PASS Information

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Country(-ies) of Study	United States
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2. List of Abbreviations

Abbreviation	Definition
Ca	Calcium
CKD	Chronic kidney disease
ESRD	End-stage renal disease
GEE	Generalized estimating equation
HD	Hemodialysis
MBD	Mineral and Bone Disorder
P	Phosphorus
PTH	Parathyroid hormone
SHPT	Secondary hyperparathyroidism
USRDS	United States Renal Data System

3. Responsible Parties

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4. 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: 31 October 2013
    - Authors: Paul Dluzniewski, Amgen, Inc.;
      M. Alan Brookhart, University of North Carolina at Chapel Hill
- 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), and subsequent diminished regulation of calcium (Ca), and phosphorus (P). Cinacalcet, an oral calcimimetic agent, is approved for the treatment of SHPT in patients with CKD on dialysis. After receiving marketing authorization in 2004, the use of cinacalcet has steadily increased in the dialysis-dependent CKD population to current levels of approximately 23% (1). 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 is likely limited. Currently, real world data on risk factors for cinacalcet discontinuation and factors that influence potential reinitiation, as well as the fluctuations in PTH, Ca, and P values during the periods of discontinuation are not well understood. Hence, we propose using data from the United States Renal Data System (USRDS) including Medicare Part D prescription claims merged with dialysis provider data from DaVita (one of the largest dialysis providers in the US), to identify risk factors of discontinuation and reinitiation of cinacalcet, and to describe the trajectory of laboratory values following cinacalcet discontinuation. In addition to describing real-world treatment patterns, these data will provide important insights related to adherence that will help guide future studies evaluating clinical outcomes related to treatment duration.

- Research Question and Objectives: Primary Objective(s):

  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.

- Study Design: Retrospective cohort study
- Population: Adult patients (18 years and older) with ESRD who received center-based hemodialysis at a DaVita facility in the United States and had Medicare as their primary insurer between 2006 and 2010.
- Summary of Patient Eligibility Criteria: Patients 18 years and older with a 30-day prescription of cinacalcet after 6 months of no cinacalcet use and ≥ 90 days of coverage in Medicare's ESRD program (Medicare Part A, B, and D coverage) at the time of their first fill of a cinacalcet prescription. For a full list of eligibility criteria, please refer to Section 9.2.2.1 and Section 9.2.2.2.
- Variables**:**
- Study Variables

Discontinuation: Patients will be defined as discontinuing cinacalcet if there is greater than a 15-day gap from their last pill day (calculated from the days supply dispensed) and the date of the next fill of cinacalcet.

Reinitiation: Patients will be defined as reinitiating cinacalcet if after discontinuation a patient fills a 30-day supply cinacalcet prescription.

- Outcome Variables

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

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

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

- Follow-up

Objective 1: Follow-up will begin at the end of the 1st 30-day fill for new users. The administrative end of follow-up will be 31 December 2010. Patients will also be censored at the earliest date of death, transplantation, parathyroidectomy, filling of >30 day prescription for cinacalcet (patients with 60 or 90 day prescriptions are not at risk of discontinuing during the following 30 day interval), loss of Medicare Part D eligibility, or disenrollment from DaVita.

Objective 2: Follow-up will begin at the first discontinuation of cinacalcet (defined above). The administrative end of follow-up will be 31 December 2010. Patients will also be censored at the earliest date of death, transplantation, parathyroidectomy, loss of Medicare Part D eligibility, or disenrollment from DaVita.

Objective 3: Follow-up will begin at the end of the 1st 30-day fill for new users. The follow-up period will be time between the end of the days supply and the fill of the next prescription. Laboratory values (timing and values) will be determined until another fill of cinacalcet is documented at which time the patient will be censored. Follow-up will begin again following the end of subsequent fills of cinacalcet, and laboratory values will be determined until the patient is censored at the next fill of cinacalcet or the administrative end of follow-up. The administrative end of follow-up will be 31 December 2010. Patients will also be censored at the earliest date of death, transplantation, parathyroidectomy, loss of Medicare Part D eligibility, or disenrollment from DaVita.

