PASS INFORMATION

Title	Effect of cinacalcet discontinuation on biochemical control for Medicare beneficiaries with Part D coverage treated within a large US dialysis provider
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Research Question and Objectives	Primary Objectives: 1. To describe risk factors for first discontinuation of cinacalcet among center-based hemodialysis patients, 2. To describe factors associated with reinitiation of cinacalcet among center-based hemodialysis patients, 3. To describe the trajectory of parathyroid hormone, calcium, and phosphorus laboratory values following the discontinuation of cinacalcet by center-based hemodialysis patients.
Countryof Study	United States
Author	Paul Dluzniewski, PhD Thousand Oaks, United States 805-447-7311

Marketing Authorization Holder(s)

Marketing Authorization Holder	Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320 United States 805-447-3505
MAH Contact Person	Paul Dluzniewski, PhD pdluznie@amgen.com

TABLE OF CONTENTS

1. ABSTRACT

- **Title**

Effect of cinacalcet discontinuation on biochemical control for Medicare beneficiaries with Part D coverage treated within a large US dialysis provider

- Version: 1.0
- Date: 20 March 2015
- Authors: Paul Dluzniewski, Amgen Inc.;
  Diane Reams, University of North Carolina at Chapel Hill
  M. Alan Brookhart, University of North Carolina at Chapel Hill

- **Keywords**

Secondary hyperparathyroidism, Cinacalcet, Persistence, Hemodialysis

- **Rationale and Background**

Secondary hyperparathyroidism (SHPT) is a condition that is present in a large portion of patients with chronic kidney disease (CKD) on dialysis resulting in reduced control of parathyroid hormone (PTH), calcium (Ca), and phosphorus (P). Cinacalcet, an oral calcimimetic agent, is approved for the treatment of SHPT in patients with CKD on dialysis. Despite evidence of the benefits of managing SHPT-related biochemistries with cinacalcet, recent real-world and clinical trial evidence indicate that treatment discontinuation is common. As with most chronically administered medications, the putative benefits of therapy are thought to manifest when patients remain persistent, and as a result, the benefit of cinacalcet among patients who discontinue may be limited. Currently, real world data are lacking regarding the risk factors for cinacalcet discontinuation and factors that influence potential reinitiation, as well as the changes in PTH, Ca, and P values that occurs after discontinuation of treatment.

- **Research Question and Objectives**

Primary Objective(s):

1. Described risk factors for first discontinuation of cinacalcet among center-based hemodialysis patients,
2. Described factors associated with reinitiation of cinacalcet among center-based hemodialysis patients,
3. Described the trajectory of parathyroid hormone, calcium, and phosphorus laboratory values following the discontinuation of cinacalcet by center-based hemodialysis patients.

- **Study Design**

Retrospective cohort study.

- **Setting**

01 January 2007 through 31 December 2010

- **Subjects and Study Size, Including Dropouts**

17,763 eligible new users of cinacalcet with Medicare coverage receiving center-based hemodialysis from a U.S. dialysis provider contributed 111,047 30-day follow-up intervals.

- **Variables and Data Sources**

Patient demographics, financial considerations, biochemical values (calcium, phosphorus, parathyroid hormone, Kt/V, albumin, and alkaline phosphatase), comorbidities, dialysis care factors, and treatment history (cinacalcet use and dose, calcium-based binders use and dose, vitamin D use and dose, and dialysate calcium) from a clinical database of a large dialysis provider merged with administrative data from the United States Renal Data System.

- **Results**

Over half of all patients discontinued cinacalcet by month 4. Proximal PTH levels <150 pg/mL were associated with discontinuation: HR = 1.23 (95% CI 1.11, 1.36), whereas low Ca (<7.5 mg/dL) was only weakly associated, HR = 1.10 (95% CI 0.92, 1.32). Entering the Medicare Part D gap period increased discontinuation risk: HR = 1.19 (95% CI 1.00,1.42), and low-income subsidy status decreased the risk of discontinuation: HR = 0.77 (95% CI 0.69, 0.86). Increasing PTH and Ca levels: HR = 1.15 (95% CI 1.08, 1.23) and HR = 1.23 (95% CI 1.15, 1.31), respectively, may be early markers of discontinuation.

- **Discussion**

Early discontinuation following cinacalcet initiation is common, and occurs frequently for clinical or economic reasons. It also appears that an unanticipated increase in biochemical levels may be an early marker of patient discontinuation. Our study does not provide data that impacts the benefit-risk profile of cinacalcet.

- **Marketing Authorization Holder**

Amgen Inc.

- **Names and Affiliations of Principal Investigators**

Paul Dluzniewski, PhD, Amgen Inc.

Susan Yue, MD, Amgen Inc.

Thy Do, PhD, formally with Amgen Inc.

Brian Bradbury, PhD, Amgen Inc.

M. Alan Brookhart, PhD, University of North Carolina at Chapel Hill

Diane Reams, PharmD, University of North Carolina at Chapel Hill

Abhijit Kshirsagar, MD, University of North Carolina at Chapel Hill

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
Ca	Calcium
CKD	Chronic kidney disease
ESRD	End-stage renal disease
KDIGO	Kidney Disease: Improving Global Outcomes
MBD	Mineral and Bone Disorder
P	Phosphorus
PTH	Parathyroid hormone
SHPT	Secondary hyperparathyroidism
USRDS	United States Renal Data System

3. INVESTIGATORS

Key Sponsor Contact: Paul Dluzniewski

pdluznie@amgen.com, 805-447-7311

External Collaborators: M. Alan Brookhart

mabrook@email.unc.edu, 919-843-2639

Diane Reams

diane.reams@unc.edu, 919-966-7123

Abhijit Kshirsagar

abhijit_kshirsagar@med.unc.edu, 919-966-2561

University of North Carolina at Chapel Hill

Thy Do

thypdo@gmail.com

Amgen Collaborators: Brian Bradbury

bradbury@amgen.com, 805-313-4343

Susan Yue

syue@amgen.com, 805-447-2041

A list of all collaborating institutions and investigators will be made available upon request.

4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned Date	Actual Date	Comments
Start of data collection	01 December 2013	01 December 2013	
End of data collection	01 February 2014	01 April 2014	Additional analyses were conducted.
Registration in the EU PASS register (*for PASS only; if not applicable delete row)*	30 November 2013	11 February 2014	Delay in process.
Final report of study results	01 February 2015	20 March 2015	Delay in process.

6. RATIONALE AND BACKGROUND

Secondary hyperparathyroidism (SHPT) among patients with chronic kidney disease (CKD) is characterized by elevated levels of parathyroid hormone (PTH) and is often accompanied by abnormal levels of calcium and phosphorus.[1,2] Treatment options to control CKD-Mineral and Bone Disorder (MBD) parameters include modulation of calcium and phosphorus balance through dietary intake and dialysis, active vitamin D compounds, and phosphate binders.[3] The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommendations for the optimal range of PTH is two to nine times the assay's upper limit of normal reference range, with levels not to exceed approximately 600 pg/mL. Practitioners are also recommended to target the assay reference range for calcium and phosphorus.[4]

Another therapeutic option for the treatment of SHPT in patients on dialysis is cinacalcet (Sensipar®/Mimpara®, Amgen Inc., Thousand Oaks, CA), a calcimimetic agent that directly lowers PTH, and subsequently, calcium and phosphorus.[5,6] However, post-marketing studies in real world settings have found adherence to cinacalcet to be sporadic, which may limit its effectiveness.[7-9] Identifying factors associated with discontinuation may help healthcare providers better understand and prevent non-adherence to therapy. Previous studies examining adherence to cinacalcet have been limited by size, the inability to identify time-varying covariates, and inaccuracies in identifying therapy start and stop dates.[7,10-12]

Using detailed clinical, laboratory, and healthcare utilization data from a large cohort of patients receiving hemodialysis, we sought to describe the experience of patients initiating cinacalcet, including the trajectory of CKD-MBD parameters following initiation, as well as factors predicting discontinuation and reinitiation of therapy.

7. RESEARCH QUESTION AND OBJECTIVES

This study had three primary objectives:

1. Described risk factors for first discontinuation of cinacalcet among center-based hemodialysis patients,

2. Described factors associated with reinitiation of cinacalcet among center-based hemodialysis patients,

3. Described the trajectory of parathyroid hormone, calcium, and phosphorus laboratory values following the discontinuation of cinacalcet by center-based hemodialysis patients.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1 Study Design

We utilized a retrospective cohort study design with a 6-month baseline period to identify laboratory values and other factors that may be risk factors for discontinuation and reinitiation among new users of cinacalcet. Using this cohort, we also described the trajectory of laboratory values at varying time points following the discontinuation of cinacalcet.

9.2 Setting

Definition of Time Periods

Study Period

The study period was 01 January 2007 through 31 December 2010. Even though cinacalcet was available prior to 01 July 2006, this time period was chosen because the start of Medicare Part D was 01 January 2006, and the first 6 months of Medicare Part D data has been noted to be unreliable for research purposes.

Baseline Period

The baseline period was 6 months prior to first filled prescription of cinacalcet.

Study Follow-up Period

Objective 1: Follow-up began at the end of the 1st 30-day fill for new users. New users were defined as no use of cinacalcet during a prior 6-month baseline period followed by a cinacalcet fill with at least a 30-day supply. The administrative end of follow-up was 31 December 2010. Patients were censored at the earliest date of death, lost to follow-up, transplantation, parathyroidectomy, loss of Medicare Part A, B, or D eligibility, or disenrollment from DaVita.

Objective 2: Follow-up began at the first discontinuation of cinacalcet. The administrative end of follow-up was 31 December 2010. Patients were censored at the earliest date of death, lost to follow-up, transplantation, parathyroidectomy, loss of Medicare Part A, B, and D eligibility, or disenrollment from DaVita.

Objective 3: Follow-up began at the end of the 1st 30-day fill for new users. The follow-up period was time between the end of the days supply and the fill of the next prescription. Laboratory values (timing and values) were determined until another fill of cinacalcet was documented at which time the patient was censored. Follow-up began again following the end of subsequent fills of cinacalcet, and laboratory values were determined until the patient was censored at the next fill of cinacalcet, death, transplantation, parathyroidectomy, 1-year after discontinuation, loss of Medicare Part A, B, or D eligibility, disenrollment from DaVita or the administrative end of follow-up, whichever came first. The administrative end of follow-up was 31 December 2010.

Time at Risk

Objective 1: The time at risk was the time from the end of the 1st 30-day use of cinacalcet, defined as the index date, until the determination of discontinuation, the administrative end of follow-up, 31 December 2010, or censoring due to death, transplantation, parathyroidectomy, loss of Medicare Part A, B, or D eligibility, or disenrollment from DaVita.

Objective 2: The time at risk was the time from first discontinuation until reinitiation of cinacalcet, the administrative end of follow-up, 31 December 2010, or censoring due to death, transplantation, parathyroidectomy, loss of Medicare Part A, B, or D eligibility, or disenrollment from DaVita.

Objective 3: The time at risk began at the end of the days supply dispensed at the index date (defined above), for example day 31 of a 30-day prescription. The follow-up period was time between the end of the days supply and the fill of the next prescription. Laboratory values (timing and values) were determined until another fill of cinacalcet is documented at which time the patient was censored. The next period of time at risk began at the end of subsequent fills of cinacalcet, and laboratory values were determined until the patient was censored at the next fill of cinacalcet, the administrative end of follow-up, 31 December 2010, or censoring due to death, transplantation, parathyroidectomy, loss of Medicare Part A, B, or D eligibility, or disenrollment from DaVita.

9.3 Subjects

The study population was derived from a source population of adult patients (18 years and older) with ESRD (end-stage renal disease) who were receiving center-based hemodialysis at a DaVita facility in the United States and had Medicare as their primary insurer between 01 July 2006 and 31 December 2010.

We included male and female patients in this study if they met the following criteria:

- Aged 18 years and older,
- Had at least 90 days of coverage in Medicare's ESRD program,
- Continuous Medicare Part A, B, and D coverage during the study period, and
- In-center hemodialysis at a DaVita facility
- Filled at least one 30 day cinacalcet prescription
- Had 6 months without cinacalcet use prior to initial prescription

We excluded patients if they met the following criteria:

- Enrollment in Medicare Advantage (Medicare's HMO)
- Parathyroidectomy prior to start of follow-up
- Initial cinacalcet prescription of >30 days or <30 days

9.4 Variables

Study Outcomes

Objective 1: The outcome was the probability of first cinacalcet discontinuation at consecutive 30-day intervals following the index date of cinacalcet.

