PASS Information

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Joint PASS	No
Research Question and Objectives	Primary Objective(s): 1. To compare characteristics of patients on hemodialysis who develop hypocalcemia while on cinacalcet with the characteristics of patients who do not develop hypocalcemia while on cinacalcet, 2. To describe patterns of treatment strategies used by physicians for patients on hemodialysis who develop hypocalcemia while on cinacalcet, 3. To describe the subsequent recovery of serum calcium among patients on hemodialysis who develop hypocalcemia while on cinacalcet, 4. To describe patterns of cinacalcet reinitiation among patients on hemodialysis who discontinued cinacalcet use following the development of hypocalcemia.
Country of Study	United States
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2. List of Abbreviations

Abbreviation	Full Term
ANOVA	Analysis of variance
Ca	Calcium
CDW	Clinical Data Warehouse
CKD	Chronic Kidney Disease
ESRD	End-stage renal disease
HCPCS	Healthcare Common Procedure Coding System
HD	Hemodialysis
IV	Intravenous
NDC	National Drug Code
P	Phosphorus
PTH	Parathyroid Hormone
SAP	Statistical analysis plan
SD	Standard deviation
SHPT	Secondary hyperparathyroidism

3. Responsible Parties

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4. Abstract

- **Title:** Characterizing the management of hypocalcemia among patients on hemodialysis receiving cinacalcet treated within a large US dialysis provider

- Version: 1.0
- Date: 05 March 2014
- Authors: Paul Dluzniewski, Amgen Inc.,
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- **Rationale and Background:** Cinacalcet is indicated for secondary hyperparathyroidism in patients with chronic kidney disease on dialysis. Cinacalcet induced reductions in parathyroid hormone are typically accompanied by reductions in serum calcium. Such declines in serum calcium can be modest and are infrequently associated with clinical sequelae; however, more pronounced reductions in serum calcium can occur resulting in more severe hypocalcemia, and potential adverse consequences. In these situations, physicians may respond by temporarily or permanently discontinuing cinacalcet or they may intervene with other therapies. These interventions can include use of vitamin D analogs, calcium supplementation, and modification of dialysate calcium concentrations, either alone or in combination. Currently, evidence regarding treatment strategies used in clinical practice to address hypocalcemia following cinacalcet therapy is scarce.

- **Research Question and Objectives:**

  Objective 1: To compare characteristics (demographic, clinical, and laboratory values) of patients on hemodialysis who develop hypocalcemia while on cinacalcet with the characteristics of patients who do not develop hypocalcemia while on cinacalcet,

  Objective 2: To describe patterns of treatment strategies used by physicians for patients on hemodialysis who develop hypocalcemia while on cinacalcet,

  Objective 3: To describe the subsequent recovery of serum calcium among patients on hemodialysis who develop hypocalcemia while on cinacalcet,

  Objective 4: To describe patterns of cinacalcet reinitiation among patients on hemodialysis who discontinued cinacalcet use following the development of hypocalcemia.

- **Study Design:** Retrospective cohort analysis of patients on hemodialysis prescribed cinacalcet.
- **Population:** Patients enrolled in DaVita Rx™ who received hemodialysis at DaVita HealthCare Partners Inc. facilities between 01 January 2011 and 31 December 2013 and filled a prescription of cinacalcet.
- **Variables:** Demographics (age, sex, weight, race, ethnicity, access, vintage), laboratory values (calcium, phosphorus, parathyroid hormone, Kt/V, albumin, and alkaline phosphatase), and treatment history (cinacalcet use and dose, calcium-based binders use and dose, vitamin D use and dose, and dialysate calcium).
- **Data Sources:** DaVita® Rx database and the DaVita Clinical Data Warehouse patient electronic medical records.
- **Study Size:** Our initial cohort will be approximately 15,000 patients. The sub-cohort will be comprised of approximately 1,500 patients who developed hypocalcemia.
- **Data Analysis:** Descriptive analyses will be conducted for the distributions of demographic, clinical, and laboratory values among patients on hemodialysis who develop hypocalcemia. In addition, baseline characteristics of patients who develop hypocalcemia will be compared to patients who do not develop hypocalcemia. Among patients who develop hypocalcemia, we will describe the percentage receiving specific physicians responses (discontinuation/reduction of cinacalcet dose, addition or up titration of calcium-based binder, addition or up titration of activated vitamin D, change to more calcemic-activated vitamin D, increase dialysate calcium, no response) and the relevant joint distributions of physician responses to the hypocalcemic event. Descriptive analyses for the number and percentage of patients who recover to previous calcium levels dependent on the cut-off used to define hypocalcemia (< 7.5 mg/dL, 7.5 to 7.9 mg/dL, and 8.0 to 8.4 mg/dL), as well as time-to-event analyses for the overall cumulative incidence of calcium recovery and reinitiation of cinacalcet for patients who discontinue use.
- **Milestones:**

Start of data collection:	14 March 2014
End of data collection:	02 May 2014
Registration in the EU PAS register:	13 March 2014
Final report of study results:	01 May 2015

5. Amendments and Updates

No amendments or updates.