- Data Source: The data source for this study will be the merged DaVita-Medicare database
- Study Size: Based on a preliminary analysis of Medicare Part D claims from 01 July 2006 to 31 December 2010 restricted to DaVita patients who were new users of cinacalcet and met all eligibility criteria, the expected number of patients for this study will be approximately 44,000.
- Data Analysis:

Objective 1: The probability of first drug discontinuation will be estimated at consecutive 30-day intervals after the start of follow-up. At the end of each 30-day interval, we will determine if the patient discontinued cinacalcet or continued treatment. Patients will be defined as discontinuing cinacalcet if there is greater than a 15-day gap from their last pill day (calculated from the days supply dispensed) and the date of the next fill of cinacalcet.

For each 30-day interval, we will create and fit a logistic model for drug discontinuation. The model will be based on various time-varying covariates determined at the end of each 30-day interval during follow up. Pooled logistic regression will be used and the average results across the 30-day intervals will be reported.

Objective 2: The probability of drug reinitiation will be estimated at consecutive 30-day intervals following the discontinuation interval. For each 30-day interval, it will be determined if the patient reinitiated cinacalcet (defined by any prescription claim for cinacalcet in the interval). Logistic regression will then be 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. Pooled logistic regression will be used and the average results across the 30-day intervals will be reported.

Objective 3: Laboratory values following discontinuation as a function of time will be modeled using smoothing splines. Population-level averages of laboratory values as a function of time since discontinuation will be presented numerically and graphically. GEE methods will be used to account for any repeated measures issues.

For a full description of statistical analysis methods, refer to Section 9.7

- Milestones:

Start of data collection:	01 December 2013
End of data collection:	01 February 2014
Registration in the EU PAS register:	30 November 2013
Final report of study results:	01 February 2015

5. Amendments and Updates

No amendments or updates.

6. Milestones

Milestone	Planned date
Start of data collection	01 December 2013
End of data collection	01 February 2014
Registration in the EU PAS register	30 November 2013
Final report of study results	01 February 2015

7. Rationale and Background

Secondary hyperparathyroidism (SHPT) is a condition that is present in a large portion of patients with chronic kidney disease (CKD) who are on dialysis. The condition is manifested by increased circulating levels of parathyroid hormone (PTH) and subsequent loss of control of calcium (Ca) and phosphorus (P), and hyperplasia within the parathyroid gland (2-4). 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 (2-7). In an effort to

improve the treatment of kidney disease, the National Kidney Foundation developed the KDOQI guidelines and highlighted the need for control of MBD biochemical parameters in the ESRD population on hemodialysis (HD). The guidelines proposed target ranges based on clinical evidence for the three MBD biochemical parameters: PTH=150-300 pg/mL; Ca= 8.4 to 9.5 mg/dL; and P= 3.5 to 5.5 mg/dL (2). In 2009, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines were released in an attempt to further assist practitioners in the care of patients on dialysis. The KDIGO recommendation for the range of PTH was two to nine times the "normal" value, with levels not to exceed approximately 600 pg/mL. However, ranges for calcium and phosphorus were not specified. Practitioners were recommended to target "normal" ranges for both calcium and phosphorus (8).

A number of treatment options exist to aid in the control of the MBD parameters. Current widely-used interventions include modulation of calcium and phosphorous balance by dietary intake and dialysis, active vitamin D compounds, and phosphate binders (9). However, these interventions suffer from the inability to lower PTH, while simultaneously controlling serum levels of calcium and phosphorous. In 2004, the Food and Drug Administration approved cinacalcet for the treatment of SHPT in patients with CKD on dialysis based on data from three 6-month multicenter, randomized, double-blind, placebo-control clinical studies that showed cinacalcet effectively lowered all three (PTH, Ca, and P) biochemical parameters.

Since the rapid uptake of cinacalcet in the HD community following its launch in 2004 (4), several studies have described its real-world use (10-12). In general, these studies have shown adherence to cinacalcet to be quite low. Most recently, a study by Kilpatrick et al. (13) estimated that, among patients receiving in-center HD, 30% discontinued cinacalcet treatment 12 months post-initiation. Identified factors associated with discontinuation in the study population included older age, non-African-American race, lower calcium or albumin before initiation, moderate doses of elemental calcium-based binders, and not receiving phosphate binders. While this study was informative, it was limited by potential inaccuracies of start and stop dates due to the use of free text fields of electronic medical records. Other studies attempting to assess adherence to cinacalcet in hemodialysis patients were limited by small sample size (14-15) or did not identify time-varying covariates associated with discontinuation (16).