Objective 2: The outcome was the probability of cinacalcet reinitiation following the first discontinuation period.

Objective 3: The outcome was population mean values of calcium, phosphorus, and parathyroid hormone up to one year following any discontinuation of cinacalcet.

Covariates

We identified from Medicare and clinical files demographic, laboratory, clinical variables, and comorbidities. Covariates included demographic characteristics (e.g., age, sex, race, Medicaid eligibility, census region, year), clinical characteristics (e.g., cause of ESRD, time on dialysis,

body mass index, type of vascular access, number of hospital days), baseline laboratory variables (e.g., PTH, calcium, phosphorus), time-varying laboratory variables divided into categories consist with recognized normal and abnormal values , and several time-varying comorbidity measures. International Classification of Diseases Ninth Revision codes, Current Procedural Terminology codes, and Healthcare Common Procedure Coding System codes were used to identify comorbidities and procedures. Descriptions and definitions of baseline and time-varying covariates are provided in Table 1 and Table 2.

Table 1. Baseline covariates

We evaluated the following covariates at baseline (6 months prior to new cinacalcet use). For the comorbid conditions identified using information provided from the Medicare claims data (part A or B), we considered comorbid conditions as present if at least one inpatient, home health, or skilled nursing facility claim, or at least two outpatient or physician/supplier claims separated by at least 7 days are identified during the baseline period.

Type of Variable	Measurement and other notes
Demographics	
Patient age	Included in model as a categorical variable with 5-year age groups
Patient sex	Indicator for female sex
Patient race	As reported on the Medical Evidence form (CMS-2728) Categories: Black, Non-Black, Hispanic, Non-Hispanic
Dialysis vintage	Time since start of renal replacement therapy Categories: $\leq$ 1 year, >1-3 years, >3-5 years, $\geq$ 5 years
Cause of end-stage renal disease	Classified as diabetes, hypertension, glomerular nephritis, or other
Body mass index	As reported in the clinical data or on the Medical Evidence form (CMS-2728)
Medicaid eligibility	As reported on the Medical Evidence form (CMS-2728)
Low income subsidy	Reported as a categorical variable for cost share for each enrollment month. Categories include: Category 1 = LIS, 100% premium-subsidy and high copayment Category 2 = LIS, 100% premium-subsidy and 15% copayment Category 3 = LIS, 75% premium-subsidy and 15% copayment Category 4 = LIS, 50% premium-subsidy and 15% copayment Category 5 = LIS, 25% premium-subsidy and 15% copayment Category 6 = LIS, 75% premium-subsidy and 15% copayment Category 7 = LIS, 50% premium-subsidy and 15% copayment Category 8 = LIS, 25% premium-subsidy and 15% copayment
Laboratory Values	
Serum Parathyroid Hormone (pg/mL)	Most proximal serum parathyroid hormone value from baseline to index date Categories:

	Low <150 pg/mL Normal 150-300 pg/mL High >300 pg/mL
Corrected serum calcium level (mg/dL)	Most proximal serum calcium value from baseline to index date Categories: Low <7.5 mg/dL Normal 7.6-9.5 mg/dL High >9.5 mg/dL
Serum phosphorus level (mg/dL)	Most proximal serum phosphorus value from baseline to index date Categories: Low <3.5 mg/dL Normal 3.5-5.5 mg/dL High 5.5 mg/dL
Serum Albumin (g/dL)	Most proximal serum albumin value from baseline to index date Categories: Low <3.2 g/dL Normal ≥ 3.2 g/dL
Comorbidities	
Rheumatoid arthritis / collagen vascular disease	ICD-9 701.0, 710.xx, 714.xx, 720.xx, 725.xx
Diabetes	ICD-9 250.xx
Angina	ICD-9 413.x
Coronary artery disease / Atherosclerosis	ICD-9 414.0x, 429.2x, 429.5x, 429.7x, 440.x
Cerebrovascular disease	ICD-9 342, 344.81, 430-438, 997.02, V12.54
Myocardial infarction	ICD-9 410.x, 411.x
Malignancy	ICD-9 140.xx – 172.xx, 179.xx – 199.xx, 174.0 – 175.9x, 202.0 – 202.3x, 202.50 – 203.01, 200.xx, 201.xx, V10, 173.3x,173.9x, 232.9x, 233.0, 233.1x, 338.3x, 799.4x, 203.8x, 238.6x, 273.3x, V67.2x, 789.51, 795.82
Congestive heart failure	ICD-9 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428, 785.51, 425.4x-425.9x HCPCS G8027, G8028
Chronic obstructive pulmonary disease and asthma	ICD-9 491.x, 492.x, 493.x, 494.x, 496.x, 510.x
Fracture	ICD-9 805.xx-828.xx
Gastrointestinal bleed	ICD-9

	578.xx
Hyperlipidemia	ICD-9 272.xx
Hypertension	ICD-9 401 - 405, but not in (402.11, 402.91, 404.11, 404.13, 404.91, 404.93)
Liver disease	ICD-9 070.32, 070.33, 070.54, 456.20, 456.21, 456.0, 456.1x, 571.0, 571.2x - 571.6x, 571.8x, 571.9x, 572.3x, 572.8x, V42.7, 570, 573.1-573.3
Hyperthyroidism	ICD-9 242.xx
Peripheral vascular disease	ICD-9 440.2x, 440.3x, 440.8x, 440.9x, 443.9x
Peptic ulcer disease	ICD-9 530.2, V12.71, 531 – 534
Parathyroidectomy	ICD-9 hospital procedure codes 06.81, 06.89
Concomitant Medications	
Number of concomitant medications at time of new cinacalcet use	Categories 1-5 6-10 ≥11
Intravenous vitamin D	Categories Yes No Vitamin D intravenous: J0635 (calcitriol 1mcg), J0636 (calcitriol 0.1mcg), J2500 (Paricalcitol 5mcg), J2501 (Paricalcitol 1mcg), J1270 (Doxercalciferol 1mcg)
Oral phosphate binder use	Categorical variable: Present yes or no Sevelamer hydrochloride (Renagel®) Sevelamer carbonate (Renvela®) Lanthanum carbonate (Fosrenol®) Calcium acetate (PhosLo®)

Table 2: Time-varying covariates

We evaluated the following time-varying covariates at 30-day intervals following the start of follow-up. Specific information concerning identification of comorbid conditions identified using information provided from the Medicare claims data (part A or B) is provided in the table below.

Type of Variable	Measurement and other notes
Laboratory Values	
Serum Parathyroid Hormone (pg/mL)	The serum parathyroid hormone value during the time-varying covariate assessment period that is most proximal to the estimated discontinuation or reinitiation date.
Corrected serum calcium level (mg/dL)	The serum calcium value during the time-varying covariate assessment period that is most proximal to the estimated discontinuation or reinitiation date.
Serum phosphorus level (mg/dL)	The serum phosphorus value during the time-varying covariate assessment period that is most proximal to the estimated discontinuation or reinitiation date.
Serum Albumin (g/dL)	The serum albumin value during the time-varying covariate assessment period that is most proximal to the estimated discontinuation or reinitiation date.
Concomitant Medications	
Intravenous Vitamin D use	Intravenous Paricalcitol and doxercalciferol doses were converted to intravenous calcitriol-equivalent doses according to the following conversion ratios: 4.6: 1 for paricalcitol: calcitriol and 3.1: 1 for doxercalciferol: calcitriol
Oral phosphate binder use	Categorical variable Present yes or no Sevelamer hydrochloride (Renagel®) Sevelamer carbonate (Renvela®) Lanthanum carbonate (Fosrenol®) Calcium acetate (PhosLo®)
Cardiovascular Events	
Acute myocardial infarction	ICD-9 410.xx in any diagnosis field of an inpatient claim
Congestive heart failure	ICD-9 428.xx in any diagnosis field of an inpatient claim
Stroke	ICD-9 codes 430, 431, 433.x1, 434, and 436 in any diagnosis field of an inpatient claim
Peripheral vascular disease event	ICD-9 and CPT codes in any diagnosis field of Part A or B files Lower extremity amputation 84.1×, 84.91 27295, 27590-92, 27598, 27880-82, 27888-89, 28800, 28805 Lower extremity peripheral angioplasty, atherectomy, or endarterectomy 38.18, 39.50 35302-06,35331, 35351, 35355, 35361, 35363, 35371-72, 35381, 35452, 35454, 35456, 35459, 35470, 35472-74, 35481-35483, 35485,

	35491-35493, 35495 Lower extremity peripheral bypass 39.25, 39.29 35521, 35533, 35537-41, 35546, 35548-49, 35551, 35556, 35558, 35563, 35565-66, 35571, 35582-83, 35585, 35587, 35621, 35623, 35637-38, 35641,35646-47, 35651, 35654, 35656, 35661, 35663, 35665-66, 35671 Repair, exploration, revision, resection of lower extremity arteries, or thrombectomy of graft 38.08, 38.38, 38.48, 39.49, 39.56, 39.57, 39.58 35226, 35256, 35286,35700, 35721, 35741, 35876, 35879, 35881, 35883, 35884 Non-coronary vessel percutaneous transluminal mechanical thrombectomy, or stents 39.90 37184-86, 37205-08
Cardiovascular mortality	Primary causes of death on CMS-Form 2746 coded as 23 (acute myocardial infarction) 25 (pericarditis, including cardiac tamponade) 26 (atherosclerotic heart disease) 27 (cardiomyopathy) 28 (cardiac arrhythmia) 29 (cardiac arrest, cause unknown) 30 (valvular heart disease) 31 (pulmonary edema due to exogenous fluid) 32 (congestive heart failure) 36 (cerebrovascular accident including intracranial hemorrhage)
Other Events	
Parathyroidectomy	ICD-9 hospital procedure codes 06.81, 06.89 in any diagnosis field of an inpatient claim
All cause mortality	
Adverse Events	
Nausea, Vomiting, diarrhea	ICD-9 564.5, 787.91, 787.0x Considered present if at least one inpatient, home health, or skilled nursing facility claim, or at least two outpatient or physician/supplier claims separated by at least 7 days are identified during the 30-day look back period. Categorical variable; yes or no
Seizure	ICD-9 333.2, 345, 345.0. 345.00, 345.01, 345.1, 345.10, 345.11, 345.2, 345.3, 345.4, 345.40, 345.41, 345.5, 345.50, 345.51, 345.8, 345.80, 345.81, 345.90, 345.91, 780.3

	Considered present if at least one inpatient, home health, or skilled nursing facility claim, or at least two outpatient or physician/supplier claims separated by at least 7 days are identified during the 30-day look back period. Categorical variable; yes or no
Hypocalcemia	Corrected serum calcium below 7.5mg/dl The serum calcium value during the time-varying covariate assessment period that is most proximal to the estimated discontinuation or reinitiation date Categorical variable; yes or no
Low parathyroid hormone level	Parathyroid hormone level below 150 pg/mL The serum parathyroid hormone value during the time-varying covariate assessment period that is most proximal to the estimated discontinuation or reinitiation date Categorical variable; yes or no
Other Covariates	
Current vascular access	Using access information obtained from the clinical data, we classified patients as having a catheter, fistula, or graft
Acute Care Hospitalization, in days	Determined from the United States Renal Data System (USRDS) file institutional claims file
Co-pay	Cost of cinacalcet prescription using Part D claims data
Donut Hole status	Determined from Medicare Part D file “Benefit Phase” variable. Categories: Covered prescription Cinacalcet prescription fill resulted in entrance into the gap period Cinacalcet prescription was filled while they were in the gap period Cinacalcet prescription fill resulted in exiting the gap period Cinacalcet prescription fill resulted in going through the gap period Other

9.5 Data Sources and Measurement

The data source for this study was the merged DaVita-Medicare database. DaVita owns and manages over 1,500 outpatient dialysis facilities located in urban, rural, and suburban areas throughout the U.S. Their database captures detailed clinical, laboratory, and treatment data on patients receiving care at all of their dialysis units. All data are collected using standardized electronic health record systems. Data from the DaVita clinical database (2004-2010) has been merged with the USRDS database for patients who have Medicare as the primary insurer from 2004 to 2010.