6. Milestones

Milestone	Planned date
Start of data collection	14 March 2014
End of data collection	02 May 2014
Registration in the EU PAS register	13 March 2014
Final report of study results	01 May 2015

7. Rationale and Background

Secondary hyperparathyroidism (SHPT) is a condition that is present in a substantial percentage of patients with chronic kidney disease (CKD) who are on dialysis. It has been estimated that about 30% of patients initiate dialysis with SHPT (iPTH >300 pg/mL) with the prevalence increasing as time on dialysis increases.[1,2] The condition is manifested by increasing circulating levels of parathyroid hormone (PTH) and associated disregulation of calcium and phosphorus (P) metabolism, as well as hyperplasia within the parathyroid gland.[3-5] Non-experimental studies conducted using large dialysis provider data have shown elevated levels of the three Mineral and Bone Disorder (MBD) biochemical parameters resulting from SHPT is associated with a wide range of adverse clinical consequences in this already grievously ill population.[3-8]

Sensipar® (cinacalcet) is indicated for SHPT in patients with CKD on dialysis. Clinical trials have shown, in addition to lowering PTH levels, use of cinacalcet results in the lowering of serum calcium levels in dialysis patients.[6,9-11] Similar reductions in serum calcium have also been reported in observational studies among patients taking cinacalcet compared to other forms of treatment. The results of these studies indicate the largest reductions in calcium can occur within 1 to 2 months after initiation and can continue to 12 months.[5,12] In three 26-week studies of patients with CKD on dialysis, 66% of patients receiving cinacalcet compared with 25% of patients receiving placebo developed at least 1 serum calcium value < 8.4 mg/dL.[6,9] Such reductions in serum calcium can result in hypocalcemia possibly leading to downstream adverse consequences. In response to the development of hypocalcemia, physicians may order the temporary or permanent discontinuation of cinacalcet, or may prescribe concomitant treatments with the goal of increasing serum calcium levels. These treatment strategies

can include the use of vitamin D analogs, calcium supplementation, and modification of dialysate calcium, and the interventions may be implemented either alone or in combination.

Currently, published literature describing the course of management of hypocalcemia while on cinacalcet by treating physicians is scarce. Information on the management of hypocalcemia in patients receiving cinacalcet and how that is operationalized by physicians in clinical practice is an important issue and one that will help to inform physicians and providers regarding treatment of SHPT with cinacalcet.

8. Research Question and Objectives

This study has four objectives:

Objective 1: To compare characteristics (demographic, clinical, and laboratory values) of patients on hemodialysis who develop hypocalcemia while on cinacalcet with the characteristics of patients who do not develop hypocalcemia while on cinacalcet,

Objective 2: To describe patterns of treatment strategies used by physicians for patients on hemodialysis who develop hypocalcemia while on cinacalcet,

Objective 3: To describe the subsequent recovery of serum calcium among patients on hemodialysis who develop hypocalcemia while on cinacalcet,

Objective 4: To describe patterns of cinacalcet reinitiation among patients on hemodialysis who discontinued cinacalcet use following the development of hypocalcemia.

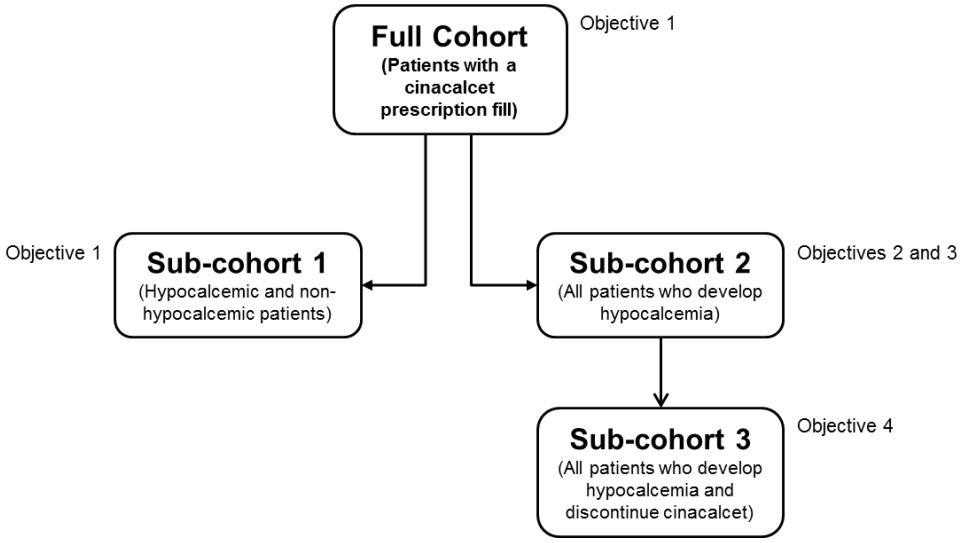
9. Research Methods

9.1 Study Design

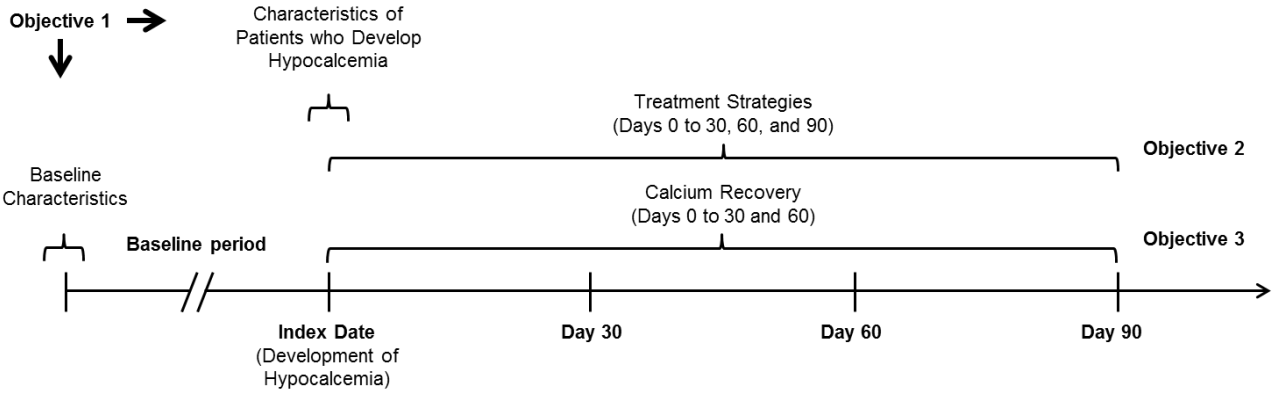
We will utilize a retrospective cohort study design, as it is the most efficient study design to answer the research questions. The cohort design will allow us to utilize available data, including data collected on covariates of interest, to study multiple outcomes (treatment strategies, calcium recovery, and reinitiation of cinacalcet) and provide an opportunity to describe the management of hypocalcemia in the hemodialysis population.

