annual Report 1	Q4 2020
Annual Report 2	Q4 2021
Annual Report 3	Q4 2022
Annual Report 4	Q4 2023
Registration in the EU PAS register	Q3 2019
Final report of study results	Q4 2024

Note: 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 Pediatric 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) (Borzych 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 focused on correcting all metabolic and clinical abnormalities that could worsen bone 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 (rHGH) (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 2 to 3 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, Bakkaloglu, Fischer, et al, 2017), active vitamin D analogs (Shroff, Wan, Nagler, Bakkaloglu, 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 being developed 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 $\leq$ 0.20 mg/kg once daily for children aged $\geq$ 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) levels 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 2 randomized controlled studies and 1 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 (≥ 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 (≥ 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 were 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 3 clinical trials, a total of 19 subjects (24%; 64.5 per 100 subject years) had at least 1 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 have their dose increased 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 children in routine clinical practice. As part of the agreement with the EMA following marketing authori**s**ation, 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 Design 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 09 November 2023. Exception: In the UK, 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.

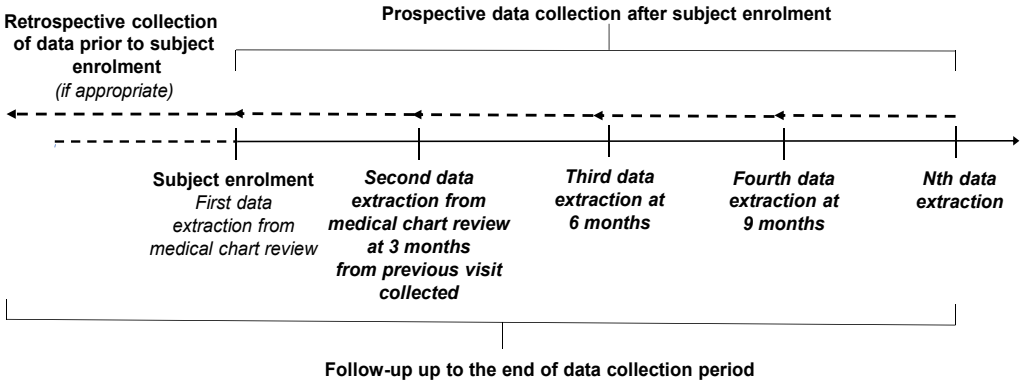
Data collection

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 (ie, end of data collection period of 09 May 2024 for all countries, but 31 December 2023 for the UK) (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), and collected in approximately 3 monthly intervals until the end of study follow-up (Study Design Schema and Figure 1).

For example, if a patient is enrolled on 15 October 2019, but they initiated cinacalcet on 20 September 2019, the next data collection timepoint will be 20 December 2019. All laboratory data values measured between 20 September 2019 to 15 October 2019 will be collected retrospectively, and all values following enrolment 15 October 2019 to 20 December 2019 will be collected prospectively. 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 3 months, then only 1 value will be collected. The volume of data collected will depend on routine clinical practice at the study site.

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

Figure 1. Data Collection



Note: For countries where prospective data collection is not possible, all data will be collected retrospectively before and up to the end of data collection period.

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, Bulgaria, Czech Republic, Finland, France, Germany, Greece, 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 Setting and Study Population

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 09 May 2024 (study end date). The end of study is defined as 09 May 2024, which is the last possible date of data collection.

Eligible patients are those patients who have initiated cinacalcet by 09 November 2023, in order for all patients to have a minimum of 6-month observation data available.

However, for countries where prospective data collection is not possible, all data will be collected retrospectively for the period spanning 30 May 2017 (if applicable) to the end of data collection period (ie, 31 December 2023, see Study Design Schema).
Furthermore, where only retrospective data will be collected, 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 1 dose of cinacalcet administration at the time of enrolment.

9.2.2 Selection and Number of Sites

Approximately **30** centres across Europe are expected to participate. Eligible sites are centres who are using cinacalcet among paediatric patients on maintenance dialysis.
The majority of sites are expected to enrol **< 3** patients each **due to scarcity of the target** 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 Parents/guardians and/or patients who have provided written informed consent/assent 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 who used cinacalcet for sHPT on or after the date of dialysis initiation.

104 Patients who have a record of cinacalcet use (ie, prescription) as per EU marketing authorisation from 28 August 2017 to 09 November 2023. Exception: All patients in the UK, must have initiated cinacalcet use by 30 June 2023.

