Title: A Prospective Cohort Study to Describe Use and Safety of Cinacalcet in Pediatric Patients Receiving Dialysis in the NAPRTCS Registry

Cinacalcet HCl

Amgen Protocol Number 20120116

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Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled "A Prospective Cohort Study to Describe Use and Safety of Cinacalcet in Pediatric Patients Receiving Dialysis in the NAPRTCS Registry," dated 18 July 2012, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice and applicable national or regional regulations/guidelines.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Protocol Synopsis

Title: A Prospective Cohort Study to Describe Use and Safety of Cinacalcet in Pediatric Patients Receiving Dialysis in the NAPRTCS Registry

Study Phase: N/A

Indication: N/A

Objectives: Describe the demographics, laboratory values, and secondary hyperparathyroidism (SHPT) medication use (specifically cinacalcet), and the occurrence of hypocalcemia, seizures, and infections (requiring hospitalization), in cinacalcet treated and untreated patients enrolled in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) receiving dialysis for chronic kidney disease (CKD).

Hypotheses: Patient characteristics, overall and for cinacalcet treated and untreated patients, will be described; the rate of hypocalcemia, seizure, and infection (requiring hospitalization) events will be estimated separately in cinacalcet treated and untreated patients enrolled in NAPRTCS.

Variables of Interest: Parameters of interest include: Age, height, dry weight, Tanner stage, sex, race, cinacalcet use (yes/no), cinacalcet start/stop dates, cinacalcet dose (mg), parathyroid hormone (PTH) (pg/mL), corrected calcium (mg/dL), phosphorus (mg/dL), phosphate binder use (yes/no), vitamin D sterol use (yes/no), hypocalcemia (yes/no), seizures (yes/no), and infections requiring hospitalization (yes/no).

Study Design: The NAPRTCS registry is a prospective, observational study of patients with CKD. This protocol will collect and tabulate a specific set of information from the NAPRTCS registry. Specifically, dialysis registry patients will be included and followed for up to three years, or for six semiannual data collection intervals. Patients will be censored at three years, transplant, death, loss to follow-up, or if no longer participating in NAPRTCS, whichever occurs first.

Sample Size: Estimated to be approximately between 1000 to 1500 patients over 3 years

Summary of Patient Eligibility Criteria: All pediatric patients < 21 years old receiving maintenance dialysis (hemodialysis or peritoneal dialysis) at a NAPRTCS affiliated center are eligible. Patients who are participating in an Amgen clinical study are ineligible. For a full list of eligibility criteria, please refer to Section 4.4.

Procedures: In this prospective, observational, noninterventional registry, physicians will continue to treat their pediatric dialysis patients as per standard medical care. There are no specific study procedures required by this protocol.

Statistical Considerations: This protocol specifies descriptive statistics that will be completed by NAPRTCS. No hypotheses will be tested or implied by the produced reports. For a full description of statistical analysis methods, please refer to Section 13.

Sponsor: Amgen Inc.

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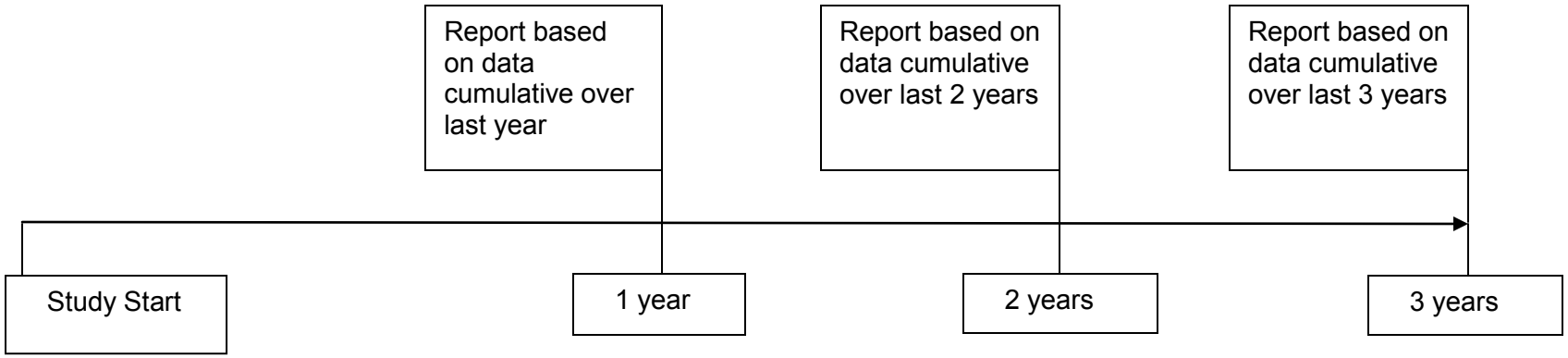
Study Schema