The USRDS is a registry that collects, analyses, and distributes national data on all ESRD patients in the United Sates, irrespective of insurance coverage or age. All Medicare Part A and B claims are also included within the USRDS Standard Analytical Files (SAFs). Institutional claims within Medicare Part A comprise all hospital inpatient, hospital-based outpatient, skilled nursing facility, home health agency, and hospice claims. Hospitalization data include admission source, length of stay, discharge destination, and associated diagnoses and procedures for each patient. Medicare Part B Physician/Supplier claims include durable medical equipment charges along with physician services (e.g., office-based outpatient visits) and supplies.

The USRDS Patient File contains information describing patient race, age, date of death, first service date, and other demographic characteristics. The Medical Evidence (Medevid) SAF derived from the Center for Medicare & Medicaid Services (CMS) End Stage Renal Disease Medical Evidence Report: Medicare Entitlement and/or Patient Registration form (Form 2728) also contains demographic information and detailed clinical information including comorbidities, baseline lab values, and body mass index (BMI). The 1995 version of Form 2728 made it mandatory for all dialysis providers to complete the form for all their new ESRD patients, irrespective of Medicare eligibility. The most recent, revised 2005 version of the form added new variables including data on pre-dialysis nephrology care, dietician care, and vascular access. Death data is obtained from the CMS-2746 ESRD Death Notification Form, providing the date along with the primary and secondary causes of death for over 99% of patients.

The USRDS Facility File contains dialysis facility-level data derived from the CMS Annual Facility Survey (AFS), a survey that all Medicare-approved dialysis facilities are mandated to complete each calendar year. In addition to facility-level characteristics such as geographic

region, for-profit status, and chain, the file reports on the number of patients being treated at each dialysis facility or treatment center at the end of each calendar year.

From 2006 forward, Medicare Part D pharmacy claims data are available in the USRDS.

Data files within the merged DaVita-Medicare database can be linked via a unique patient identifier for each patient. The linkage between the data files within the DaVita clinical database and the USRDS database, as well as the merge between these two databases was completed prior to the database being delivered to UNC.

Validity and Reliability

The validity, completeness and reliability of the USRDS data have been examined by two early studies conducted by the USRDS.[13] In a study to validate the USRDS data, data on a sample of over 1,500 ESRD patients were compared with data from the patient's medical chart. Fifty variables were examined with an average concordance rate of 90.6%.[14] In the second study, completeness and reliability of the USRDS data was evaluated by comparing data on Medicare ESRD patients living in Michigan to available data from the Michigan Kidney Registry. Approximately 5% of the patients were unmatched, suggesting a high level of completeness of the USRDS data set.[13] Prospective validation of the data, however, is not performed on a continuous basis.

9.6 Bias

For our final results, we report predictors of discontinuation and reinitiation independent of other covariates. We adjusted for possible confounding from other covariates when modeling the association between the individual factors and discontinuation and reinitiation.

9.7 Study Size

We identified 17,763 patients who met our study entry requirements and contributed 111,047 30-day follow-up intervals.

9.8 Data Transformation

Refer to Table 1 (Baseline covariates), Table 2 (Time-varying covariates), and Table 3 (Baseline Characteristics Overall and by Sex).

9.9 Statistical Methods

9.9.1 Main Summary Measures

To describe the treatment groups, we report means and frequencies of all covariates within each treatment group and subgroups of interest. Trends in means for each lab value were

plotted for the months after initiation and discontinuation. These plots were smoothed and 95% confidence intervals computed using smoothing splines. For each 30-day interval, we fit a logistic model and estimated the probability of discontinuation or reinitiation given the most recent time-varying covariates in the 90 days prior to the 30-day interval in which discontinuation or reinitiation was thought to have occurred. Although each patient could contribute multiple 30-day intervals to the analytic dataset, we did not adjust for repeated measures since each patient, per our study design, could only discontinue once. Patients were censored administratively on December 31, 2010, and for loss to follow-up, transplant, discontinuation of hemodialysis, death, parathyroidectomy, or loss of Medicare Parts A, B, or D coverage.

9.9.2 Main Statistical Methods

Objective 1

For objective 1, the probability of drug discontinuation was estimated at 30-day intervals after the start of follow-up. At the end of each 30-day interval, we determined if the patient discontinued cinacalcet or continued treatment. Patients were defined as discontinuing cinacalcet if there was greater than a 30-day gap from their last pill day, calculated from the days supply dispensed, and the next fill of cinacalcet.

For each 30-day interval, we created and fit a logistic model for drug discontinuation. The model was based on various time-varying covariates determined at the end of each 30-day interval during follow up. Although each patient may have contributed multiple 30-day intervals to the analysis dataset, we did not adjust for repeated measures since each patient could only discontinue once. In addition, a pooled logistic regression was used and we report the average effects of covariates across the 30-day intervals.

Objective 2

For objective 2, the probability of drug reinitiation was estimated at each 30-day interval following the discontinuation interval. For each 30-day interval, it was determined if the patient reinitiated cinacalcet (defined by any prescription claim for cinacalcet in the interval). The effect of covariates on the probability of reinitiation was estimated using logistic regression. Logistic regression was used to estimate the probability of reinitiating or not reinitiating cinacalcet given the various covariates determined at the end of the previous 30-day interval. Although each patient may have contributed multiple 30-day intervals to the analysis dataset, we did not adjust for repeated measures since each patient could only reinitiate once. In addition, a pooled

logistic regression was used and we report the average effects of covariates across the 30-day intervals.

Objective 3

For objective 3, follow-up began at the end of the days supply of the 1st prescription fill for new users. Laboratory values (timing and values) were determined until another fill of cinacalcet was documented at which time the patient was censored. Laboratory values immediately preceding discontinuation were used as the anchor point for the calculations of trajectories. Laboratory values following discontinuation as a function of time (up to one year) were modeled using cubic smoothing splines. Cubic smoothing splines are defined as the function $f()$ that minimizes the following penalized least-squares objective function:

$$\sum_{i=1}^{n}[y_i - f(x_i)]^2 + \lambda \int_a^b [f''(t)]^2 dt ,$$

where $a \le x_1 .... \le x_n \le b$ and $f()$ must have continuous first and second derivatives. The solution to this problem is a spline that has knots at the unique values of x_i. The penalty term penalizes the fit for non-linearity and reduces the effective dimensionality of the spline and makes it identifiable (estimable). We let the smoothing parameter be set by the cross-validation approach that attempts to minimize the mean-squared error of the resulting fit. Generalized estimating equation methods were used to account for any repeated measures.

9.9.3 Missing Values

For missing laboratory values we used the carry forward method, considered to be synonymous with clinical practice. For other covariates, we conducted a complete case analysis and removed patients for whom not all data are available.

9.9.4 Sensitivity Analyses

A sensitivity analysis was performed to determine if reinitiation results were modified when biochemical results from 5, 7, and 14 days prior to the date of the laboratory value most proximal to reinitiation were used to predict reinitiation. This lag time could account for any delays between physician recognition of a laboratory abnormality and a decision to reinitiate cinacalcet.

9.9.5 Amendments to the Statistical Analysis Plan

Not applicable.

9.10 Quality Control

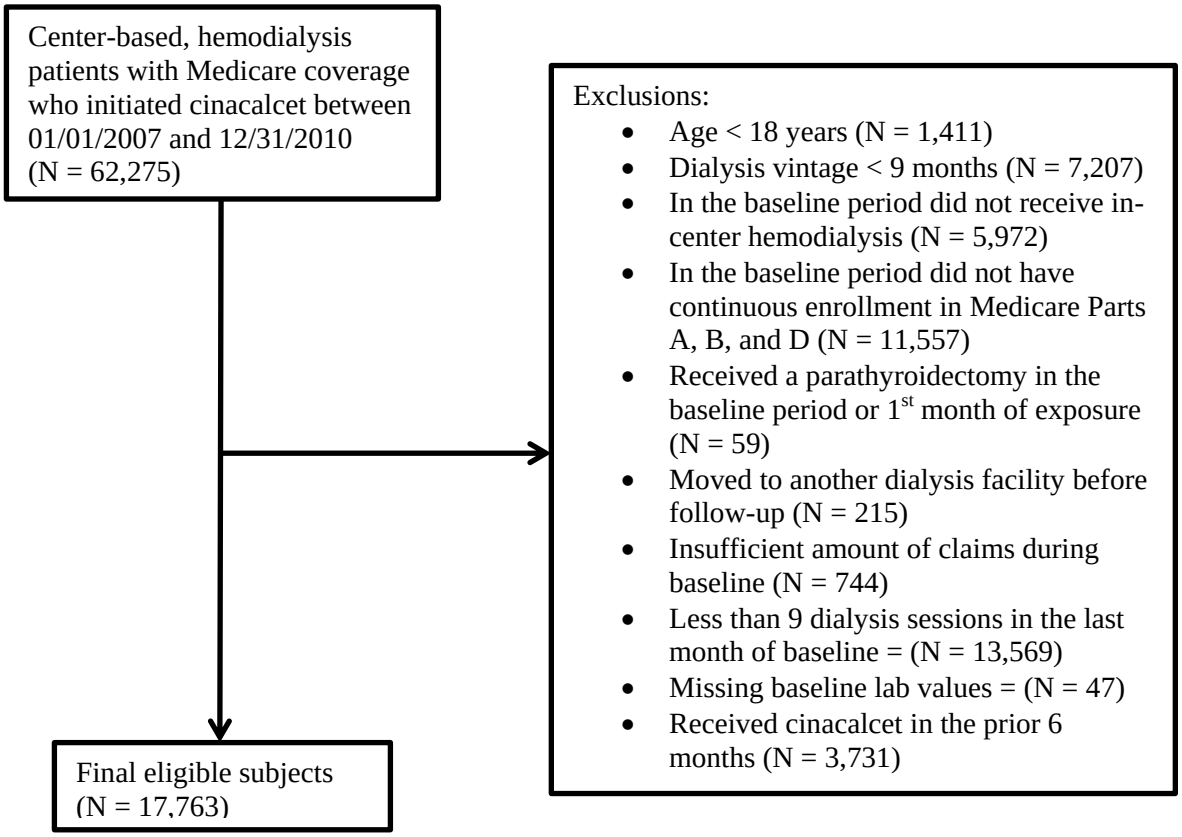
All data were pre-collected through CMS reimbursement systems and DaVita dialysis facilities. Because the data are either reimbursement-related or undergo institutional quality control systems, the quality and accuracy of the data were not a major concern. Clinician-informed trimming rules for lab values and doses of medications were used during the construction of the analytic data file.

10. RESULTS

10.1 Participants

We identified 17,763 patients who met our study entry requirements and contributed 111,047 30-day follow-up intervals. Table 3 presents patient characteristics of the primary cohort stratified by sex.

Figure 1. Cohort construction



10.2 Descriptive Data

At cinacalcet initiation, the average age was 56.7 years (standard deviation (SD) 14.5 years) and the average time on dialysis was 4.5 years (SD 4.3 years), 49.3% of the cohort was female, and 53.8% were African American. Several baseline financial factors were also identified. A history of receiving Medicaid benefits or having low-income subsidy was identified in 68.7% and 83.9%, respectively. Mean PTH calcium, and phosphorus at initiation were 642 pg/mL (SD 519 pg/mL), 9.4 mg/dL (SD 0.7 mg/dL), and 5.9 mg/dL (SD 1.7 mg/dL), respectively.

10.3 Outcome Data

The probability of discontinuation by month 4 was 56% and by month 12 was 73%. Of those who discontinued (N = 12,521), 76.3% (N = 9,558) reinitiated cinacalcet. The mean time to reinitiation was 4.0 months.