9.2.3.2 Exclusion Criteria

201 Patients who have participated in cinacalcet or etelcalcetide clinical trials at the time of cinacalcet initiation.

202 If a **patient** took cinacalcet prior to initiation of dialysis, they must have at least 90 days between the cinacalcet stop date (before starting dialysis) and restart date (after starting dialysis).

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 patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, withdrawal of consent, starts a new clinical trial, or end of the study period (ie, end of data collection period), 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).
- Any known medical history that is present before the date of enrolment (underlying renal disease and presence of comorbidities, hepatocyte nuclear factor-1ß (HNF1ß) 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], rHGH) in terms of dose, frequency, route of administration, date first taken, and date last taken.
- Laboratory parameters (PTH, **c**Ca, ionised Ca, serum phosphorus, albumin, alkaline phosphatase, bicarbonate [HCO_3], 25OH-Vitamin D3, and HN1Fß 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; and/or reported adverse event due to hypocalcaemia (eg, 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 if available at 3 months and 1 year after the kidney transplant).
- 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 of dialysis, dialysis frequency, dialysis dose, duration, dialysate calcium, ionised 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.

All laboratory data that is taken as a standard of care will be collected if available in the observation period.

- Every three-month (Q3M) collection for all labs: If the analyte measurement was carried out only once in the three-month period, then only one value will be collected within the month "X" folder. There is no need to open an unscheduled laboratory folder.
- PTH: Any PTH values deemed clinically significant by the **investigator**.
- Total or ionised calcium: Monthly collection between the Q3M visits, and collection of any low calcium values or calcium values deemed clinically significant by the **investigator** until resolution.
- cCa (albumin & total calcium): Monthly collection between the Q3M visits, and collection of any low corrected calcium values or corrected calcium values deemed clinically significant by the **investigator** until resolution.
- Phosphorus: Monthly collection between the Q3M visits and any values deemed clinically significant by the **investigator**.

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 **was** expected to double. **However, based on more recent enrolment experience of the IPDN cohort aged 3 to < 18 years of age on maintenance dialysis, use of cinacalcet since August 2017 (month of the EU paediatric marketing authorisation) was observed in approximately 65 paediatric patients (IPDN, unpublished)**. 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 **45** paediatric patients will provide an estimate of hypocalcaemia incidence with a two-sided confidence interval half-width of **12.7**% (ie, two-sided 95% CI: **12.3**%, **37.7**%) (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		
Sample size	20.0%	25.0%	30.0%
40	**12.4%**	**13.4%**	**14.2%**
45	**11.7%**	**12.7%**	**13.4%**
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

9.6.1 Obtaining Data Files

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.

9.6.2 Linking Data Files

Not applicable.

9.6.3 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 Analysis/Analyses

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

9.7.1.2 Final Analysis

The final analysis will be performed at a single time point at the end of the study period (ie, end of data collection period of 09 May 2024, 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 2 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 Enrolment

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.

9.7.2.4 Analysis of the Primary Endpoint(s)

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 3 months (90 days) following the index date and following hypocalcaemia events. Data will be presented overall and stratified by baseline Ca values (low, medium, or high), baseline PTH values (mild, moderate, or severe), and severity of hypocalcaemia events (mild, moderate, and severe hypocalcaemia) to show the longitudinal trajectory of laboratory values.

To describe the time-to-event for 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 (described in 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.

Hypocalcaemia event is defined in 2 ways by cCa laboratory value and/or reported adverse events. Hypocalcaemia and treatment responses following hypocalcaemia event will be analysed as follows:

- Incidence of hypocalcaemia:
  - Incidence of hypocalcaemia will be examined, overall and according to disease severity as defined by cCa thresholds for mild (2.0- < 2.1 mmol/L), moderate (1.87-< 2.0 mmol/L), and severe (< 1.87 mmol/L).
  - Frequency of reported hospitalisation due to hypocalcaemia event.
  - The number of hypocalcaemia events during the observation period will be summarised.