Note: Patients will be followed from study start until death, transplant, withdrawal, transfer to a nonparticipating facility, or the end of the study period

Study Glossary

Abbreviation or Term	Definition/Explanation
AESI	Adverse Event of Special Interest
CKD	Chronic Kidney Dialysis
eGRF	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration
HD	Hemodialysis
HPT	Hyperparathyroidism
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NKF KDOQI	National Kidney Foundation – Kidney Disease Outcomes Quality Initiative™
PD	Peritoneal Dialysis
PTH	Parathyroid Hormone
SHPT	Secondary Hyperparathyroidism
USRDS	United States Renal Data Systems

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1. INTRODUCTION

The purpose of this protocol is to detail the rationale, objectives, data source, and methods, along with limitations, of a planned report describing patient characteristics and safety events among real-world-treated pediatric patients receiving dialysis for chronic kidney disease (CKD) in North America, who are participants in the ongoing North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) pediatric kidney disease registry (https://web.emmes.com/study/ped/).

2. OBJECTIVES

Specific objectives of this study are to tabulate and report the listed characteristics and events for subjects with data in the NAPRTCS registry who have end stage renal disease (ESRD), who are managed in medical practice with or without cinacalcet treatment. The following data characteristics and events are of interest:

- demographic characteristics
- laboratory values
- secondary hyperparathyroidism (SHPT) medication use
- occurrence of hypocalcemia
- occurrence of seizures
- occurrence of infections requiring hospitalization

3. BACKGROUND AND RATIONALE

CKD in children, as in adults, is a devastating illness. The mortality rate in children receiving dialysis is 30 to 150 times greater than that of the general pediatric population (U.S. Renal Data System, USRDS 2006 Annual Data Report; McDonald and Craig, 2004).

As in adults, pediatric patients on dialysis often have SHPT associated with substantial elevations of parathyroid hormone (PTH) as well as dysregulation of calcium and phosphorus metabolism. SHPT can lead to the development of high-turnover bone disease, and the resultant changes in structural bone integrity may lead to an increased risk of deformities and fractures in children on dialysis (Cundy et al, 1985; Spasovski et al, 2003; Coen et al, 1996; Sanchez, 2003; Salusky et al, 1987; Slatopolsky et al, 1999). SHPT is also felt to play a role in growth retardation in children potentially through

alterations in bone architecture (including lesions in the epiphyseal growth plate), which interfere with bone formation and lead to impaired bone growth (Kuizon and Salusky, 1999). Additionally, studies have shown that young adults with ESRD and childhood-onset CKD also display a high incidence of cardiovascular complications (Cheung et al, 2000; Oh et al, 2002), which may be in part attributable to SHPT.

Phosphate binders and vitamin D sterols are indicated for use in pediatric patients with ESRD, however there remains a significant unmet need for additional therapies for SHPT. A recent survey conducted among 18 sites belonging to NAPRTCS (NAPRTCS, unpublished data) included 320 pediatric hemodialysis (HD) and peritoneal dialysis (PD) patients between the ages of 2 to less than 18 years. Results of the survey show that overall, 53% of the pediatric dialysis population have PTH levels above 300 pg/mL, which was the upper limit recommended by the NKF KDOQI™ guidelines for all pediatric age groups (NKF KDOQI ™ 2004) at the time of the survey.

3.1 Rationale for the Study

The purpose of this study is to collect data to inform on the use of cinacalcet in pediatric patients receiving dialysis in clinical practice. No comparisons will be made due to potential confounding by indication, in which patients who receive cinacalcet are different with respect to risk factors for adverse events of special interest (AESI), which is likely to bias any comparison between cinacalcet use groups.

This study will generate a report specifically looking at the AESI in pediatric patients treated with or without cinacalcet in a real-world setting.