Study Schema

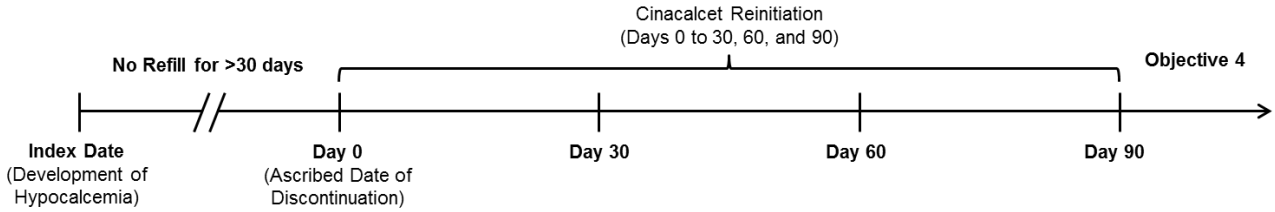
Study population (Cohort and sub-cohorts)



Objectives 1, 2, and 3: Follow-up time



Objective 4: Follow-up time



9.2 Setting

9.2.1 Study population

We will derive our study population of patients who are new users of cinacalcet from a source population of adult patients (18 years and older) with ESRD enrolled in DaVita Rx between 01 January 2011 and 31 December 2013 who were receiving center-based hemodialysis at a DaVita facility in the United States.

9.2.2 Inclusion criteria

We will include male and female patients in this study if they meet the following criteria:

- Aged 18 years and older,
- Received in-center hemodialysis at a DaVita facility for ≥ 3 months,
- Enrolled in DaVita Rx,
- Filled a prescription for cinacalcet after the beginning of the study period, 01 January 2011.

For patients defined as developing hypocalcemia:

- Had a serum calcium lab measurement reflecting hypocalcemia (defined at three separate cut points: < 7.5 mg/dL, 7.5 to 7.9 mg/dL, and 8.0 to 8.4 mg/dL),
- Had an active supply of cinacalcet from DaVita Rx at the time of their hypocalcemic event.

For patients defined as not developing hypocalcemia:

- Had an active supply of cinacalcet from DaVita Rx,
- All serum calcium lab measurements over the course of follow-up >8.4 mg/dL.

9.2.3 Definition of Time Periods

Study Period

The study period will be 01 January 2011 through 31 December 2013.

Index date

The index date will be the date of the lab measurement indicating hypocalcemia while on cinacalcet.

Baseline period

For Objective 1, the baseline period will be the 90 days prior to the date of the 1st fill of a cinacalcet prescription.

For Objectives 2, 3, and 4 the baseline period will be the 90 days prior to date of the index date (development of hypocalcemia).

Follow-up period

Objective 1: Follow-up will begin at the fill of the initial prescription and extend to earliest of the development of hypocalcemia or censoring for death, discontinuation of cinacalcet, transfer of care from DaVita, modality change, transplant, withdrawal from dialysis or renal functional recovery.

Objective 2: Follow-up will begin at the index date and extend up to 90 days.

Objective 3: Follow-up will begin at the index date and extend up to 90 days. Patients will be observed forward until calcium recovery is observed or censoring for death, transfer of care from DaVita, modality change, transplant, withdrawal from dialysis or renal functional recovery.

Objective 4: Follow-up will begin at discontinuation of cinacalcet following a diagnosis of hypocalcemia and extended up to 90 days. Patients will be observed forward until reinitiation of cinacalcet is observed or censoring for death, transfer of care from DaVita, modality change, transplant, withdrawal from dialysis or renal functional recovery.

9.3 Variables

9.3.1 Study Outcomes

Objective 1: The outcome will be the development of hypocalcemia using the following cutpoints for serum calcium levels: < 7.5 mg/dL, 7.5 to 7.9 mg/dL, and 8.0 to 8.4 mg/dL.

Objective 2: The outcome will be the percent of patients receiving the below response over the first 30-day interval following the index date of hypocalcemia:

- Discontinue cinacalcet
    - For 30 days supply, discontinuation will be defined as no prescription fill occurring before, on, or within 30 days following the date on which prior supply was exhausted (e.g., if there had been a fill for a 30-day supply on 01 September and no subsequent fill was observed by 30 October). For 90 days supply, discontinuation will be defined as no prescription fill occurring before, on, or within 90 days following the date on which prior supply was exhausted.

  - Date ascribed to discontinuation will be the later of date of last fill or index date

- Reduce cinacalcet dose defined as a decrease in daily dose as indicated in the DaVita Rx database (e.g., 60 mg to 30 mg).
- Add calcium-based binder or up-titrate dose of binder. Up-titration will be defined as a filled prescription for next dosage up in the DaVita Rx database.
- Add activated vitamin D or up-titrate dose of activated vitamin D. Up-titration will be defined as receipt of an increased dose as recorded in the clinical database.
- Change to more calcemic-activated vitamin D (e.g., switch from paricalcitol to calcitriol)
- Increase dialysate calcium
- No response
- Joint distributions of above responses

Objective 3: The outcome will be the percent of patients who achieve calcium recovery based on the pre-defined cut points during the first 30, 60, and 90 days following the index date of hypocalcemia.