10.4 Main Results

Trends in the mean serum lab values of PTH, calcium, and phosphorus for the first 12 months following cinacalcet initiation, as well as after discontinuation, are shown in Figures 2-4. Following cinacalcet initiation, the levels of the three lab values fell and stabilized at approximately month 4. Mean PTH levels decreased from a baseline level of 642 pg/mL (SD 519 pg/mL) to levels between 375 and 400 pg/mL in months 4 through 12. Mean calcium levels decreased from a baseline level of 9.4 mg/dL (SD 0.7 mg/dL) to approximately 8.9 mg/dL during the 1st month and remained at levels slightly higher than 8.9 mg/dL between months 4 through 12. Of the 111,047 30-day intervals examined, 17,980 intervals (16.7%) had a PTH level less than 150 pg/mL and 1,934 (1.8%) had a calcium level less than 7.5 mg/dL, Table 5. Phosphorus levels decreased from a baseline mean level of 5.9 mg/dL (SD 1.7 mg/dL) to between 5.2 and 5.4 mg/dL in months 4 through 12. Following discontinuation, mean levels of PTH, calcium, and phosphorus increased and then stabilized at higher mean levels than those achieved while on therapy.

The probability of discontinuation by month 4 was 56% and by month 12 was 73%. Of those who discontinued (N = 12,521), 76.3% (N = 9,558) reinitiated cinacalcet. The mean time to reinitiation was 4.0 months. Predictors of cinacalcet discontinuation and reinitiation are presented in Table 4. All covariates considered can be found in Table 6. Baseline PTH, calcium, and phosphorus serum levels were not associated with discontinuation; however, levels most proximal to discontinuation were. Low proximal levels of PTH (<150 pg/mL) were associated with discontinuation, HR 1.23 (95% CI 1.12, 1.36). There was a slight association between calcium (<7.5 mg/dL) and discontinuation, HR 1.09 (95% CI 0.91, 1.32). Increasing levels of PTH and calcium over time, based on changes in quintile distributions, were also associated with discontinuation, HR 1.15 (95% CI 1.07, 1.23) and HR 1.24 (95% CI 1.16, 1.32), respectively. Other factors associated with discontinuation included increasing copay, in the follow-up period, HR 1.04 (95% CI 1.02, 1.07); time spent in the hospital, HR 2.02 (95% CI 1.84, 2.22); being in the Medicare Part D gap period, HR 1.09 (95% CI 1.03, 1.16); and a diagnosis of stroke during follow-up, HR 1.30 (95% CI 1.06, 1.60). Nausea, vomiting, and diarrhea were not common in our study given the limitation of ICD-9 diagnosis codes to identify these outcomes, N

= 1,308 30-day intervals (1.2%) and were only slightly predictive of discontinuation, HR 1.09 (95% CI 0.91, 1.32). Proximal PTH values in all categories examined did not predict reinitiation of cinacalcet. Both increasing and decreasing levels of PTH over time, based on changes in quintile distributions, were both associated with reinitiation of PTH, HR 1.08 (95% CI 1.03, 1.14) and HR 1.12 (95% CI 1.06, 1.19), respectively. Proximal calcium levels both lower and higher were predictive of cinacalcet reinitiation; however, the results of the sensitivity analysis, which used the calcium value 14 days prior to the date of the laboratory value most proximal to reinitiation, showed that only higher calcium levels were associated with reinitiation, HR 1.26 (95% CI 1.19, 1.33), Table 7. All other sensitivity analysis results were not greatly changed when prior laboratory values were used to predict reinitiation. Other predictors of reinitiation included low-income subsidy, HR = 1.32 (95% CI 1.22, 1.43), African American race, HR = 1.08 (95% CI 1.03, 1.13), and higher albumin level, HR = 1.23 (95% CI 1.10, 1.36).

10.5 Other Analyses

Not applicable.

10.6 Adverse Events/Adverse Reactions

Individual event collection and reporting was not applicable to this study. Reporting of adverse events was not applicable as the data abstracted from the healthcare/claims databases in this study did not contain information on adverse events, nor did they contain physician attribution of causality of adverse events to any medicinal products.

11. DISCUSSION

11.1 Key Results

In a cohort of contemporary hemodialysis patients, we observed the effectiveness of cinacalcet in lowering levels of PTH, calcium, and phosphorus, and determined predictors of early cinacalcet discontinuation and subsequent re-initiation. The reductions in these lab values are observed soon after initiation of cinacalcet and mean levels of PTH, calcium, and phosphorus appear to be sustained within recommended target ranges. Yet, discontinuation occurs frequently and relatively soon after initiation of cinacalcet treatment, on average within 4 months following initiation. Furthermore, discontinuation in this population resulted in the loss of biochemical control. Several variables predicted discontinuation. Some of these variables were biochemical, including declining PTH and calcium levels, and others were related to drug prescription drug coverage and novel findings associated with changes in health status. Variables predicting reinitiation were generally similar to those predicting discontinuation.

11.2 Limitations

Several limitations of our study must be noted. First, medication use information was obtained from pharmacy claims, which are an imperfect measure of actual medication consumed. It is possible that patients were obtaining medications outside of their Medicare Part D benefit.[15,16] We also cannot precisely determine the day when patients stops or reinitiates treatment. However, we adopted a design to minimize the likelihood that predictors would be assessed following discontinuation or reinitiation events, thus avoiding the problem of predictors being consequences of discontinuation or reinitiation, rather than causes. In addition, we performed a sensitivity analysis to determine if a delay in physician recognition and response to a laboratory value could affect reinitiation results. Adding a lag in the dates of the biochemical values affected calcium reinitiation results, a biochemical test drawn frequently, but not PTH results, a biochemical test drawn less frequently. In future studies using claims data, consideration of the time frame of when frequent biochemical values are drawn and when a physician would realistically identify and act on a biochemical value should be considered. Finally, many of our variables were assessed using ICD-9 codes associated with health care encounters. Many of these definitions, such as those for acute myocardial infarction,[17] are known to have very high sensitivity and specificity, but others, such as those for nausea, are likely to be much less sensitive.

11.3 Interpretation

Average PTH, calcium, and phosphorus levels achieved following cinacalcet initiation in our study were consistent with the 2009 KDIGO guideline update, despite a portion of the follow-up period occurring prior to the release of the guidelines.[4] These guidelines suggest a PTH level in the range of approximately 2 to 9 times the upper reference limit for the assay, which corresponds to approximately 130 to 600 pg/mL, taking into account variability in commercial assays. In our study, average serum calcium levels were maintained in the reference range, in which the recommended upper level of the range is 10.0 mg/dL to 10.5mg/dL, depending on the assay used. Average phosphorus levels in our study decreased toward the reference range, which is 2.4 to 4.1 mg/dL, differing slightly among assays. For patients who remained on cinacalcet, biochemical control persisted for up to one year of follow-up. Our results are also similar to those from a recent retrospective cohort study that showed decreases in all three biochemistries that were sustained for 1-year following cinacalcet initiation, although we did not assess dose-titration and its impact on control.[7] Following discontinuation of cinacalcet in the current study, biochemical values increased quickly then leveled off or decreased slightly, Figures 2-4. The slight decreases in biochemical levels are likely due to a selection effect that would result from patients with higher levels restarting treatment and thus being censored from the analysis. Similar to a prior study,[18] vitamin D doses in our population decreased following cinacalcet initiation and increased following cinacalcet discontinuation, Figure 5.

Despite evidence of improved control of SHPT-related biochemical parameters, discontinuation of cinacalcet was common, with 56% discontinuing by month 4 and 73% discontinuing by month 12. This rate of discontinuation is greater than what has been reported in previous cinacalcet studies; however, ours is the first to include a large sample size and verify use through Medicare Part D prescription claims, which overcomes many of the possible inaccuracies in start and stop dates.[7,10-12] Our results are consistent with prior studies of medication adherence in the general and CKD populations, where >50% of patients have been found to demonstrate poor adherence to chronic medications.[19] However, reinitiation was also common and on average occurred 4 months after the first discontinuation. This suggests that poor adherence factors are multi-factorial and likely to encompass both patient-initiated (non-adherence) and physician-initiated (biochemical value influences) factors.

Our study identified possible predictors that may illuminate why certain patients are discontinued from cinacalcet. While the prescribing information for cinacalcet indicates that administration should be withheld if serum calcium falls below 7.5 mg/dL, only a small

proportion of patients experienced hypocalcemia and the modeling revealed it as a weak predictor of discontinuation. PTH levels falling below 150 pg/mL was more common and was predictive of discontinuation, consistent with prescribing information. Other possible cinacalcet side effects, nausea, vomiting, and diarrhea,[20] were also not common in our study, but did have a weak association with discontinuation. However, because nausea and vomiting are likely to be under reported when retrospectively obtaining data utilizing a claims database, measuring this well-recognized side effect is difficult and definitive conclusions from the observed results cannot be drawn for this variable.

We also identified factors related to medication cost that were predictive of discontinuation and reinitiation, suggesting that financial issues could play a role in patients' decisions to discontinue and reinitiate treatment. Patients identified as ever having low-income subsidy status, indicating a lower-out-of pocket cost for cinacalcet, were less likely to discontinue and more likely to reinitiate therapy following discontinuation. Entering the Medicare Part D gap period or being in the Medicare Part D gap period, when out-of-pocket costs are significant, increased the risk of discontinuation. Increasing copay during follow-up also slightly increased the risk of discontinuation. Our results are similar to the findings of a recent study of adherence and persistence of oral medications, defined as ≥ 80% medication possession ratio and duration of use, among Medicare Part D beneficiaries receiving dialysis.[21] The investigators found patients not receiving the low-income subsidy and patients entering into the coverage gap were more likely to be non-adherent and had less persistent use of cinacalcet.[21] The investigators found similar relationships with other oral medications indicating that the impact of economic burden in this population is not specific to cinacalcet. Therapy regimens for patients receiving dialysis are burdensome, and patients are prescribed on average 10-12 tablets per day, all likely leading to financial burden.[10,22,23]

It has been recommended that therapeutic decisions in CKD patients be based on trends, rather than single laboratory values.[4] Therefore, in addition to examining the laboratory values most proximal to the time of discontinuation, we also examined the changes in lab values leading up to discontinuation. Our most striking finding was that trends of increasing levels of PTH and calcium over time were associated with discontinuation. This finding could be an early signal of non-adherence. As patients become non-adherent to cinacalcet due to side effects, financial issues, or medication complexity, rising levels of PTH and calcium could be apparent and a signal to clinicians to consider that factors other than medication ineffectiveness may be an

issue. Identifying ways to decrease medication complexity, financial burden, and side effects could enable patients to persist longer on cinacalcet therapy.

11.4 Generalizability

Based on the selection of the database for this study, patients must have been receiving hemodialysis from a DaVita facility, a large dialysis organization. Although DaVita is one of the largest dialysis providers in the United States, results from this study may not be completely generalizable to patients who receive hemodialysis in non-DaVita facilities if programs exist that impact adherence to oral medications at DaVita or other facilities. However, the observed biochemical trajectories following initiation and discontinuation is likely generalizable to other patients in the United States receiving hemodialysis initiating and/or discontinuing cinacalcet.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

The results of our study indicate that on average biochemical control of PTH, calcium, and phosphorus following cinacalcet initiation were consistent with recommendations in the 2009 KDIGO guideline update. Yet, early discontinuation of cinacalcet was frequent and resulted in the loss of control of PTH, calcium, and phosphorus. Both economic and clinical factors contribute to cinacalcet discontinuation, as well as reinitiation. Examining trends in laboratory values over time could identify early signals of non-adherence and present an opportunity for clinicians to intervene. In conclusion, prolonged biochemical control was achieved by continued cinacalcet therapy and factors associated with discontinuation and reinitiation indicate persistent use of and adherence to cinacalcet are impacted by a range of factors. Our study does not provide data that impacts the benefit-risk profile of cinacalcet.