Poor adherence to oral medications is a common problem in the dialysis population, with reported non-adherence rates ranging from 3 - 80% for 19 studies included in a recent systematic review (17). Variables identified as being associated with increased adherence differed across studies, but included older age, long-term HD use, higher education levels and low cost of medications (17). Other reported factors leading to decreased adherence include the high pill burden and the complex medication regimens for the dialysis population (18-20). The need for better understanding of factors influencing adherence to oral medications is highlighted by the association between non-adherence and increased mortality in the dialysis population (21).

Although a link between non-adherence to oral medications and mortality exists, more research is needed specifically focusing on the effect of non-adherence to cinacalcet. There have been few observational studies describing what changes, if any, are observed in the biochemical parameters (PTH, Ca, and P) following discontinuation of cinacalcet. A single study described biochemical values at the time of discontinuation, but lab values after the act of discontinuation were not collected (22). Biochemical control is assumed to be limited when cinacalcet therapy is stopped, but the full extent to which control is limited is still unknown.

Further research is warranted to better understand i) what clinical risk factors are associated with discontinuation, and ii) what changes, if any, are observed in the biochemical parameters (PTH, Ca, and P) following discontinuation. Unlike in a clinical trial, patients treated in the real world can, and often do reinitiate therapy, and therefore it is also worthwhile to examine the characteristic of patients reinitiating treatment.

Our proposed study will utilize merged data from the United States Renal Data System (USRDS) and DaVita (one of the largest dialysis providers in the US) to identify risk factors of discontinuation and reinitiation of cinacalcet and to describe the trajectory of laboratory values following discontinuation of cinacalcet. As Medicare Part D prescription claims data (which are a component of the USRDS database) have only recently become available for observational research, our study will be the first to detail cinacalcet use and its effect on biochemistries one level closer to actual patient use (versus two levels removed from actual patient use when physician prescribing data are

used). Additionally, we will use a new, simple epidemiologic approach to study the time-varying predictors of cinacalcet discontinuation and reinitiation using claims data where the exact dates of discontinuation and reinitiation are unknown.

8. Research Question and Objectives

This study has three 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.

9. Research Methods

Formal hypotheses will not be tested.

This study will estimate:

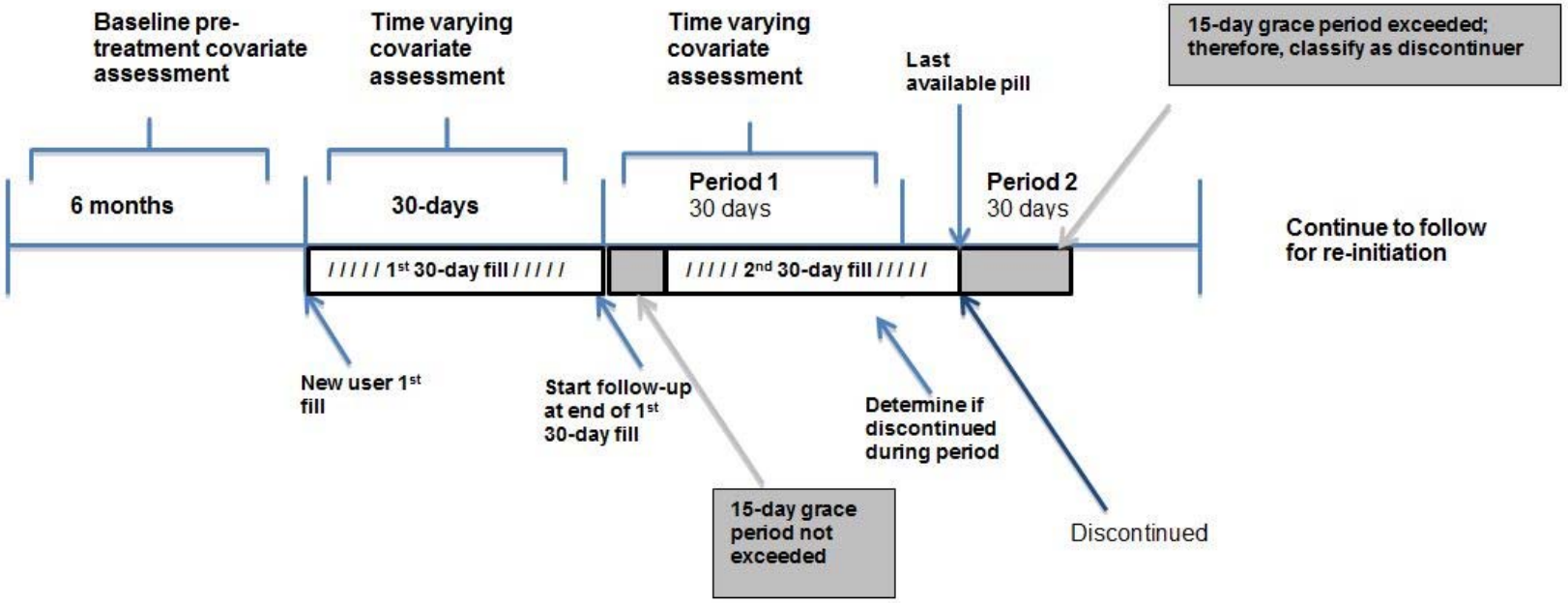
- For Objective 1: the effect of various pre-specified covariates and laboratory values on the probability of cinacalcet discontinuation during defined intervals
- For Objective 2: the effect of various pre-specified covariates and laboratory values on the probability of cinacalcet reinitiation during defined intervals
- For Objective 3: the average parathyroid hormone, calcium, and phosphorus levels over time up to one year following the discontinuation of cinacalcet

9.1 Study Design

We will utilize 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 will also describe the trajectory of laboratory values at varying time points following the discontinuation of cinacalcet.

9.1.1 Study Schema

Study Design Schema: Objective 1 Primary Analysis

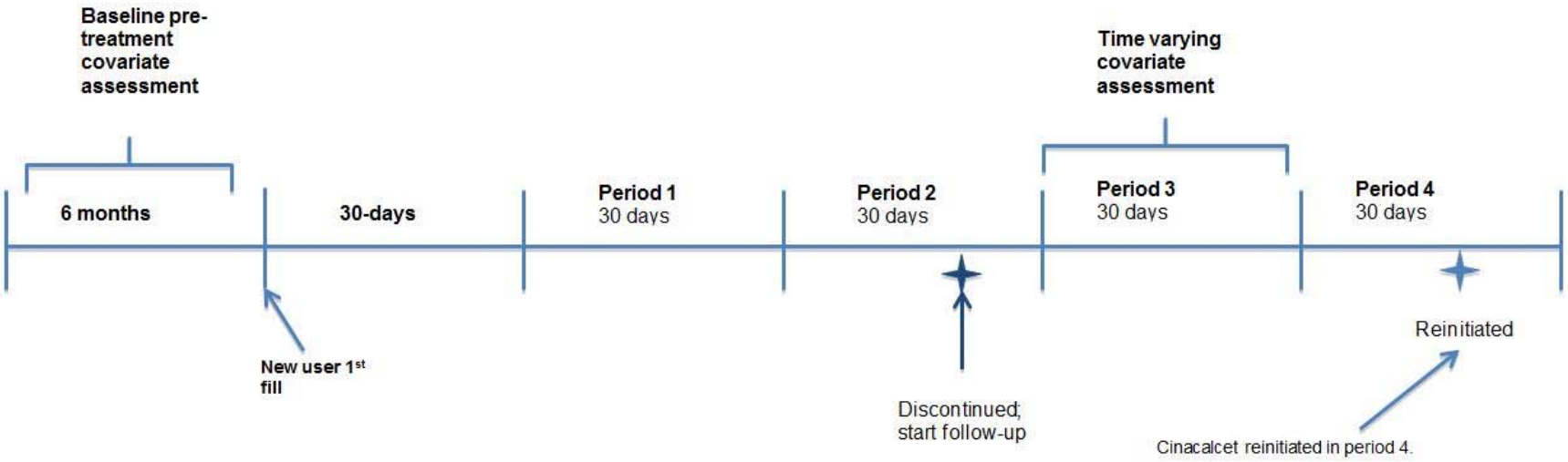


OBJECTIVE 1: To describe risk factors for first discontinuation of cinacalcet among dialysis-dependent patients