Objective 4: The outcome will be the percent of patients who re-initiate cinacalcet during the 90 days following cinacalcet discontinuation. We will define reinitiation as a patient filling a 30 or 90-day supply cinacalcet prescription after discontinuation.

9.3.2 Covariates

Table 1: Baseline and time-varying covariates

Variables	Description	Data Source
Demographics		
Age	Continuous (≥18)	DaVita Clinical Data Warehouse
Sex	Male Female	DaVita Clinical Data Warehouse
Race	Patients of Black, White, or Other Race	DaVita Clinical Data Warehouse
Ethnicity	Patients of Hispanic and Non-Hispanic Ethnicity	DaVita Clinical Data Warehouse
Access	Arteriovenous fistula Graft Catheter Other/unknown	DaVita Clinical Data Warehouse

Weight	kg	DaVita Clinical Data Warehouse
Time on dialysis	Months	DaVita Clinical Data Warehouse
ESRD Cause	Diabetes Hypertension Glomerulonephritis Other	DaVita Clinical Data Warehouse
Laboratory values		
Calcium (Ca)	mg/dL	DaVita Clinical Data Warehouse
Phosphorus (P)	mg/dL	DaVita Clinical Data Warehouse
Parathyroid Hormone (PTH)	pg/mL	DaVita Clinical Data Warehouse
Kt/V	unitless	DaVita Clinical Data Warehouse
Albumin	g/dL	DaVita Clinical Data Warehouse
Alkaline phosphorus	U/L	DaVita Clinical Data Warehouse
Treatment		
Cinacalcet		
30mg cinacalcet hydrochloride, oral coated tablet	NDC 55513-0073-30	DaVita Rx
60mg cinacalcet hydrochloride, oral coated tablet	NDC 55513-0074-30	DaVita Rx
90mg cinacalcet hydrochloride, oral coated tablet	NDC 55513-0075-30	DaVita Rx
Phosphate binders		
Renagel® (sevelmar)	NDC 58468-0130	DaVita Rx
Phoslo® (calcium acetate)	NDC 54868-5691	DaVita Rx
Renvela® (sevelamer carbonate)	NDC 58468-013x	DaVita Rx
Fosrenol® (lanthanum carbonate)	NDC 54092-25x	DaVita Rx
Intravenous (IV) vitamin D		
Calcitriol	HCPCS J0635	DaVita Clinical Data Warehouse
Calcitriol	HCPCS J0636	DaVita Clinical Data Warehouse
Paricalcitol	HCPCS J2500	DaVita Clinical Data Warehouse
Paricalcitol	HCPCS J2501	DaVita Clinical Data Warehouse
Doxercalciferol	HCPCS J1270	DaVita Clinical Data Warehouse
Other treatment information		
Dialysate calcium	mEq/L	DaVita Clinical Data Warehouse

For Objective 1, we will use baseline laboratory values to compare patients who develop hypocalcemia to those who do not. For all other analyses, we will consider the laboratory value concurrent with or most proximally preceding the index date of hypocalcemia.

For each treatment (cinacalcet, phosphate binders, intravenous (IV) vitamin D and dialysate calcium) we will describe, where appropriate:

  - % use at index date (will be 100% for cinacalcet by design)

- Among patients defined as users:
  - Daily cinacalcet dose at index date
  - % that are new users (does not apply to dialysate calcium)
    - New users will be defined as having a medication supply spanning the index date AND no days supply for days -90 to -31
    - Continuing users will be defined as having a medication supply spanning index date AND 1+ day supply for days -90 to -31
- Among continuing users, patterns of dosing:
  - Stable (supplied dose at day 0 = supplied dose at day -31)
  - Up titration (supplied dose at day 0 > supplied dose at day -31)
  - Down titration (supplied dose at day 0 < supplied dose at day -31)
- For vitamin D, we will describe the percentage of patients who transitioned between individual pairwise combinations of agents (e.g., calcitriol to doxercalciferol, doxercalciferol to paracalcitol).
- New user status will not be defined for dialysate calcium use, but we will describe dose at index date and titrations as described above (stable, up, or down).
- Relevant joint distributions of treatment strategies will be examined (e.g., up titration of cinacalcet + reduction in Vitamin D) and the empiric distributions (i.e., those that are sufficiently frequent) of the strategies will be used to decide on the appropriate categories to report.

9.4 Data Sources

The DaVita Rx clinical database and the CDW will be used for this project and data will be linked via a unique identifier.

DaVita Rx is a full-service pharmacy that is dedicated to serving patients with kidney disease and will provide data on drug information (dispense date, dose, and quantity).

The CDW contains data from approximately 1,700 DaVita dialysis clinics in the United States for up to 150,000 patients with end-stage renal disease patients per year. The dataset contains information on patient demographics, disease history, comorbidities, dialysis-specific information for each treatment session (including treatment and biometric data), laboratory results, quality-of-life evaluations, and detailed information on hospitalizations.

9.5 Study Size

Based on enrollment of approximately 48,000 patients 18 years and older in DaVita Rx in 2012,[13] we assumed 30% of patients would be on cinacalcet[12] for an estimated sample size for the full cohort equal to 15,000 patients. We also assumed, based on observational data, 10% of patients on cinacalcet would experience hypocalcemia,[5] for an estimated study size equal to approximately 1,500 patients for Objectives 2, 3, and 4.

The table below shows confidence interval half-widths for a range of sample sizes for patients who develop hypocalcemia, from 500 to 1,500. For example, the table below shows half-widths around estimates of the percentage of patients receiving an increase in dialysate calcium concentration for Objective 2. Precision around percentage estimates for Objectives 3 and 4 will be the same.