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15. SUMMARY TABLES, FIGURES, AND LISTINGS

Table 3. Baseline Characteristics Overall and by Sex

Characteristic[1]	Total	Female	Male
Demographics			
Patients, N	17,763	8,764	8,999
Age, mean (SD), years[2]	56.7 (14.5)	59.1 (14.8)	54.4 (13.9)
Time on dialysis, mean (SD), years[2]	4.5 (4.3)	4.4 (4.1)	4.7 (4.4)
Race, N (%)			
White	7,242 (40.8)	3,436 (39.2)	3,806 (42.3)
African American	9,555 (53.8)	4,856 (55.4)	4,699 (52.2)
Other Race	966 (5.4)	472 (5.4)	494 (5.5)
Cause of ESRD, N (%)			
Diabetes	7,629 (42.9)	4,233 (48.3)	3,396 (37.7)
Hypertension	5,612 (31.6)	2,458 (28.0)	3,154 (35.0)
Glomerular Nephritis	2,236 (12.6)	1,067 (12.2)	1,169 (13.0)
Other	2,286 (12.9)	1,006 (11.5)	1,280 (14.2)
Body Mass Index, mean (SD), kg/m^2	28.0 (7.3)	28.7 (7.8)	27.4 (6.7)
Financial Considerations			
Medicaid, N (%)	12,206 (68.7)	6,351 (72.5)	5,855 (65.1)
Low-income subsidy, N (%)	14,906 (83.9)	7,515 (85.7)	7,391 (82.1)
Concomitant medications, N (%)[3]	4.7 (3.6)	5.1 (3.7)	4.4 (3.5)
Biochemical Values			
Albumin, mean (SD), g/dL[4]	3.9 (0.4)	3.8 (0.4)	4.0 (0.4)
Calcium, mean (SD), mg/dL[4]	9.4 (0.7)	9.4 (0.7)	9.4 (0.7)
Phosphorus, mean (SD), mg/dL[4]	5.9 (1.7)	5.8 (1.7)	6.0 (1.7)
Parathyroid hormone, mean (SD), pg/mL[4]	642 (519)	640 (519)	644 (520)
Comorbidities			
Congestive heart failure, N (%)	4,823 (27.2)	2,592 (29.6)	2,231 (24.8)
Coronary artery	4,703	2,434	2,269

disease / atherosclerosis, N (%)	(26.5)	(27.8)	(25.2)
Cerebrovascular disease, N (%)	1,891 (10.6)	1,087 (12.4)	804 (8.9)
Hypertension, N (%)	12,393 (69.8)	6,481 (74.0)	5,912 (65.7)
Peripheral vascular disease, N (%)	2,352 (13.2)	1,208 (13.8)	1,144 (12.7)
Hyperlipidemia, N (%)	4,658 (26.2)	2,519 (28.7)	2,139 (23.8)
Chronic obstructive pulmonary disease or asthma, N (%)	2,727 (15.4)	1,530 (17.5)	1,197 (13.3)
Diabetes, N (%)	10,052 (56.6)	5,491 (62.7)	4,561 (50.7)
Dialysis Care			
Phosphorus binder drug, N (%)[5]	14,135 (79.6)	7,037 (80.3)	7,098 (78.9)
Catheter access, N (%)	3,351 (18.9)	1,994 (22.8)	1,357 (15.1)
Mean intravenous vitamin D dosage, micrograms (SD)[6]	12.5 (10.3)	11.9 (9.9)	13.1 (10.7)

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, x0.2495; phosphorus in mg/dL to mmol/L, x0.3229.

[1]Characteristics were identified using information from Medicare Part A or B claims. A characteristic was considered present if at least one inpatient, home health, or skilled nursing facility claim, or at least two outpatient or physician/ supplier claims separated by at least 7 days, were identified during the 6-month baseline period.

[2]Age and time on dialysis are at the time of cinacalcet initiation.

[3]Concomitant medications are the number of concomitant medications at the time of cinacalcet initiation.

[4]Laboratory values were those most proximal to the index date during the baseline period.

[5]Phosphate binders included in the analysis: Sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, and calcium acetate.

[6]Mean intravenous vitamin D dose per person in the last month of the baseline period. Paricalcitol and doxercalciferol doses were converted to calcitriol-equivalent doses according to the following conversion ratios: 4.6: 1 for paricalcitol: calcitriol and 3.1: 1 for doxercalciferol: calcitriol.

Table 4. Predictors of Discontinuation and Reinitiation

Characteristic[1]	Discontinuation (HR, 95% CI)	Reinitiation (HR, 95% CI)
Number of time intervals for analysis, N (%)	100,706 (90.7%)	78,789 (96.0%)
Demographics		
Age, years, reference 46-55		
≤45	0.93 (0.85, 1.00)	0.95 (0.90, 1.02)
56-65	1.05 (0.97, 1.13)	0.98 (0.92, 1.04)
66-75	1.05 (0.97, 1.14)	0.90 (0.85, 0.97)
≥75	0.98 (0.88, 1.08)	0.95 (0.87, 1.04)
Time on dialysis, years, reference <1		
1-3	1.15 (1.01, 1.30)	1.00 (0.91, 1.11)
≥4	1.15 (1.01, 1.31)	1.03 (0.92, 1.14)
Female	1.07 (1.01, 1.13)	1.00 (0.96, 1.05)
African American	1.05 (0.99, 1.11)	1.08 (1.03, 1.13)
Cause of ESRD, reference diabetes mellitus		
Hypertension	1.02 (0.94, 1.10)	1.04 (0.98, 1.11)
Glomerular nephritis	1.01 (0.91, 1.12)	1.08 (0.99, 1.17)
Other	0.96 (0.87, 1.06)	1.03 (0.95, 1.12)
Body mass index, kg/m^2, reference normal		
Underweight	1.07 (0.93, 1.23)	0.98 (0.87, 1.10)
Overweight	1.03 (0.96, 1.10)	1.03 (0.98, 1.09)
Obese	0.98 (0.91, 1.05)	1.11 (1.05, 1.17)
Financial considerations		
Medicaid	1.03 (0.96, 1.11)	0.96 (0.91, 1.02)
Low-income subsidy	0.77 (0.69, 0.86)	1.32 (1.22, 1.43)
Concomitant medications in baseline period[2]	0.98 (0.97, 0.99)	1.00 (0.99, 1.01)
Concomitant medications in follow-up period[2]	0.96 (0.95, 0.97)	0.98 (0.97, 0.99)
Copay in follow-up period[3]	1.04 (1.02, 1.07)	1.04 (1.02, 1.06)
Last benefit phase in follow-up, reference: covered[4]		
Entering the gap period	1.19 (1.00, 1.42)	1.01 (0.85, 1.21)
Exiting or going through gap period	0.98 (0.78, 1.24)	1.03 (0.81, 1.32)
In the gap period	1.09 (1.03, 1.16)	1.01 (0.96, 1.06)
Biochemical values		
Albumin in baseline period, reference: <3.3 g/dL		
3.3-3.9 g/dL	1.11 (0.97, 1.28)	1.13 (1.00, 1.27)
>3.9 g/dL	1.05 (0.91, 1.22)	1.09 (0.96, 1.23)
Albumin in follow-up period, reference: <3.3 g/dL		

3.3-3.9 g/dL	0.85 (0.76, 0.95)	1.13 (1.02, 1.25)
>3.9 g/dL	0.78 (0.69, 0.88)	1.23 (1.10, 1.36)
Phosphorus in baseline period, mg/dL	1.02 (1.00, 1.04)	0.98 (0.96, 0.99)
Phosphorus in follow-up period, mg/dL	1.02 (1.00, 1.04)	0.99 (0.98, 1.01)
Parathyroid hormone in baseline period, pg/mL[5]	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)
Parathyroid hormone in follow-up period, reference: >600 pg/mL		
<150 pg/mL	1.23 (1.12, 1.36)	0.70 (0.64, 0.76)
150-300 pg/mL	0.90 (0.83, 0.98)	0.71 (0.66, 0.75)
301-600 pg/mL	0.89 (0.82, 0.97)	0.85 (0.80, 0.90)
Parathyroid hormone in follow-up period, change in quintiles, reference: no change[6]		
Increase	1.15 (1.07, 1.23)	1.08 (1.03, 1.14)
Decrease	0.90 (0.84, 0.97)	1.12 (1.06, 1.19)
Calcium in baseline period, mg/dL	0.96 (0.92, 1.00)	1.16 (1.12, 1.20)
Calcium in follow-up period, reference: >8.7mg/dL[7]		
<7.5mg/dL	1.09 (0.91, 1.32)	1.12 (0.91, 1.39)
7.5-8.7mg/dL	0.86 (0.81, 0.91)	1.26 (1.19, 1.33)
Calcium in follow-up period, change in quintiles, reference: no change[6]		
Increase	1.24 (1.16, 1.32)	1.07 (1.02, 1.13)
Decrease	0.94 (0.88, 1.00)	1.04 (0.99, 1.10)
Comorbidities		
Congestive heart failure in baseline period	1.05 (0.99, 1.13)	0.96 (0.91, 1.01)
Congestive heart failure in follow-up period	1.01 (0.90, 1.14)	1.11 (0.94, 1.31)
Coronary artery disease / atherosclerosis in baseline period	1.01 (0.95, 1.09)	0.93 (0.88, 0.99)
Cerebrovascular disease in baseline period	0.94 (0.86, 1.02)	1.00 (0.93, 1.07)
Stroke in follow-up period	1.30 (1.06, 1.60)	0.82 (0.55, 1.20)
Hypertension in baseline period	1.12 (1.05, 1.19)	1.03 (0.98, 1.08)
Peripheral vascular disease in baseline period	1.02 (0.94, 1.11)	1.11 (1.03, 1.19)
Peripheral vascular disease in follow-up period	0.99 (0.85, 1.16)	0.91 (0.76, 1.09)
Hyperlipidemia in baseline	1.01 (0.95, 1.07)	1.06 (1.01, 1.12)

period		
Chronic obstructive pulmonary disease and asthma in baseline period	1.00 (0.93, 1.08)	1.00 (0.94, 1.06)
Diabetes in baseline period	1.05 (0.98, 1.14)	0.98 (0.92, 1.04)
Nausea, vomiting, diarrhea in follow-up period	1.09 (0.91, 1.32)	1.05 (0.85, 1.31)
Seizure in follow-up period	1.17 (0.93, 1.49)	1.11 (0.82, 1.50)
Dialysis care		
Intravenous vitamin D in baseline period [8]	1.01 (0.98, 1.05)	0.98 (0.96, 1.00)
Intravenous vitamin D in follow-up period [8]	0.94 (0.91, 0.98)	1.02 (0.99, 1.04)
Phosphorus binder drug in baseline period[9]	1.01 (0.95, 1.09)	1.12 (1.06, 1.18)
Phosphorus binder drug in follow-up period[9]	0.77 (0.73, 0.82)	1.03 (0.98, 1.08)
Catheter access in baseline period	0.97 (0.88, 1.06)	1.07 (0.99, 1.15)
Catheter access in follow-up period	1.10 (1.00, 1.21)	0.83 (0.77, 0.90)
Days in the hospital in follow-up period, reference: 0 days		
1-4 days	2.02 (1.84, 2.22)	0.85 (0.75, 0.96)
≥5 days	1.90 (1.73, 2.09)	0.79 (0.69, 0.89)

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, x0.2495; phosphorus in mg/dL to mmol/L, x0.3229.

[1]Baseline characteristics were identified using information from Medicare Part A or B claims. A characteristic was considered present if at least one inpatient, home health, or skilled nursing facility claim, or at least two outpatient or physician/ supplier claims separated by at least 7 days, were identified during the 6-month baseline period. Additional information concerning baseline characteristics can be found in Table 5. Time-varying (follow-up) characteristics were evaluated at 30-day intervals following the start of follow-up.

[2]Concomitant medications are the number of concomitant medications at the time of cinacalcet discontinuation or reinitiation.

[3]Changes in co-pay were based on increments of $100. The last co-pay prior to discontinuation was used to predict cinacalcet reinitiation.

[4]Benefit phase reflects the status of Medicare Part D coverage at the time of the fill of cinacalcet.

[5]Changes in parathyroid hormone level were based on increments of 100 pg/mL.

[6]Distributions of parathyroid hormone and calcium were examined across all of follow-up and quintiles were based on these distributions. Increase indicates an increase to another quintile and trend of increasing laboratory levels. Decrease indicates a decrease to another quintile and a trend of decreasing laboratory levels.

[7]Results presented for prediction of reinitiation associated with follow-up calcium levels are those from the sensitivity analysis utilizing a lag time of 14 days. The calcium level recorded 14 days prior to the date of the laboratory value most proximal to discontinuation was used to predict reinitiation. All other results were not significantly changed when lag times were considered.