3.2 Adverse Events of Special Interest

In response to a specific regulatory request, hypocalcemia, seizures, and infections requiring hospitalization are being collected as AESI. Hypocalcemia and seizures have been identified in prior clinical trials in adults and are listed in the product label for cinacalcet. Infections are a common occurrence in pediatric patients on hemodialysis and peritoneal dialysis.

3.3 Study Hypotheses

Patient demographics overall and for cinacalcet treated and untreated patients will be described, and the rate of hypocalcemia, seizure, and infection (requiring hospitalization) events, will be estimated separately in cinacalcet treated and untreated patients enrolled in the pediatric dialysis registry.

4. STUDY PLAN

4.1 Study Design

This is a prospective, observational study with semiannual data collection and reporting of descriptive findings. The single data source will be the NAPRTCS registry.

4.2 Number of Sites

Approximately 130 sites in the United States, Canada, Mexico, and Costa Rica currently contribute data to the NAPRTCS registry.

4.3 Description of Data Source

NAPRTCS is a voluntary registry of pediatric patients who have chronic kidney disease and who are receiving dialysis, and who are receiving care in approximately 130 pediatric nephrology centers in the United States, Canada, Mexico, and Costa Rica. Aside from the participating centers, the registry consists of a Clinical Coordinating Center and a Data Coordinating Center. Patients are eligible for inclusion if they are < 21 years of age, and are being treated for chronic renal insufficiency or ESRD at a participating center. Patients are treated according to local standards of care. Upon inclusion in the registry, patient data are collected via an electronic data capture form, which is completed by each center on a voluntary basis. For dialysis patients, baseline data (within 30 days of dialysis start) are collected, including predialysis serum creatinine concentration, and length/height (used to derive estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2 via Schwartz's method). Data currently collected by NAPRTCS include demographic and clinical characteristics, select laboratory, hospitalization, and medication variables. Data also include transplant evaluation, access revisions, dialysis modality termination, transplant and vital status. After the baseline assessment, data on these parameters are collected every six months.

Since its beginning in 01 January 1992, the registry has included data from approximately 7000 pediatric dialysis patients. Data from approximately 300 patients are expected in every 6-month interval assessment.

4.4 Summary of Patient Eligibility Criteria

Tabulations will include all patients < 21 years of age receiving maintenance dialysis at a NAPRTCS affiliated center, and who are enrolled in the registry. The tabulation analyses will be repeated to include only those patients < 18 years of age.

Patients who are currently enrolled in an Amgen clinical trial will not be included.

4.5 Study Period and Follow-up

Data to be included in the report will be from a time period of approximately 3 years, from July 2012 to July 2015.

The start of time at risk (index date) will begin at the time of each eligible patient's entry into the NAPRTCS registry.

Patients will be followed from study start until death, transplant, withdrawal, transfer to a nonparticipating facility, or end of the study period.

The primary completion date is defined as 01 July 2015.

5. PATIENT ENROLLMENT

All patients who meet entry criteria and who contribute data to the NAPRTCS registry during the time period of this study will be enrolled and included in the report.

6. DATA COLLECTION PROCEDURES

Data used to generate the reports for this study will be collected by the NAPRTCS registry, and that data will remain with NAPRTCS. NAPRTCS will generate all reports.

No data, nor datasets of any type, will be available from NAPRTCS to Amgen as part of this study.

7. DEFINITION OF EXPOSURE, OUTCOME, AND OTHER STUDY VARIABLES

7.1 Exposure

The exposure is defined as cinacalcet therapy. Patients are considered exposed for the duration from start to stop date of receiving cinacalcet, and for 7 days afterwards.

7.2 Variables of Interest

Variables of interest for this study are as follows:

- cinacalcet prescription start and stop dates
- dose of cinacalcet (mg)
- occurrence and date of seizures
- occurrence and date of infections requiring hospitalization
- occurrence and date of hypocalcemia (defined as corrected serum calcium below the age-appropriate lower limit of normal range), and categorically < 9.0 mg/dL

(patients 0 to < 2 years), < 8.4 mg/dL (patients 2 to 6 years), < 8.0 mg/dL, < 7.5 mg/dL, and < 7.0 mg/dL among subjects who are treated with or without cinacalcet

- occurrence and date of hypocalcemia (as defined by investigator) requiring treatment and action(s) taken

7.3 Other Study Variables

Other study variables of interest are as follows:

- age
- sex
- race
- height
- dry weight
- Tanner stage
- PTH (pg/mL)
- corrected calcium (mg/dL)
- phosphorus (mg/dL)
- phosphate binder use (yes/no) and dates of use
- vitamin D sterol use (yes/no) and dates of use

8. TIME AT RISK FROM EXPOSURE

Patients accumulate time at risk (either exposed or unexposed) from the study time of start of follow-up until death, censored, or transplanted.