Expected percentage	**N**		
	500	**1,000**	**1,500**
5%	1.91%	1.35%	1.10%
10%	2.63%	1.86%	1.52%
15%	3.13%	2.21%	1.81%
20%	3.51%	2.48%	2.02%
25%	3.80%	2.68%	2.19%
30%	4.02%	2.84%	2.32%
35%	4.18%	2.96%	2.41%
40%	4.29%	3.04%	2.48%
45%	4.36%	3.08%	2.52%

9.6 Data Management

Amgen will not be obtaining any data sources for this study. All required data sources currently exist on DaVita secure servers, and data analyses will be performed solely by DaVita.

9.7 Data Analysis

For Objective 1, we will first report the baseline characteristics of the whole cohort. We will also describe the characteristics of patients at the time they develop hypocalcemia. Formal hypothesis will not be tested for these descriptive components of the analyses. However, we will estimate the association between each of the baseline characteristics and the development of hypocalcemia (yes vs. no). Analyses for Objective 2, 3, and 4 are descriptive in nature and formal hypotheses will not be tested. Patients included in the study population for all analyses will be required to be new users of cinacalcet during the study period.

Objective 1

For the descriptive comparison between patients who develop hypocalcemia and those who do not, baseline characteristics will be described in terms of means, standard deviations, medians, p25s, and p75s. Categorical demographic, clinical, and laboratory variables at baseline will also be described as frequencies and proportions.

To formally compare baseline characteristics between patients who develop hypocalcemia and those that do not, we will create a sub-cohort. Entry into this closed cohort will be based on the requirement of a minimum follow-up time determined empirically from the data. We will use logistic regression to identify baseline predictors of the development of hypocalcemia adjusting for the other risk factors.

In addition, continuous demographic, clinical, and laboratory variables at the index date (date of hypocalcemia) will be described in terms of means, standard deviations, medians, p25s, and p75s. Categorical demographic, clinical, and laboratory variables at the index date of hypocalcemia will be described as frequencies and proportions.

Additionally, we will stratify our analyses by calcium dialysate concentrations (< 2.5 mEq/L vs. ≥ 2.5 mEq/L) to determine if the associations between risk factors and the development of hypocalcemia differ between bath concentrations.

Objective 2

For Objective 2, an aggregate analysis will examine the number and proportion of patients to whom individual management responses (as defined in Section 9.3.1) were directed over the 30-day period following index hypocalcemia. A 30 day follow-up period

was selected to correctly capture the physician's first response(s) to the development of hypocalcemia, based on input from our clinical collaborators.This analysis also will consider the joint distribution of combinations of responses; the combinations considered will be determined based on the empiric distribution of individual responses.

Additional analyses are planned to better understand choices regarding cinacalcet discontinuation. In these analyses, we will limit consideration to patients who remained in the study through day 90 post index hypocalcemia. Patients will be stratified based on whether cinacalcet was discontinued by day 90. Within each stratum, we will report the number and percent of patients to whom other individual interventions were directed over the periods: days 0-30, days 0-60, and days 0-90. The ranges of days were decided upon to account for the additional modifications taken if an initial response does not improve calcium levels. 90 days is considered the maximum amount of allowable time to accurately capture direct responses to the development of hypocalcemia. Shorter windows of follow-up time were deemed appropriate as the effect of cinacalcet initiation on calcium is fast given the known mechanism of action.[14] Again, these analyses will consider the joint distribution of combinations of responses; the combinations considered will be determined based on the empiric distribution of individual responses.

Parallel analyses will be conducted in cohorts defined by the severity of hypocalcemia: calcium < 7.5 mg/dL, calcium = 7.5 to 7.9 mg/dL, and calcium = 8.0 to 8.4 mg/dL.

Objective 3

For Objective 3, all analyses will be conducted in parallel and recovery of serum calcium will be defined in three ways based on severity of initial hypocalcemia:

- Calcium ≥ 7.5 mg/dL for patients whose index calcium < 7.5 mg/dL
- Calcium ≥ 8.0 mg/dL (separately) for patients whose index calcium < 7.5 mg/dL and index calcium = 7.5-7.9 mg/dL
- Calcium ≥ 8.5 mg/dL (separately) for patients whose index calcium < 7.5 mg/dL, index calcium = 7.5-7.9 mg/dL and index calcium = 8.0-8.4 mg/dL

Time-to-event analyses will be used to describe the overall cumulative incidence of calcium recovery over time based on the criteria above. Cumulative incidence plots to describe time to recovery will be estimated using Kaplan Meier methods. Patients will be considered at risk beginning on index date and observed forward until recovery is

observed or censoring (for death, transfer of care away from DaVita, modality change, transplant, withdrawal from dialysis or renal functional recovery).

For each analysis, we will describe the number and percent of patients who recover as defined above over the first 30 day interval and then extended over the initial 60 and 90 day intervals. The 30 day window was selected to capture any recovery due to initial responses, and the maximum window was set to 90 days to ensure recovery occurred in a relevant time-frame, based on input from our clinical collaborators. Shorter windows of follow-up time were deemed appropriate as the effect of cinacalcet initiation on calcium is fast given the known mechanism of action.[14]

We will conduct an additional sensitivity analysis using the nadir of calcium levels. We will assess if treatment strategies and time to recovery differ when patients have calcium levels that continue to decline after the initial development of hypocalcemia and we will use the date of the lowest measure of calcium as our index date.