[8]Mean intravenous vitamin D dose was assessed in the last month of the baseline period. Changes in intravenous vitamin D dose were based in increments of 10mcg. Paricalcitol and doxercalciferol doses were converted to calcitriol-equivalent doses according to the following conversion ratios: 4.6: 1 for paricalcitol: calcitriol and 3.1: 1 for doxercalciferol: calcitriol.
[9]Phosphate binders included in the analysis: Sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, and calcium acetate

FIGURES

Figure 2. Mean PTH levels and 95% confidence intervals by month following cinacalcet initiation and discontinuation.

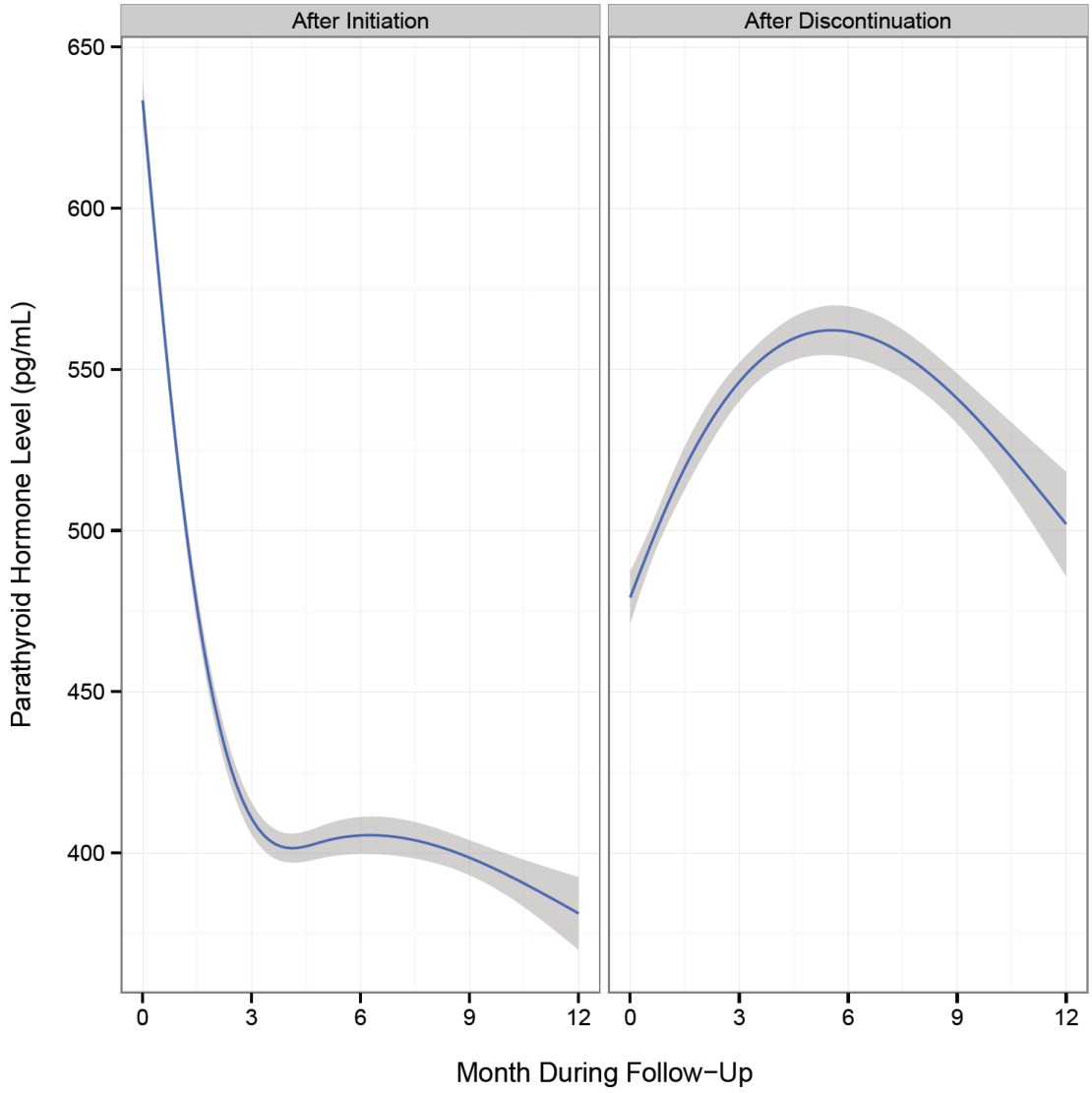


Figure 3. Mean calcium levels and 95% confidence intervals by month following cinacalcet initiation and discontinuation.

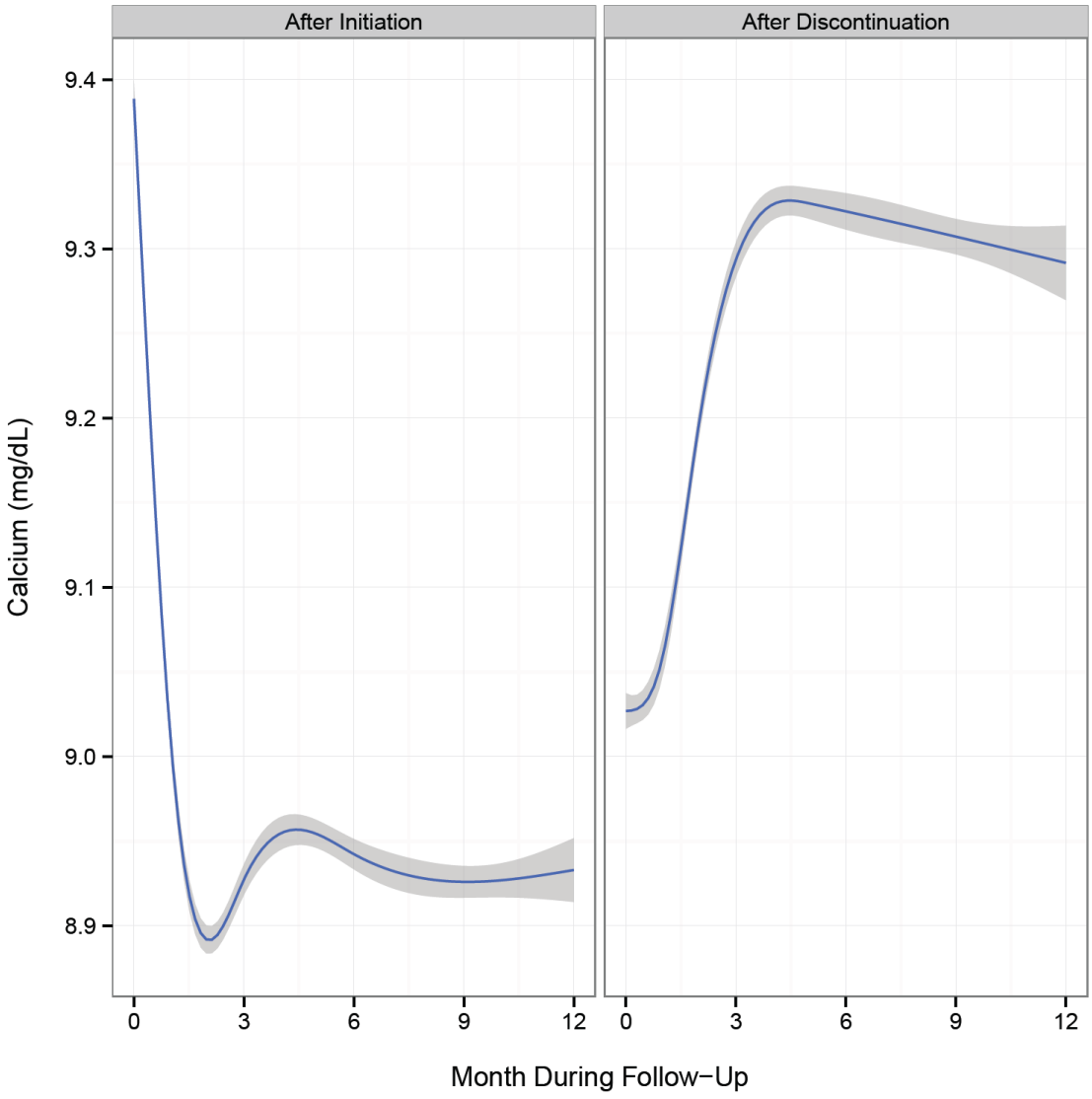


Figure 4. Mean phosphorus levels and 95% confidence intervals by month following cinacalcet initiation and discontinuation.

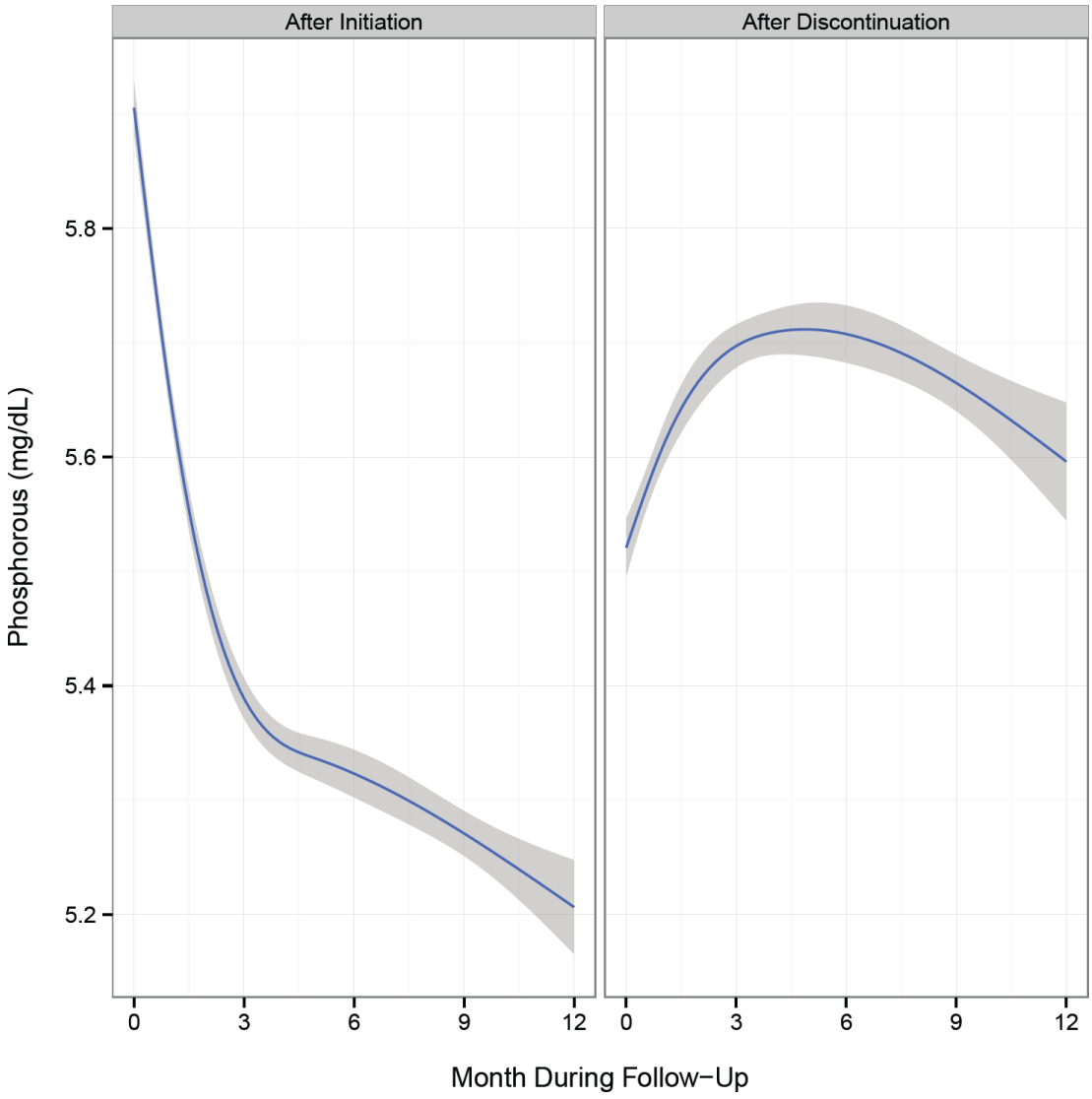


Figure 5. Vitamin D trends following cinacalcet initiation and discontinuation

Paricalcitol and doxercalciferol doses were converted to calcitriol-equivalent doses according to the following conversion ratios: 4.6: 1 for paricalcitol: calcitriol and 3.1: 1 for doxercalciferol: calcitriol.