- Cinacalcet use at index date and treatment response within 90 days after hypocalcaemia event, and re-initiation
  - Average daily dose at index date.
  - Treatment response: up-titration (average daily dose after hypocalcaemia event greater than the average daily dose before hypocalcaemia event), stable (no change in average daily dose after hypocalcaemia event), down-titration (average daily dose after hypocalcaemia event less than the average daily dose before hypocalcaemia event), drug withheld or discontinued.
  - Drug withheld users are those who stop within 7 days of the hypocalcaemic event and restart within ≤ 90 days.
  - Discontinued users are those with stop date within 7 days after the hypocalcaemia event, and without a restart within ≤ 90 days; this definition includes users who discontinue permanently or who restart > 90 days.
  - Cinacalcet re-initiation: re-starting cinacalcet after > 90 days following cinacalcet discontinuation.
- Concomitant medication use at index date, time of hypocalcaemia event, and within 90 days after hypocalcaemia event
  - Average daily dose at index date, at time of hypocalcaemia event, and after hypocalcaemia event.
  - Treatment response: medication initiation (new user: no prescription before hypocalcaemia event and new prescription after hypocalcaemia event), up-titrated (average daily dose after hypocalcaemia event greater than the average daily dose before hypocalcaemia event), stable (no change in average daily dose after hypocalcaemia event), down-titration (average daily dose after hypocalcaemia event less than the average daily dose before hypocalcaemia event), drug withheld (stop date within 7 days of the hypocalcaemia event and restart within ≤ 90 days), or discontinued (stop date within 7 days after the hypocalcaemia event, and without a prescription restart within ≤ 90 days) will be described.

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 (eg, blood decreased cCa or symptomatic hypocalcaemia) or 3) according to local site cCa definition of hypocalcaemia

9.7.2.5.1 Subgroup Analysis

Not applicable.

9.7.2.5.2 Stratified Analysis

The following summarized analyses may be performed:

- To describe hypocalcaemia incidence, hypocalcaemia (cCa < 2.1 mmol/L) will be summarised for patients who had normal and high baseline cCa levels as follows: 2.1- < 2.5 mmol/L, 2.5- < 2.75 mmol/L, and ≥ 2.75 mmol/L.

- Hypocalcaemia may be summarised 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 < 30 mg (ie, crushed tablet), tablet ≥ 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 authorised 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 authori**s**ed 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 **patient** 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 authori**s**ed 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 authori**s**ed 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 prospective data collection is not possible, all data will be collected retrospectively before and up to the end of data collection period (ie, 31 December 2023). Data available prior to enrolment into the registry will be retrospectively collected (if appropriate). Prospective data collection is defined as data collected after enrolment (ie, defined as date of consent). This data will be prospectively collected at 3-month intervals until patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, or end of the study period (ie, end of data collection period of 09 May 2024), 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).
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline (such as kidney transplant) is not considered an adverse event.

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, 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 authorised 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. This study is collecting data from patient medical records.

Retrospective data includes data spanning from 30 May 2017 or date of first cinacalcet prescription, (whichever comes first) until the date of enrolment (ie, date of consent). For countries, where prospective data collection is not possible, all data will be collected retrospectively before and up to the end of data collection period (ie, 31 December 2023). 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 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 final study contact defined as patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, or end of the study period (ie, end of data collection period of 09 May 2024), whichever comes first.

Regardless of whether a patient discontinued cinacalcet, all serious adverse events considered to have occurred following patient exposure to cinacalcet will be collected from subject enrolment and follow-up will continue until final study contact, as defined above.

All non-serious adverse events, product complaints, and other safety findings will considered to have occurred following patient exposure to cinacalcet will be collected from subject enrolment to 14 days after each cinacalcet discontinuation, considering that the terminal half-life of cinacalcet is 30 to 40 hours.

If, and every time cinacalcet is resumed after been discontinued during the study period, non-serious adverse events, product complaints, and other safety findings will be again collected from the first resuming dose of cinacalcet to 14 days after each cinacalcet discontinuation until the final study contact, as defined above.

The investigator is responsible for ensuring that all safety events (adverse events, product complaints, and other safety findings) they become aware of during the study period, are recorded in the patient's appropriate study documentation (eg, medical notes and eCRF). 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 must be reported in an expeditious manner, not to exceed 15 calendars 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 must be reported in an expeditious manner, not to exceed 15 calendars 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

Female Subjects Who Become Pregnant

Investigator will collect pregnancy information on any female subject who becomes pregnant during the whole study period, from 30 May 2017 or date of first cinacalcet prescription through patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, or end of the study period (ie, end of data collection period), up to 14 days after permanent discontinuation of cinacalcet, whichever comes first, regardless of whether data is being collected in a retrospective or prospective manner.

Information will be recorded on the Pregnancy Notification Worksheet (see Appendix E). The worksheet must be submitted to Amgen Safety within 1 business day of learning of a subject's pregnancy. (Note: investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws).