Objective 4

For Objective 4, three parallel analyses (0-30 days, 0-60 days, and 0-90 days) will be conducted. The first analysis will consider all patients who remained alive and in study for 30 days following the ascribed date of cinacalcet discontinuation; for these, we will report the number and percent of patients who resumed cinacalcet within 30 days of initial discontinuation. The second and third analyses will follow the same structure as the first analysis, but within 60 and 90 days following the ascribed date of cinacalcet discontinuation, respectively.

In addition, among all patients who resumed cinacalcet at any time, we will describe the following parameters at the time of reinitation (most proximate observation preceding) and at the index time:

- Demographics
- Calcium
- Phosphorus
- PTH
- Relevant combinations (choices based on empiric distributions):
    - Calcium-based binder use
    - Calcium-based binder dose

  - Activated vitamin D use
  - Activated vitamin D dose
  - Dialysate calcium
- Cinacalcet dose

9.8 Quality Control

All data were previously collected through DaVita dialysis facilities or DaVita Rx database. Because the data undergo institutional quality control systems, the quality and accuracy of the data should not be a major concern. We anticipate no data editing for the data within the 2 data sources.

Data quality will be managed by DaVita and will include both production and quality control programming. Programming for the construction of the analytic file will be done by the primary programmer and will be verified by an independent programmer. Once completed, the primary statistical analysis programmer will conduct the analysis. Specific analyses will be targeted for evaluation and independent programming to ensure accuracy.

9.9 Limitations of the Research Methods

Because the study is retrospective/observational, confounding may be present. For comparing the distribution of covariates in Objective 1 between patients who develop hypocalcemia compared to those who do not, we will be adjusting for other covariates using logistic regression. However, we will not be addressing time-varying predictors of the development of hypocalcemia in this analysis. For the descriptive component of the analysis, we will present unadjusted results for the number and percentages of treatment strategies, patients recovering, and patients reinitiation cinacalcet. We acknowledge the exact discontinuation dates will not be known, but a time frame of discontinuation will be. We will account for this imprecision by stratifying by cinacalcet discontinuation in our descriptive analyses of treatment strategies over the 90 days following the index date of hypocalcemia.

Additional limitations include the possibility that data on calcium laboratory values proximal to the development of, and recovery from, hypocalcemia may be lacking.

Calcium laboratory draws usually occur on a monthly basis and we may not have the ability to capture declines or rises in serum calcium close to the events of interest. We believe additional testing is likely to occur around the development of hypocalcemia due to increased surveillance. However, data indicating that additional laboratories draws are not being ordered will still be informative for future research. We will also not be able to capture over-the-counter medication use and verbal stop and reinitiation orders. We will additionally lack the ability to identify irregular cinacalcet users who fill prescriptions within the specified allowable gap and are classified as continuing users.

Considering the data quality, we do not anticipate measurement error or misclassification to significantly affect our study results. Considering the study design and study objectives, selection bias is not a likely source of bias in this study. Information bias may be present due to our lack of data on patients who have severe hypocalcemic events that result in hospitalization. Although, we believe this will be a small percentage of patients and will not impact our results as discussions with our Clinical Development colleagues indicate that hospitalization due to hypocalcemia is not highly prevalent. In addition, the adjusted comparison of patients who do and do not develop hypocalcemia may be incomplete because not all factors are accounted for. Finally, we are studying patients being treated in a large dialysis organization utilizing a highly-managed pharmacy system and our results may not be generalizable to other populations. However, we are utilizing a robust data source that may better capture treatment strategies compared to other database with other patient populations.

9.10 Other Aspects

9.10.1 Analysis Limitations

Analyses using DaVita data will be limited to years 2011-2013. Missing data will likely be minimal and will not likely impact interpretation of the results.

10. Protection of Human Subjects

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy.

To further ensure the privacy and confidentiality of the data utilized for this project, DaVita Clinical Research will store and analyze the identifiable data on both a single

SQL Server (SEA-DATAWH1) and a server dedicated for analysis (SEA-DCRSAS01, identified as the "SAS Server"). Network access to the servers is granted via an Active Directory account (user name and password) when a person is authorized to work within DaVita via DaVita personnel systems. Access to the data utilized for this project will be granted by Joe Weldon, Director and Data Custodian. Access to data on the server(s) will be restricted to research team participants providing attestation of training and acceptance of policies and procedures.

Research with the data will be performed on a client-server basis, with data residing only within the server(s) along with all processing. Researchers will physically work with the data in many remote locations utilizing encrypted CISCO VPN (168bit 3-DES HMAC-MD5) connectivity. All research reports, publications, and aggregates stored locally are protected by Credant Mobile Guardian encryption software on DaVita owned equipment, governed by signed attestation. It is required that they use both fixed equipment and portable devices to access protected health information, since they have no company-provided workspace, and the use of portable devices is covered in both DaVita policies and compliance training require annually.

All protected health information is governed by the DaVita Code of Conduct and Compliance policies. Data removal, transport and transmission restrictions are refreshed and attested annually. In addition, special extensions of this policy govern the specific inventory, handling and usage of patient data.

11. Management and Reporting of Adverse Events/Adverse Reactions

Individual event collection and reporting is not applicable to this study. Reporting of adverse events is not applicable as the data abstracted from the healthcare/claims databases in this study do not contain physician attribution of causality of adverse events to any medicinal products.

11.1 Safety Event Definitions

11.1.1 Definition of Adverse Events

Not applicable.

11.1.2 Adverse Drug Reactions (ADRs)

Not applicable. This is a non-interventional study based on secondary use of data and the data source being used does not contain attribution to specific medications.

11.2 Definition of Serious Adverse Events

Not applicable.

11.2.1 Serious Adverse Drug Reactions (SADRs)

Not applicable. This is a non-interventional study based on secondary use of data and the data source being used does not contain attribution to specific medications.