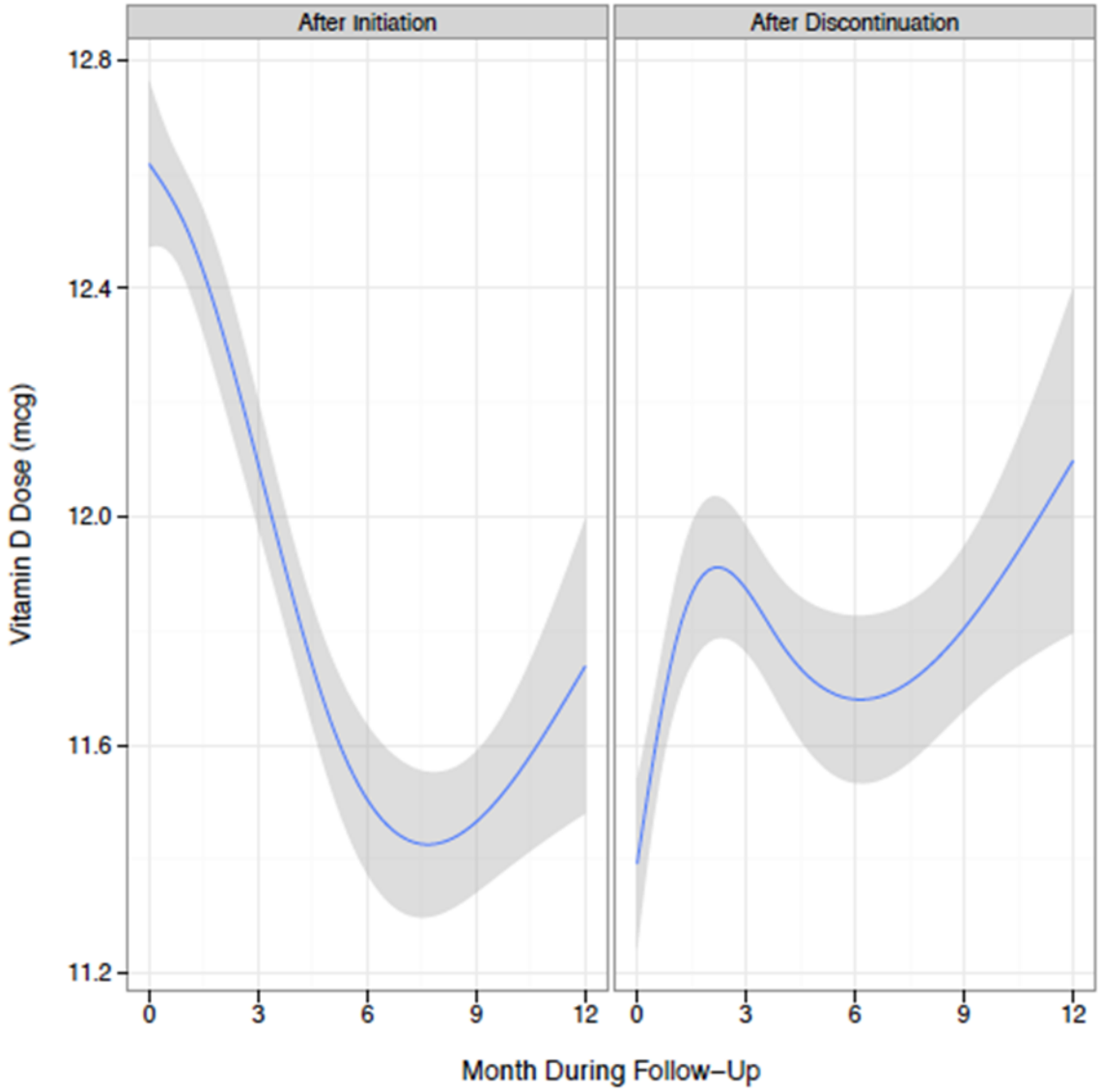


Table 5. Time-dependent covariates by follow-up months

	Total	**Year 1**				**Year 2**		**Year 3**	**Year 4**
Characteristics	**48 months**	**Month 1**	**Month 2**	**Month 3**	**Month 7**	**Month 1**	**Month 7**	**Month 1**	**Month 1**
Number of intervals, N	111,047	17,763	11,436	9,292	5,210	2,649	1,491	900	262
Discontinuation, N (%)	12,521 (11.3)	5,944 (33.5)	1,736 (15.2)	927 (10.0)	345 (6.6)	143 (5.4)	33 (2.2)	30 (3.3)	5 (1.9)
Average number of days in an interval	26.8	20.4	26.5	27.6	28.0	28.4	28.9	28.6	28.5
Albumin in the follow-up period, mean (SD), g/dL	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	3.9 (0.4)	4.0 (0.4)
Calcium in the follow-up period, mean (SD), mg/dL	8.9 (0.7)	9.0 (0.7)	8.9 (0.8)	8.9 (0.7)	8.9 (0.7)	8.9 (0.7)	8.9 (0.7)	8.8 (0.6)	8.9 (0.7)
Phosphorus in the follow-up period, mean (SD), mg/dL	5.3 (1.6)	5.6 (1.7)	5.5 (1.7)	5.4 (1.7)	5.3 (1.6)	5.2 (1.6)	5.1 (1.6)	5.1 (1.6)	5.0 (1.5)
PTH in the follow-up period, mean (SD) pg/mL	415 (428)	497 (513)	450 (469)	424 (436)	392 (389)	396 (398)	364 (395)	367 (414)	352 (282)
Congestive heart failure,[1] N (%)	4,273 (3.8)	717 (4.0)	551 (4.8)	397 (4.3)	209 (4.0)	85 (3.2)	52 (3.5)	29 (3.2)	9 (3.4)
MI, [1] N (%)	766 (0.69)	127 (0.71)	107 (0.94)	80 (0.86)	29 (0.56)	12 (0.45)	14 (0.94)	4 (0.44)	1 (0.38)
Stroke, [1] N (%)	799 (0.72)	99 (0.56)	107 (0.94)	76 (0.82)	52 (1.00)	10 (0.38)	8 (0.54)	8 (0.89)	1 (0.38)
Peripheral vascular disease, [2] N (%)	2,148 (1.9)	279 (1.6)	263 (2.3)	193 (2.1)	97 (1.9)	43 (1.6)	31 (2.1)	14 (1.6)	4 (1.5)
Phosphorus binder drug in the follow-up period, N (%)	62,616 (56.4)	9,278 (52.2)	6,127 (53.6)	4,996 (53.8)	2,942 (56.5)	1,552 (58.6)	911 (61.1)	547 (60.8)	143 (54.6)
Recent catheter access in the follow-up period, N (%)	16,716 (15.2)	3,186 (18.0)	2,015 (17.8)	1,540 (16.8)	747 (14.6)	359 (13.7)	176 (12.0)	98 (11.0)	29 (11.2)
Intravenous vitamin D dosage in the last 30 days, mean (SD), micrograms [4]	12.0 (10.8)	12.8 (10.4)	12.2 (10.5)	12.0 (10.5)	11.5 (10.7)	11.6 (10.8)	12.3 (11.6)	12.7 (11.9)	12.0 (12.3)
Days in hospital, mean (SD)	1.0 (3.5)	0.78 (2.69)	1.2 (3.6)	1.2 (4.0)	1.1 (3.8)	0.94 (3.33)	0.81 (2.88)	0.89 (3.50)	1.1 (3.9)
Nausea, Vomiting, diarrhea, [5] N (%)	1,308 (1.2)	190 (1.1)	156 (1.4)	134 (1.4)	60 (1.2)	18 (0.68)	12 (0.80)	10 (1.1)	3 (1.1)

	Total	**Year 1**				**Year 2**		**Year 3**	**Year 4**
Characteristics	**48 months**	**Month 1**	**Month 2**	**Month 3**	**Month 7**	**Month 1**	**Month 7**	**Month 1**	**Month 1**
Seizure, [5] N (%)	765 (0.69)	89 (0.50)	101 (0.88)	66 (0.71)	35 (0.67)	21 (0.79)	8 (0.54)	3 (0.33)	0
Monthly copay, mean (SD), dollars	22.9 (93.3)	29.3 (103.6)	29.1 (108.6)	29.9 (111.2)	22.1 (88.6)	15.7 (71.5)	14.2 (69.0)	12.4 (67.0)	13.4 (66.5)
Concomitant number of medications in past month, mean (SD)	5.8 (3.7)	5.3 (3.6)	5.6 (3.6)	5.7 (3.7)	6.0 (3.7)	6.0 (3.8)	6.1 (3.9)	6.2 (4.1)	6.0 (3.8)
Hypocalcemia (<7.5 mg/dL), N (%)	1,934 (1.8)	331 (1.9)	244 (2.1)	167 (1.8)	94 (1.8)	49 (1.9)	16 (1.1)	16 (1.8)	4 (1.5)
Low PTH (<150 pg/mL), N (%)	17,980 (16.7)	2,514 (16.2)	1,946 (17.5)	1,646 (17.8)	844 (16.4)	420 (16.1)	261 (17.7)	125 (14.0)	36 (13.9)
Gap period activity, [5] N (%)	44,708 (41.3)	7,375 (41.5)	5,594 (50.0)	4,736 (52.8)	1,996 (39.7)	930 (36.5)	432 (29.6)	322 (36.8)	97 (38.2)

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, x0.2495; phosphorus in mg/dL to mmol/L, x0.3229.
[1]Myocardial infarction, congestive heart failure, stroke, and parathyroidectomy were considered in any diagnosis field of an inpatient claim only.
[2]Peripheral vascular disease was considered in any diagnosis field of Medicare Part A and B files.
[3]Phosphate binders included in the analysis: Sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, and calcium acetate
[4]Paricalcitol and doxercalciferol doses were converted to calcitriol-equivalent doses according to the following conversion ratios: 4.6: 1 for paricalcitol: calcitriol and 3.1: 1 for doxercalciferol: calcitriol.
[5]Seizure, nausea, vomiting, and diarrhea considered present if at least one inpatient, home health, or skilled nursing facility claim, or at least two outpatient or physician/supplier claims separated by at least 7 days are identified during the 30-day look back period.
[6]Gap period activity was defined as the percentage of participants who in the prior 30-day period had a prescription filled that resulted in entering, being in, exiting, or going through the doughnut hole.