After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide investigator with an authorisation form and questionnaire to collect additional information. After obtaining the female subject's signed authori**s**ation for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female subject who becomes pregnant from 30 May 2017 or date of first cinacalcet prescription through patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, or end of the study period (ie, end of data collection period), or up to 14 days after permanent discontinuation of cinacalcet, whichever comes first. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to Amgen Safety, regardless of foetal status (presence or absence of anomalies) or indication for procedure. While pregnancy itself is not considered to be an adverse event or serious adverse event, any pregnancy complication or report of a congenital anomaly or developmental delay, foetal death, or suspected adverse reactions in the neonate will be reported as an adverse event or serious adverse event. Note that an elective termination with no information on a foetal

congenital malformation or maternal complication is generally not considered an adverse event, but still must be reported to Amgen as a pregnancy exposure case. If the outcome of the pregnancy meets a criterion for immediate classification as a serious adverse event (eg, female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a foetal or neonatal congenital anomaly) the investigator will report the event as a serious adverse event.

Male Subjects with Partners who Become Pregnant or Were Pregnant at the Time of Enrolment

The investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire in the event a male subject fathers a child during the study period, from 30 May 2017 or date of first cinacalcet prescription, through patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, end of the study period (ie, end of data collection period), or up to 14 days after permanent discontinuation of cinacalcet, whichever comes first regardless of whether data is being collected in a retrospective or prospective manner. The information will be recorded on the Pregnancy Notification Worksheet. The worksheet (see Appendix E) must be submitted to Amgen Safety within 1 business day of the investigator awareness of the pregnancy. (Note: investigator is not required to provide any information on the Pregnancy Notification Worksheet that violates the country or regions local privacy laws). After receipt of the Pregnancy Notification Worksheet, Amgen Safety will provide investigator with an authorisation form and questionnaire to collect additional information. The investigator will attempt to obtain a signed authori**s**ation for release of pregnancy and infant health information directly from the pregnant female partner to obtain additional pregnancy information. After obtaining the female partner's signed authori**s**ation for release of pregnancy and infant health information, the investigator will collect pregnancy outcome and infant health information on the pregnant partner and her baby and complete the pregnancy questionnaires. This information will be forwarded to Amgen Safety. Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable). Any termination of the pregnancy will be reported to Amgen Safety regardless of foetal status (presence or absence of anomalies) or indication for procedure.

Collection of Lactation Information

The investigator will collect lactation information on any female subject who breastfeeds from 30 May 2017 or date of first cinacalcet prescription through patient death,

lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, end of the study period (ie, end of data collection period), or up to 14 days after permanent discontinuation of cinacalcet, whichever comes first. Information will be recorded on the Lactation Notification Worksheet (see Appendix E) and submitted to Amgen Safety within 1 business day of the investigator's awareness. With the female subjects signed authori**s**ation for release of mother and infant health information, the investigator will collect mother and infant health information and complete the lactation questionnaire on any female subject who breastfeeds from 30 May 2017 or date of first cinacalcet prescription through patient death, lost-to-follow-up, transfers to another centre that is not participating in this registry, turns age 18-years, starts a new clinical trial, withdrawal of consent, or end of the study period (ie, end of data collection period), or up to 14 days after permanent discontinuation of cinacalcet, whichever comes first.

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 SA, Wesseling-Perry K, Pereira RC, **et al**. Value of the new bone classification system in pediatric renal osteodystrophy. *Clin J Am Soc Nephrol*. 2010;5**(10)**:1860-1866. **doi:10.2215/CJN.01330210**

Borzych D, Rees L, Ha IS, **et al**. International Pediatric Network **(IPPN)**. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. *Kidney Int*. 2010;78**(12)**:1295-**1**304. **doi:10.1038/ki.2010.316**

Denburg, MR. Skeletal manifestations of renal disease in childhood. *Curr Opin Nephrol Hypertens*. 2016;25**(4)**:292-300. **doi:10.1097/MNH.0000000000000233**

European Renal Association-European Dialysis and Transplant Association (ERA-EDTA). ERA-EDTA Registry Annual Report 2016. Department of Medical Informatics, **Academic Medical Center,** Amsterdam, the Netherlands, 2018. https://www.era-edta-reg.org/files/annualreports/pdf/AnnRep2016.pdf. **doi.org/10.1093/ckj/sfz011**

Furth SL, Pierce C, Hui WF, **et al**. Estimating Time to ESRD in Children With CKD. *Am J Kidney Dis*. 2018;71**(6)**:783-**7**92. **doi:10.1053/j.ajkd.2017.12.011**