9. POTENTIAL SOURCES OF BIAS IN STUDY

There are 2 key potential sources of bias in this study.

9.1 Confounding by Indication and Information Bias

Confounding by indication and information bias have the potential to adversely affect the validity of any comparison between cinacalcet users and nonusers in this study.

Specifically, differences in the frequency of safety events may be attributed to cinacalcet use when, in fact, they are indicative of either:

- underlying differences in risk factors between patients receiving and not receiving cinacalcet (confounding by indication)
- differential capture of safety data by cinacalcet use (information bias)

An example of the former would be if patients receiving cinacalcet are less likely to have a history of seizures (due to perceived safety concerns about cinacalcet and seizure risk), or if cinacalcet use is associated with a higher underlying disease severity.

Differential capture/missingness could occur if physicians were more diligent in recording hospitalization events for their cinacalcet patients, due to higher vigilance around use of off-label therapy (information bias).

In either of the aforementioned scenarios, the frequency of events for cinacalcet treated patients would appear spuriously higher than for untreated patients.

There may be misclassification in the NAPRTCS-generated summary table of cinacalcet users and users, as any use of cinacalcet will define cinacalcet exposed in the table. Start and stop dates of time of cinacalcet use, however, will be collected, and appropriate linkage between treatment window and events will be reported.

9.2 Ascertainment of Adverse Events of Special Interest Bias

In addition, ascertainment of the AESI is made solely by the individual physicians treating his/her patients. While determination of the occurrence of seizures and infections requiring hospitalization may appear to be more straightforward, NAPRTCS does not have a registry wide definition of hypocalcemia. Each physician entering data into the registry uses his/her individual judgment.

10. REMOVAL AND REPLACEMENT OF SUBJECTS

Since this study is based upon real-life clinical practice, data from all enrolled patients will be collected. There will be no specific procedures for removal and replacement of patients.

11. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

This study is based upon data from a single database registry. Amgen will not collect data directly from patients, and all AESI reports will be obtained from the NAPRTCS registry. All data are collected by NAPRTCS through retrospective chart review, and reports will be provided to Amgen annually. Upon receipt of this annual report, Amgen will provide this information to regulatory agencies.

12. SAMPLE SIZE CONSIDERATIONS

The expected number of patients to be enrolled (during the years 2012 to 2015) is estimated to be between 1000 to 1500, with approximately 200 to 300 of these patients likely to receive cinacalcet over the life of the study. The objective of the study is to describe demographic characteristics, laboratory values, and events of interest (hypocalcemia, seizures, or infections requiring hospitalization) for patients in this population who do or do not receive treatment with cinacalcet.

The background rate of hypocalcemia and seizures is <1%. The rate of infection is expected to be higher, as infections are more common in the pediatric population.

Table 1 below illustrates the half-width of 95% confidence intervals for events with varying incidence rates, stratified by the expected number of cinacalcet (N = 300) and non-cinacalcet (N = 1200) patients:

Table 1. Confidence Intervals for Event Probabilities

N	True Probability of Event	95% CI Half-width
1200	0.1	0.017
1200	0.05	0.012
1200	0.01	0.006
1200	0.005	0.004
300	0.1	0.034
300	0.05	0.025
300	0.01	0.011
300	0.005	0.008

13. STATISTICAL ANALYSIS

13.1 Data Collection and Management

Data for this study will be collected and managed solely by the NAPRTCS registry, and there will be no data editing required.

13.1.1 Descriptive Analyses

Since the study is descriptive in nature, the analyses will describe the study population and outcomes in all study cohorts, for age < 21 years, for age < 18 years, as well as in different follow-up time periods (before and after cinacalcet exposure). This will include the following:

- total number of patients and total number of patient-years observation based on the annual data reporting periods, and for the cumulative 3-year study period
- estimation of rates of cinacalcet use based on the annual data reporting periods, and for the cumulative 3-year study period
- estimation of rates of AESI based on the annual data reporting periods, and for the cumulative 3-year study period
- proportion of patients who received at least 1 dose of cinacalcet within 7 days preceding an episode of hypocalcemia (from amongst all patients who developed hypocalcemia)

In addition, the following descriptive analyses using summary statistics will also be conducted:

- a tabular summary (eg, frequency, percent, rate) of categorical baseline demographic and clinical characteristics by cinacalcet-exposed and cinacalcet-unexposed
- for continuous variables (eg, age, weight, laboratory values) summary statistics for measures of central tendency (mean, median, SD, Q1, Q3, min, max) will be provided by cinacalcet-exposed and cinacalcet-unexposed

The cinacalcet utilization pattern will also be assessed (eg, dosing, duration of treatment).