11.2.2 Definition of Other Safety Findings

Not applicable. Data on other safety findings will not be available.

11.2.3 Not applicable Definition of Product Complaints

Not applicable. Product complaints will not be collected.

11.2.4 Reportable Events and Reporting Timeframes

Not applicable.

12. Plans for Disseminating and Communicating Study Results

The protocol and final report of results will be posted to the European Medicines Agency and other appropriate entities according to the guidelines for post authorization safety studies.

12.1 Publication Plan

Results generated from this analysis will be published in a relevant nephrology, epidemiology, or general medicine journal. Results will also be presented at a highly frequented professional conference.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to: the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; (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, 3, and 4.

- When a large, multicenter 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 (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The contractual agreement between the institution, Investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

13. References

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11. Messa P, Macario F, Yaqoob M, et al. The OPTIMA study: assessing a new cinacalcet (Sensipar/Mimpara) treatment algorithm for secondary hyperparathyroidism. *Clinical journal of the American Society of Nephrology : CJASN.* Jan 2008;3(1):36-45.
12. Kilpatrick RD, Newsome BB, Zaun D, et al. Evaluating real-world use of cinacalcet and biochemical response to therapy in US hemodialysis patients. *American journal of nephrology.* 2013;37(4):389-398.
13. *U.S. Renal Data System, USRDS 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2013.*

14. Harris RZ, Padhi D, Marbury TC, Noveck RJ, Salfi M, Sullivan JT. Pharmacokinetics, pharmacodynamics, and safety of cinacalcet hydrochloride in hemodialysis patients at doses up to 200 mg once daily. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* Dec 2004;44(6):1070-1076.

14. Annexes

Annex 1. List of Stand-alone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	7-8
1.1.2 End of data collection[2]	☒	☐	☐	7-8
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	7-8
1.1.6 Final report of study results.	☒	☐	☐	7-8

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	8-9
2.1.2 The objective(s) of the study?	☒	☐	☐	9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	11
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	17
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	17

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	12

[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.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	17-19

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	11
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	11
4.2.2 Age and sex?	☒	☐	☐	11
4.2.3 Country of origin?	☒	☐	☐	11
4.2.4 Disease/indication?	☒	☐	☐	11
4.2.5 Co-morbidity?	☒	☐	☐	14
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	11

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	12-14
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	20
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	11
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	12-13
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	12-13, 20-21

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	13, 17
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	17

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	15-16
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	15-16
8.1.3 Covariates?	☒	☐	☐	15-16
8.2 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)	☒	☐	☐	15-16
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	15-16
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	13-14
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of	☐	☒	☐	

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
Diseases (ICD)-10) 8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐ ☒	☐ ☐	☒ ☐	14
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	15

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	16

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	17-19
10.3 Are descriptive analyses included?	☒	☐	☐	17-19
10.4 Are stratified analyses included?	☒	☐	☐	17-19
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	17
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	17-19

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	21
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	16

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.3 Are methods of quality assurance described?	☒	☐	☐	20
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	20
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Independent review of study results will only be through submission to peer-reviewed journal.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	20-21
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	20-21
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	16
12.3 Does the protocol address other limitations?	☒	☐	☐	20-21

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	21-22
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	21-22

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	8

Comments:

Per SOPs, a process is in place to amend study protocols.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	23-24
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	23-24

Comments:

Annex 3. Sample Safety Reporting Form

Not applicable.

Annex 4. Pregnancy and Lactation Notification Worksheets

Not applicable.

Annex 5.

Tables

Table 2: Mock-up demographic descriptions of patients on hemodialysis taking cinacalcet who were followed up for x months

Variable	Overall (N)	Ca > 8.4 mg/dL (n)	Ca < 8.4 mg/dL (n)
Age, years*	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Sex			
Male	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)
Race/ethnicity			
White	n (%)	n (%)	n (%)
Black	n (%)	n (%)	n (%)
Hispanic	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
Access			
Catheter	n (%)	n (%)	n (%)
Fistula	n (%)	n (%)	n (%)
Graft	n (%)	n (%)	n (%)
Post-dialysis weight, kg[a]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Vintage, months[a]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Calcium, mg/dL[b] (including prior trajectory)	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Phosphorus, mg/dL[b] (including prior trajectory)	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
PTH, pg/mL[b] (including prior trajectory)	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Kt/V[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Albumin, g/dL[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Alkaline phosphatase, U/L[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max

Abbreviations: PTH, parathyroid hormone; SD, standard deviation.

[a] Described as of date of hypocalcemia diagnosis.

[b] Value concurrent with or most proximally preceding index date.

Table 3: Mock-up demographic descriptions of patients on hemodialysis who develop hypocalcemia while taking cinacalcet

Variable	Overall (N)	Ca < 7.5 mg/dL (n)	Ca = 7.5-7.9 mg/dL (n)	Ca = 8.0-8.4 mg/dL (n)
Age, years*	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Sex				
Male	n (%)	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)	n (%)
Race/ethnicity				
White	n (%)	n (%)	n (%)	n (%)
Black	n (%)	n (%)	n (%)	n (%)
Hispanic	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)
Access				
Catheter	n (%)	n (%)	n (%)	n (%)
Fistula	n (%)	n (%)	n (%)	n (%)
Graft	n (%)	n (%)	n (%)	n (%)
Post-dialysis weight, kg[a]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Vintage, months[a]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Calcium, mg/dL[b] (including prior trajectory)	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Phosphorus, mg/dL[b] (including prior trajectory)	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
PTH, pg/mL[b] (including prior trajectory)	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Kt/V[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Albumin, g/dL[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Alkaline phosphatase, U/L[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max

Abbreviations: PTH, parathyroid hormone; SD, standard deviation.