Goodman, WG. The consequences of uncontrolled secondary hyperparathyroidism and its treatment in chronic kidney disease. *Semin Dial*. 2004;17**(3)**:209-**2**16. **doi:10.1111/j.0894-0959.2004.17308.x**

Goodman, WG, Quarles LD. Development and progression of secondary hyperparathyroidism in chronic kidney disease: lessons from molecular genetics. *Kidney Int*. 2008;74**(3)**:276-**2**88. **doi:10.1038/sj.ki.5002287**

Haffner D, Schaefer F. Searching the optimal PTH target range in children undergoing peritoneal dialysis: new insights from international cohort studies. *Pediatr Nephrol.* 2013;28**(4)**: 537-**5**45. **doi:10.1007/s00467-012-2270-1**

Hamilton AJ, Braddon F, Casula A, **et al**. '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*. 2016;132**(**suppl 1**)**: 237-**2**52. **doi:10.1159/000444824**

Ketteler, M, Block GA, Evenepoel P, **et al**. 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.* 2017;92**(1)**: 26-36. **doi:10.1016/j.kint.2017.04.006**

Kidney Disease: Improving Global Outcomes **(KDIGO) CKD-MBD Work Group**. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney Int Suppl*. 2009;S1-130. **doi:10.1038/ki.2009.188**

Klaus, G, Watson A, Edefonti A, **et al**. Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. *Pediatr Nephrol*. 2006;21**(2)**:151-**15**9. **doi:10.1007/s00467-005-2082-7**

Kuizon, BD, Salusky IB. Growth retardation in children with chronic renal failure. *J Bone Miner Res*. 1999;14**(10)**:1680-**16**90. **doi:10.1359/jbmr.1999.14.10.1680**

Langman, CB, Salusky IB, Greenbaum L, **et al**. K/DOQI clinical practice guidelines for bone metabolism and disease in children with chronic kidney disease: Work group membership. Am J Kidney Dis. 2005;46**(suppl 1):S4-S121**. **doi:10.1053/j.ajkd.2005.07.028**

Loder, RT, Hensinger RN. Slipped capital femoral epiphysis associated with renal failure osteodystrophy. *J Pediatr Orthop*. 1997**;**17**(2)**: 205-**2**11. **doi:10.1097/00004694-199703000-00013**

Mimpara**®** **[**product **information].** European Medicines Agency **(EMA)**. 2017. Accessed 14 November 2018 https://www.ema.europa.eu/documents/product-information/mimpara-epar-product-information_en.pdf.'

Moe, SM. Vitamin D, cardiovascular disease, and survival in dialysis patients. *J Bone Miner Res*. 2007;22(suppl 2):V95-**9**9. **doi:10.1359/jbmr.07s218**

Nemeth, EF, Heaton WH, Miller M, **et al**. Pharmacodynamics of the type II calcimimetic compound cinacalcet HCl. *J Pharmacol Exp Ther*. 2004**;**308**(2)**:627-**6**35. **doi:10.1124/jpet.103.057273**

Oh, J, Wunsch R, Turzer M, **et al**. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation*. 2002;106**(1)**:100-**10**5. **doi:10.1161/01.cir.0000020222.63035.c0**

Parsabiv [product information]. European Medicines Agency **(**EMAB**)**. 2016 Accessed 16 November 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003995/WC500217100.pdf

Rees, L, Schaefer F, Schmitt CP, Shroff R, Warady BA. Chronic dialysis in children and adolescents: challenges and outcomes. *Lancet Child Adolesc Health*. 2017;1**(1)**:68-77. **doi:10.1016/S2352-4642(17)30018-4**

Schaefer, F, Borzych-Duzalka D, Azocar M, **et al**. 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*. 2012;32**(4)**:399-409. **doi:10.3747/pdi.2012.00126**

Schaefer, F, Drozdz D, Fouqueray B, **et al**. 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. American Society of Nephrology. 2017. **Abstract FR-PO292**

Shroff, R, Wan M, Nagler EV, **et al**. 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*. 2017**;**32:1114-**11**27. **doi:10.1093/ndt/gfx080**

Shroff R, Wan M, Nagler EV, **et al**. Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease Stages 2-5 and on dialysis. *Nephrol Dial Transplant*. 2017**;**32**(7)**:1098-**1**113. **doi:10.1093/ndt/gfx065**

Sohn WY, Portale AA, Salusky IB, **et al**. 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*. 2019;34**(1)**:145-**1**54. **doi:10.1007/s00467-018-4054-8**