13.1.2 Analyses

All analyses will be performed by NAPRTCS.

Amgen will receive reports on an annual basis, reflecting the (cumulative) two prior 6-month data collection periods. One final cumulative report will be received at the end of the 3-year study period.

13.2 Planned Methods of Analysis

Descriptive analyses will consist of summary statistics: mean, standard deviation, standard error, minimum, maximum, median, and quartiles for continuous variables, and frequency and percent for categorical variables.

13.3 Missing Data and Loss to Follow-up

Data may be missing as previously discussed in Section 9.1, and lead to bias.

Because entry of data into the NAPRTCS registry is completely voluntary, patients are lost to follow-up if there is a relocation, if they are no longer treated by a physician in a NAPRTCS affiliated institution, etc.

13.4 Annual Analysis

Annual reports from NAPRTCS are planned for this study. For each prespecified analysis, NAPRTCS will generate a report based on the available data in the annual

data reporting period, and cumulative for the entire 3 year study period. The analysis will be limited to the analyses described in Section 13.

13.5 Final Analysis

A final report will be completed within 6 months after the end of the study (Q2, 2015). The final report will be comprehensive for all objectives and for the specific outcomes of interest.

14. STRENGTHS AND LIMITATIONS

Potential strengths (advantages) of the study include the following:

- utilization of the largest registry in North America for pediatric patients on dialysis
- prospective design allows for contemporary assessment of practice patterns
- utilizes existing data that are routinely collected from clinical practice settings reducing cost/burden on investigators and patients
- findings from this study may be evaluated collectively with those from other clinical studies conducted in other countries to complement a comprehensive global pediatric program to evaluate safety and efficacy

Potential limitations (disadvantages) of the proposed study include:

- small sample size due to the low prevalence of dialysis dependent CKD pediatric patients (estimated 2000 point prevalent patients in the United States)
- estimated event counts will be low or very low for rare AESIs
- voluntary nature of data entry into the NAPRTCS registry, which may result in missing data and information bias

15. REGULATORY OBLIGATIONS

This study is based upon routinely collected data from the NAPRTCS registry. Analyses using this data source will be conducted by NAPRTCS, whose investigators have access to the data through their respective institutions, with analysis reports presented to Amgen. Study results will only be presented in an aggregate form, and individuals will not be identified.

Informed consent for participation in the registry is obtained and maintained by NAPRTCS.

16. COMMUNICATION OF STUDY RESULTS

The health risk findings of the study associated with Amgen products must be reported to regulatory agencies according to local and international requirements. This study will conduct an assessment annually. The assessment results will be submitted to regulatory agencies accordingly.

17. ADMINISTRATIVE OBLIGATIONS

17.1 NAPRTCS Responsibilities

NAPRTCS, which comprises its study investigators, its Clinical Coordinating Center, and its Data Coordinating Center, is responsible for the following:

- maintaining investigational review board (IRB) and independent ethics committee (IEC) approvals
- prospectively collecting, managing, and organizing data to meet study objectives
- providing relevant case-level and aggregate clinical data, including all predefined AESI
- completing all statistical analyses
- developing ongoing and final study reports, and sending these completed reports to Amgen
- complying with required auditing procedures
- working with Amgen to prepare relevant publications

17.2 Amgen's Responsibilities

Amgen will provide financial support for this study. Amgen will work with NAPRTCS to ensure the study objectives are met. Other responsibilities of Amgen include the following:

- review and approve final study analyses, statistical methodologies and report format prior to report generation
- facilitate communication with regulatory authorities on study design, protocol and results, as applicable
- fulfill Amgen's regulatory responsibilities, including submission of reports, as required
- facilitate requests from regulatory authorities, as applicable
- collaborate with study teams to prepare relevant publications, as needed

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