OBJECTIVE 1 PRIMARY ANALYSIS DETAILS

- New users of cinacalcet, defined as no other use of cinacalcet during the prior 6 months
- Follow-up begins at the end of the first 30-day fill and at this point patients are at risk for discontinuation
- Patient is a discontinuer if there is no refill within 15 days from last available pill, classified as a discontinuer regardless of any later fills
- Determine if a patient has discontinued for each 30-day period
- Use baseline covariates and time varying covariates from the interval prior to the discontinuation interval to estimate the effect of covariates and laboratory values on risk of cinacalcet discontinuation. Use laboratory values from the interval prior to the discontinuation interval that are most proximal to the discontinuation period

Study Design Schema: Objective 2 Primary Analysis



OBJECTIVE 2: To describe factors associated with reinitiation of cinacalcet among dialysis-dependent patients

OBJECTIVE 2 PRIMARY ANALYSIS DETAILS

- New users of cinacalcet, defined as no other use of cinacalcet during the prior 6 months
- Follow-up begins after first discontinuation, as defined in Objective 1, of cinacalcet and at this point patients are eligible to reinitiate cinacalcet
- Determine if patient reinitiated cinacalcet at the end of each 30-day period following a discontinuation
- Use baseline covariates and time varying covariates from the interval prior to the reinitiation interval to estimate the effect of covariates and laboratory values on risk of cinacalcet reinitiation. Use laboratory values from the interval prior to the reinitiation interval that are most proximal to the reinitiation period

9.2 Setting

9.2.1 Study Population

The study population will be derived from a source population of adult patients (18 years and older) with ESRD 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.

9.2.2 Patient Eligibility

9.2.2.1 Inclusion Criteria

We will include male and female patients in this study if they meet 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

9.2.2.2 Exclusion Criteria

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

9.2.3 Definition of Time Periods

9.2.3.1 Study Period

The study period will be 01 July 2006 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.

9.2.3.2 Baseline Period

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

9.2.3.3 Study Follow-up Period

Objective 1: Follow-up will begin at the end of the 1st 30-day fill for new users. New users will be 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 will be 31 December 2010. Patients will also be censored at the earliest date of death, transplantation, parathyroidectomy, filling of >30 day prescription for cinacalcet (patients with 60 or 90 day prescriptions are not at risk of discontinuing during the following 30 day interval), loss of Medicare Part D eligibility, or disenrollment from DaVita.

Objective 2: Follow-up will begin at the first discontinuation of cinacalcet. The administrative end of follow-up will be 31 December 2010. Patients will also be censored at the earliest date of death, transplantation, parathyroidectomy, loss of Medicare Part D eligibility, or disenrollment from DaVita.

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

9.2.3.4 Time at Risk

Objective 1: The time at risk will be the time from the end to 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, filling of >30 day prescription for cinacalcet (patients with 60 or 90 day prescriptions are not at risk of discontinuing during the following 30 day interval), loss of Medicare Part D eligibility, or disenrollment from DaVita.

Objective 2: The time at risk will be 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 D eligibility, or disenrollment from DaVita.

Objective 3: The time at risk will begin 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 will be time between the end of the days supply and the fill of the next

prescription. Laboratory values (timing and values) will be determined until another fill of cinacalcet is documented at which time the patient will be censored. The next period of time at risk will begin at the end of subsequent fills of cinacalcet, and laboratory values will be determined until the patient is 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 D eligibility, or disenrollment from DaVita.

9.2.3.5 Endpoints Assessment

Objective 1: The endpoint will be an indicator of cinacalcet discontinuation, assessed at consecutive 30-day intervals following the end of the 1st 30-day fill for new users.

Objective 2: The endpoint assessed will be an indicator of cinacalcet reinitiation, assessed at consecutive 30-day intervals following the first discontinuation of cinacalcet.