Table 6. Full-list of predictors of discontinuation and reinitiation

Characteristic[1]	Discontinuation (HR, 95% CI)	Reinitiation (HR, 95% CI)
Number of time intervals for analysis, N (%)	100,706 (90.7%)	78,789 (96.0%)
Demographics		
Age, years, reference 46-55		
≤45	0.93 (0.85, 1.00)	0.95 (0.90, 1.02)
56-65	1.05 (0.97, 1.13)	0.98 (0.92, 1.04)
66-75	1.05 (0.97, 1.14)	0.90 (0.85, 0.97)
≥75	0.98 (0.88, 1.08)	0.95 (0.87, 1.04)
Time on dialysis, years, reference <1		
1-3	1.15 (1.01, 1.30)	1.00 (0.91, 1.11)
≥4	1.15 (1.01, 1.31)	1.03 (0.92, 1.14)
Female	1.07 (1.01, 1.13)	1.00 (0.96, 1.05)
African American	1.05 (0.99, 1.11)	1.08 (1.03, 1.13)
Cause of ESRD, reference diabetes mellitus		
Hypertension	1.02 (0.94, 1.10)	1.04 (0.98, 1.11)
Glomerular nephritis	1.01 (0.91, 1.12)	1.08 (0.99, 1.17)
Other	0.96 (0.87, 1.06)	1.03 (0.95, 1.12)
Body mass index, kg/m^2, reference normal		
Underweight	1.07 (0.93, 1.23)	0.98 (0.87, 1.10)
Overweight	1.03 (0.96, 1.10)	1.03 (0.98, 1.09)
Obese	0.98 (0.91, 1.05)	1.11 (1.05, 1.17)
Financial considerations		
Medicaid	1.03 (0.96, 1.11)	0.96 (0.91, 1.02)
Low-income subsidy	0.77 (0.69, 0.86)	1.32 (1.22, 1.43)
Concomitant medications in baseline period[2]	0.98 (0.97, 0.99)	1.00 (0.99, 1.01)
Concomitant medications in follow-up period[2]	0.96 (0.95, 0.97)	0.98 (0.97, 0.99)
Copay in follow-up period[3]	1.04 (1.02, 1.07)	1.04 (1.02, 1.06)
Last benefit phase in follow-up, reference: covered[4]		
Entering the gap period	1.19 (1.00, 1.42)	1.01 (0.85, 1.21)
Exiting or going through gap period	0.98 (0.78, 1.24)	1.03 (0.81, 1.32)
In the gap period	1.09 (1.03, 1.16)	1.01 (0.96, 1.06)
Biochemical values		
Albumin in baseline period, reference: <3.3 g/dL		
3.3-3.9 g/dL	1.11 (0.97, 1.28)	1.13 (1.00, 1.27)
>3.9 g/dL	1.05 (0.91, 1.22)	1.09 (0.96, 1.23)
Albumin in follow-up period, reference: <3.3 g/dL		
3.3-3.9 g/dL	0.85 (0.76, 0.95)	1.13 (1.02, 1.25)

>3.9 g/dL	0.78 (0.69, 0.88)	1.23 (1.10, 1.36)
Phosphorus in baseline period, mg/dL	1.02 (1.00, 1.04)	0.98 (0.96, 0.99)
Phosphorus in follow-up period, mg/dL	1.02 (1.00, 1.04)	0.99 (0.98, 1.01)
Parathyroid hormone in baseline period, pg/mL[5]	1.00 (0.99, 1.01)	1.00 (0.99, 1.00)
Parathyroid hormone in follow-up period, reference: >600 pg/mL		
<150 pg/mL	1.23 (1.12, 1.36)	0.70 (0.64, 0.76)
150-300 pg/mL	0.90 (0.83, 0.98)	0.71 (0.66, 0.75)
301-600 pg/mL	0.89 (0.82, 0.97)	0.85 (0.80, 0.90)
Parathyroid hormone in follow-up period, change in quintiles, reference: no change[6]		
Increase	1.15 (1.07, 1.23)	1.08 (1.03, 1.14)
Decrease	0.90 (0.84, 0.97)	1.12 (1.06, 1.19)
Calcium in baseline period, mg/dL	0.96 (0.92, 1.00)	1.16 (1.12, 1.20)
Calcium in follow-up period, reference: >8.7mg/dL[7]		
<7.5mg/dL	1.09 (0.91, 1.32)	1.12 (0.91, 1.39)
7.5-8.7mg/dL	0.86 (0.81, 0.91)	1.26 (1.19, 1.33)
Calcium in follow-up period, change in quintiles, reference: no change[6]		
Increase	1.24 (1.16, 1.32)	1.07 (1.02, 1.13)
Decrease	0.94 (0.88, 1.00)	1.04 (0.99, 1.10)
Comorbidities		
Angina in baseline period	1.27 (1.07, 1.52)	1.06 (0.91, 1.23)
Congestive heart failure in baseline period	1.05 (0.99, 1.13)	0.96 (0.91, 1.01)
Congestive heart failure in follow-up period	1.01 (0.90, 1.14)	1.11 (0.94, 1.31)
Coronary artery disease / atherosclerosis in baseline period	1.01 (0.95, 1.09)	0.93 (0.88, 0.99)
Cerebrovascular disease in baseline period	0.94 (0.86, 1.02)	1.00 (0.93, 1.07)
Myocardial infarction in baseline period	1.00 (0.87, 1.15)	1.02 (0.90, 1.15)
Myocardial infarction in follow-up period	1.05 (0.83, 1.32)	0.65 (0.42, 0.99)
Stroke in follow-up period	1.30 (1.06, 1.60)	0.82 (0.55, 1.20)
Hypertension in baseline period	1.12 (1.05, 1.19)	1.03 (0.98, 1.08)
Peripheral vascular disease in baseline period	1.02 (0.94, 1.11)	1.11 (1.03, 1.19)
Peripheral vascular disease	0.99 (0.85, 1.16)	0.91 (0.76, 1.09)

in follow-up period		
Hyperlipidemia in baseline period	1.01 (0.95, 1.07)	1.06 (1.01, 1.12)
Chronic obstructive pulmonary disease and asthma in baseline period	1.00 (0.93, 1.08)	1.00 (0.94, 1.06)
Rheumatoid arthritis in baseline period	1.15 (0.98, 1.35)	1.05 (0.93, 1.19)
Diabetes in baseline period	1.05 (0.98, 1.14)	0.98 (0.92, 1.04)
Fracture in baseline period	1.01 (0.89, 1.15)	1.03 (0.92, 1.15)
Gastrointestinal bleed in baseline period	0.82 (0.69, 0.97)	0.96 (0.84, 1.11)
Hyperthyroidism in baseline period	0.96 (0.70, 1.33)	1.02 (0.76, 1.38)
Peptic ulcer disease in baseline period	1.21 (0.98, 1.48)	0.91 (0.77, 1.09)
Liver disease in baseline period	1.06 (0.92, 1.22)	1.07 (0.96, 1.20)
Cancer in baseline period	0.96 (0.85, 1.08)	1.02 (0.92, 1.13)
Nausea, vomiting, diarrhea in follow-up period	1.09 (0.91, 1.32)	1.05 (0.85, 1.31)
Seizure in follow-up period	1.17 (0.93, 1.49)	1.11 (0.82, 1.50)
Dialysis care		
Intravenous vitamin D in baseline period [8]	1.01 (0.98, 1.05)	0.98 (0.96, 1.00)
Intravenous vitamin D in follow-up period [8]	0.94 (0.91, 0.98)	1.02 (0.99, 1.04)
Phosphorus binder drug in baseline period[9]	1.01 (0.95, 1.09)	1.12 (1.06, 1.18)
Phosphorus binder drug in follow-up period[9]	0.77 (0.73, 0.82)	1.03 (0.98, 1.08)
Catheter access in baseline period	0.97 (0.88, 1.06)	1.07 (0.99, 1.15)
Catheter access in follow-up period	1.10 (1.00, 1.21)	0.83 (0.77, 0.90)
Days in the hospital in follow-up period, reference: 0 days		
1-4 days	2.02 (1.84, 2.22)	0.85 (0.75, 0.96)
≥5 days	1.90 (1.73, 2.09)	0.79 (0.69, 0.89)

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, x0.2495; phosphorus in mg/dL to mmol/L, x0.3229.

[1]Baseline characteristics were identified using information from Medicare Part A or B claims. A characteristic was considered present if at least one inpatient, home health, or skilled nursing facility claim, or at least two outpatient or physician/ supplier claims separated by at least 7 days, were identified during the 6-month baseline period. Additional information concerning baseline characteristics can be found in Table S1. Time-varying (follow-up) characteristics were evaluated at 30-day intervals following the start of follow-up. Additional information concerning time-varying (follow-up) characteristics can be found in Table S2.

[2]Concomitant medications are the number of concomitant medications at the time of cinacalcet discontinuation or reinitiation.
[3]Changes in co-pay were based on increments of $100. The last co-pay prior to discontinuation was used to predict cinacalcet reinitiation.
[4]Benefit phase reflects the status of Medicare Part D coverage at the time of the fill of cinacalcet.
[5]Changes in parathyroid hormone level were based on increments of 100 pg/mL.
[6]Distributions of parathyroid hormone and calcium were examined across all of follow-up and quintiles were based on these distributions. Increase indicates an increase to another quintile and trend of increasing laboratory levels. Decrease indicates a decrease to another quintile and a trend of decreasing laboratory levels.
[7]Results presented for prediction of reinitiation associated with follow-up calcium levels are those from the sensitivity analysis utilizing a lag time of 14 days. The calcium level recorded 14 days prior to the date of the laboratory value most proximal to discontinuation was used to predict reinitiation. All other results were not significantly changed when lag times were considered.
[8]Mean intravenous vitamin D dose was assessed in the last month of the baseline period. Changes in intravenous vitamin D dose were based in increments of 10mcg. Paricalcitol and doxercalciferol doses were converted to calcitriol-equivalent doses according to the following conversion ratios: 4.6: 1 for paricalcitol: calcitriol and 3.1: 1 for doxercalciferol: calcitriol.
[9]Phosphate binders included in the analysis: Sevelamer hydrochloride, sevelamer carbonate, lanthanum carbonate, and calcium acetate

Table 7. Predictors of reinitiation sensitivity analysis

A sensitivity analysis was performed to determine if reinitiation results were modified when biochemical results from 5, 7, and 14 days prior to the date of the laboratory value most proximal to reinitiation were used to predict reinitiation. This lag time could account for any delays between physician recognition of a laboratory abnormality and a decision to reinitiate cinacalcet.

Biochemical Parameter	Use of Most Proximal Value (HR, 95% CI)	Addition of 5 days (HR, 95% CI)	Addition of 7 days (HR, 95% CI)	Addition of 14 days (HR, 95% CI)
Phosphorus in follow-up period, mg/dL	0.99 (0.98, 1.01)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)	0.98 (0.97, 1.00)
Parathyroid hormone in follow-up period, reference: >600 pg/mL				
<150 pg/mL	0.70 (0.64, 0.76)	0.70 (0.65, 0.77)	0.71 (0.65, 0.78)	0.73 (0.67, 0.80)
150-300 pg/mL	0.71 (0.66, 0.75)	0.71 (0.66, 0.75)	0.72 (0.67, 0.77)	0.73 (0.69, 0.78)
301-600 pg/mL	0.85 (0.80, 0.90)	0.86 (0.81, 0.91)	0.87 (0.82, 0.92)	0.88 (0.83, 0.93)
Parathyroid hormone in follow-up period, change in quintiles, reference: no change[1]				
Increase	1.08 (1.03, 1.14)	1.08 (1.02, 1.13)	1.05 (0.99, 1.10)	1.07 (1.01, 1.13)
Decrease	1.12 (1.06, 1.19)	1.14 (1.07, 1.20)	1.12 (1.06, 1.19)	1.14 (1.08, 1.21)
Calcium in follow-up period, reference: >8.7mg/dL				
<7.5mg/dL	1.27 (1.03, 1.57)	1.28 (1.04, 1.57)	1.25 (1.02, 1.54)	1.12 (0.91, 1.39)
7.5-8.7mg/dL	1.37 (1.30, 1.45)	1.31 (1.23, 1.38)	1.29 (1.22, 1.37)	1.26 (1.19, 1.33)
Calcium in follow-up period, change in quintiles, reference: no change[1]				
Increase	1.07 (1.02, 1.13)	1.04 (0.99, 1.10)	1.04 (0.99, 1.10)	1.01 (0.95, 1.06)
Decrease	1.04 (0.99,	1.05 (1.00,	1.06 (1.00,	1.04 (0.99,

	1.10)	1.11)	1.11)	1.09)

Note: Conversion factors for units: Calcium in mg/dL to mmol/L, x0.2495; phosphorus in mg/dL to mmol/L, x0.3229.

[1]Distributions of parathyroid hormone and calcium were examined across all of follow-up and quintiles were based on these distributions. Increase indicates an increase to another quintile and trend of increasing laboratory levels. Decrease indicates a decrease to another quintile and a trend of decreasing laboratory levels.

16. ANNEXES

Annex 1. List of Stand-alone Documents

None.

Annex 2. Study Protocol and Amendments

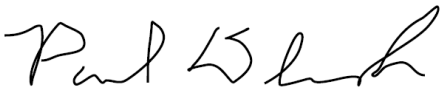
Annex 3. Signature of Coordinating Investigator

Investigator Signature

STUDY NUMBER: 20130335

STUDY REPORT TITLE: Effect of cinacalcet discontinuation on biochemical control for Medicare beneficiaries with Part D coverage treated within a large US dialysis provider

I have read the above named Observational Research Study Report and signify my agreement with the overall conclusions.

Name of Coordinating Investigator:	Paul Dluzniewski
Institution:	Amgen Inc.
Signature of Investigator:	
Date:	20 March 2015