Waller, S, Ledermann S, Trompeter R, van't Hoff W, Ridout D, Rees L. Catch-up growth with normal parathyroid hormone levels in chronic renal failure. *Pediatr Nephrol*. 2003**;**18**(12)**:1236-**12**41. **doi:10.1007/s00467-003-1284-0**

Warady, BA, Iles JN, Ariceta G, **et al**. '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*. 2019**;**34**(3)**:475-**4**86. **doi:10.1007/s00467-018-4116-y**

16. Appendices

Appendix A. List of Stand-alone Documents

No.	Document Reference/ Version Number	Date	Title
1	1	23 August 2019	20180204 German Country-specific Supplement
2	2	01 April 2020	20180204 German Country-specific Supplement
3	3	20 July 2020	20180204 German Country-specific Supplement
4	4	10 March 2023	20180204 German Country-specific Supplement
5	1	24 March 2023	20180204 United Kingdom Country-specific Supplement
6	**5**	**13 October 2023**	**20180204 German Country-specific Supplement**
7	**2**	**13 October 2023**	**20180204 United Kingdom Country-specific Supplement**

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	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.

	Yes	No	N/A	Section Number
Section 2: Research question				
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)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	9.5

Comments:

No hypothesis testing for this observational study

	Yes	No	N/A	Section Number
Section 3: Study design				
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	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)	☒	☐	☐	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)	☒	☐	☐	11

Comments:

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

ENCePP Checklist for Study Protocols (Revision 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)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.9
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	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?	☐	☐	☒	

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?	☒	☐	☐	9.3
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	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)	☒	☐	☐	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)	☐	☐	☒	

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?	☒	☐	☐	9.9.1.4
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.9.1.4
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9.1.3

ENCePP Checklist for Study Protocols (Revision 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)	☒	☐	☐	9.9.1.2
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	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)	☒	☐	☐	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.)	☒	☐	☐	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.)	☒	☐	☐	9.3.2
9.1.3 Covariates?	☒	☐	☐	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)	☒	☐	☐	9.3.1
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

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?	☒	☐	☐	

ENCePP Checklist for Study Protocols (Revision 3)

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

Comments:

Section 11: Data management and quality control	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)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

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

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.1.3
12.1.2 Information bias?	☒	☐	☐	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)	☒	☐	☐	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)	☒	☐	☐	9.5

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.6

ENCePP Checklist for Study Protocols (Revision 3)

Section 13: Ethical issues	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.

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13

Comments:

Name of the main author of the protocol: PPD, PhD MSc

Date: 11/02/2019

Signature: PPD Digitally signed by PPD PPD Date: 2019.02.11 13:17:58 Z

ENCePP Checklist for Study Protocols (Revision 3)

Appendix C. Sample Safety Reporting Forms

A Study # 20180204 Cinacalcet	**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	Race	If applicable, provide End of Study date
		☐F ☐M		

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 diagnosis or syndrome If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report *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.*	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 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?	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐ Yes ☐ No		Cinacalcet: No ✓ / Yes ✓ [redacted]		
				☐ Yes ☐ No				
				☐ Yes ☐ 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

A Study # 20180204 Cinacalcet	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

5. Was drug under study administered/taken prior to this event? ☐No ☐Yes If yes, please complete all of Section 5

Amgen Drug/Amgen Device:		Date of Initial Dose Day Month Year	Prior to, or at time of Event Date of Dose Day Month Year	Dose	Route	Frequency	Action Taken with Product 01 Still being Administered 02 Permanently discontinued 03 Withheld	Lot # and Serial #
Cinacalcet	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown
<< Drug/Device>>	☐ blinded ☐ open label							Lot # _____ ☐ Unknown Serial # _____ ☐ Unavailable / Unknown

6. CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Medications? ☐ No ☐ Yes If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Test Unit											

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

Date Day Month Year	Additional Tests	Results	Units

FORM-099346 *Version 1.0 Effective Date: 1 February 2016*

Page 2 of 3

A Study # 20180204 Cinacalcet	**Electronic Adverse Event Contingency Report Form** For Restricted Use

Site Number	Subject ID Number

10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)* Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee - _____ *I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.*	Title	Date

FORM-099346 *Version 1.0 Effective Date: 1 February 2016*

Page 3 of 3

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 Proprietary - Confidential

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:** _____

FORM-115199 Version 1.0 Effective Date: 24-Sept-2018

Amgen Proprietary - Confidential

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: _____

FORM-115201 Version 1.0 Effective Date: 24-Sept-2018