[a] Described as of date of hypocalcemia diagnosis.

[b] Value concurrent with or most proximally preceding index date.

Table 4: Mock-up treatment history among patients on hemodialysis who develop hypocalcemia while taking cinacalcet[a]

	Overall (N)	Ca <7.5 mg/dL (n)	Ca 7.5-7.9 mg/dL (n)	Ca 8.0-8.4 mg/dL (n)
Cinacalcet				
Use	100%	%	%	%
Dose	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
New Users, %	%	%	%	%
Stable Dose titration[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Up Titration[c]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Down Titration[d]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Calcium-Based Binders				
Use, %	%	%	%	%
Dose	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
New Users, %	%	%	%	%
Stable Dose titration[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Up Titration[c]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Down Titration[d]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Vitamin D				
Use, %	100%	%	%	%
Dose	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
New Users, %	%	%	%	%
Stable Dose titration[b]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Up Titration[c]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Down Titration[d]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Transition: Calcitriol to doxercalciferol, %	100%	%	%	%
Transition: doxercalciferol to paracalcitol, %	%	%	%	%

Dialysate Calcium, mEq/L	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Joint Distributions	%	%	%	%

Abbreviations: Ca, calcium.

[a] At index date

[b] Stable dose titration defined as those supplied dose day = 0 supplied dose day -31.

[c] Up titration defined as those supplied dose day 0 > supplied dose day -31.

[d] Down titration defined as those supplied dose day 0 < supplied dose day -31.

Table 5: Mock-up of initial physician response to hypocalcemia among patients on hemodialysis taking cinacalcet

	Responses (measures undertaken between days 0 to 30) (N)
Discontinue Cinacalcet[a]	n, %
Reduce Cinacalcet Dose	n, %
Add or Up Titrate Calcium-based Binder	n, %
Add or Up Titrate Activated Vitamin D	n, %
Change to More Calcemic-activated Vitamin D	n, %
Increase Dialysate Calcium	n, %
No Response	n, %
Joint distributions[b]	n, %

[a] Defined as no prescription fill occurring before, on, or within 30 days following the date on which prior supply of cinacalcet is exhausted. Date ascribed to discontinuation will be the later of date of last fill or index date.

[b] Particular joint distributions of interest will be determined once the empiric distribution of individual responses is observed.

Table 6: Mock-up of physician responses to hypocalcemia stratified by discontinuation of cinacalcet[a]

	Days 0-30	Days 0-60	Days 0-90
Cinacalcet discontinued by day 90 (n)			
Add or Up Titrate Calcium-based Binder	n, %	n, %	n, %
Add or Up Titrate Activated Vitamin D	n, %	n, %	n, %
Change to More Calcemic-activated Vitamin D	n, %	n, %	n, %
Increase Dialysate Calcium	n, %	n, %	n, %
No Response	n, %	n, %	n, %
Joint distributions[b]	n, %	n, %	n, %
Cinacalcet not discontinued by day 90 (n)			
Reduce Cinacalcet Dose	n, %	n, %	n, %
Add or Up Titrate Calcium-based Binder	n, %	n, %	n, %
Add or Up Titrate Activated Vitamin D	n, %	n, %	n, %
Change to More Calcemic-activated Vitamin D	n, %	n, %	n, %
Increase Dialysate Calcium	n, %	n, %	n, %
No Response	n, %	n, %	n, %
Joint distributions[b]	n, %	n, %	n, %

[a] Analysis considers patients who remained in study through day 90.

[b] Particular joint distributions of interest will be determined once the empiric distribution of individual responses is observed.

Table 7: Mock-up of calcium recovery in patients on hemodialysis who develop hypocalcemia while taking cinacalcet

Index Calcium (recovery definition)	**% of patients who recovered**		
	Day 30	**Day 60**	**Day 90**
Ca < 7.5 mg/dL (recovery defined as Ca ≥ 7.5 mg/dL) (n)	n, %	n, %	n, %
Ca = 7.5 – 7.9 mg/dL (recovery defined as Ca ≥ 8.0 mg/dL) (n)	n, %	n, %	n, %
Ca = 8.0 – 8.5 mg/dL (recovery defined as Ca ≥ 8.5 mg/dL) (n)	n, %	n, %	n, %

Table 8: Mock-up of cinacalcet reinitiation in patients on hemodialysis who develop hypocalcemia who discontinue cinacalcet use

Index Calcium	**% of patients who reinitiated cinacalcet**		
	Day 30	**Day 60**	**Day 90**
Ca < 7.5 mg/dL (n)	n, %	n, %	n, %
Ca = 7.5 – 7.9 mg/dL (n)	n, %	n, %	n, %
Ca = 8.0 – 8.5 mg/dL (n)	n, %	n, %	n, %

Table 9: Mock-up of demographics of patients who resumed cinacalcet following hypocalcemia

Variable	Ca < 7.5 mg/dL (n)		Ca =7.5-7.9 mg/dL (n)		Ca = 8.0-8.5 mg/dL (n)	
	Index Time	Cinacalcet Reinitiation	Index Time	Cinacalcet Reinitiation	Index Time	Cinacalcet Reinitiation
Age, years[a]	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Sex						
Male	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Race/ethnicity						
White	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Black	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Hispanic	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Access						
Catheter	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fistula	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Graft	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Post-dialysis weight, kg	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Vintage, months	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Calcium, mg/dL	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Phosphorus, mg/dL	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
PTH, pg/mL	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Kt/V	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max
Cinacalcet Dose	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max	mean +/- SD median [IQR] min-max

Abbreviations: PTH, parathyroid hormone; SD, standard deviation.