Objective 3: The endpoints assessed will be the calcium, phosphorus, and parathyroid hormone values up to one year following any discontinuation of cinacalcet.

9.3 Variables

9.3.1 Study Outcome(s)

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

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

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

9.3.2 Covariates

We will evaluate the following covariates at baseline (6 months prior to the 1st cinacalcet fill for new users). For the comorbid conditions identified using information provided from the Medicare claims data (part A or B), we will consider comorbid conditions as being present based on one in-patient claim or two out-patient claims in any position separated by 30 days.

TABLE 1: BASELINE COVARIATES

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)
Dialysis Vintage	Time since start of renal replacement therapy
Cause of ESRD	Classify as diabetes, hypertension, glomerular nephritis, or other
Body Mass Index (BMI)	As reported in DaVita data or on the Medical Evidence form (CMS-2728)
Medicaid Eligibility	As reported on the Medical Evidence form (CMS-2728)
Low Income Subsidy	
Laboratory Values	
Serum Parathyroid Hormone (pg/mL)	Most proximal PTH lab value to start of follow-up period. PTH is marker of bone mineral dysregulation
Serum calcium level (mg/dL)	Most proximal serum calcium lab value to the start of follow-up period
Serum phosphorus level (mg/dL)	Most proximal phosphorus lab value to the start of follow-up period
Serum Albumin (g/dL)	Based on the most proximal value reported in the Davita Clinical Database
Hemoglobin (g/dL)	Based on the most proximal value reported in the Davita Clinical Database
Transferrin Saturation (TSAT) %	Most proximal TSAT to start of follow-up period. TSAT is a measure of iron availability and an important determinant of iron treatment
Serum Ferritin (ng/mL)	Most proximal TSAT to start of follow-up period. Ferritin is a measure of iron storage and, in combination with TSAT, is an important determinant of iron treatment
Comorbidities	
Frequency of Lipid Test (Proxy for cardiovascular disease risk (25))	Frequency of lipid tests entered as a categorical variable (<=1, 2-3, 3+)
Evidence of serious coronary artery disease	History of PTCA, stent placement, acute myocardial infarction, CABG surgery, ischemic stroke, venous thromboembolism, and unstable angina as determined by the examination of Medicare claims (Covariate will be Yes/No categorical variable)
Other CAD risk factors	History of diabetes, angina, peripheral vascular disease, obesity, and hypertension as determined by the examination of Medicare claims (Covariates will be Yes/No categorical variables)
Other cardiovascular risk factors	History of arrhythmias and heart failure as determined by the examination of Medicare claims (Covariates will be Yes/No categorical variables)
Autoimmune comorbidities	History of rheumatoid arthritis, inflammatory bowel disease, psoriasis, lupus as determined by examination of Medicare claims (Covariates will be Yes/No categorical variables)
Other non-cardiovascular, autoimmune comorbidities	Indicators for history of liver disease, congestive obstructive pulmonary disease, asthma, peptic ulcer disease, GI bleeding, osteoarthritis, osteoporosis, gout, cancer, hyperthyroidism, depression, and other psychiatric disorders as determined by

	examination of Medicare claims (Covariates will be Yes/No categorical variables)
Overall patient comorbidity	Charlson comorbidity score, a weighted sum of 19 conditions that may be prevalent in individual patients

See Annex 5 for the detailed description of certain baseline covariates.

We will evaluate the following time-varying covariates at 30-day intervals following the start of follow-up.

TABLE 2: TIME-VARYING COVARIATES

Type of Variable	Measurement and other notes
Laboratory Values	
Serum Parathyroid Hormone (pg/mL)	The two most proximal PTH lab values prior to the end of the time-varying covariate assessment period.
Serum calcium level (mg/dL)	The two most proximal calcium lab values prior to the end of the time-varying covariate assessment period.
Serum phosphorus level (mg/dL)	The two most proximal phosphorus lab values prior to the end of the time-varying covariate assessment period.
Serum Albumin (g/dL)	Most proximal albumin lab value to the end of the time-varying covariate assessment period.
Transferrin Saturation (TSAT) %	Most proximal TSAT value to the end of the time-varying covariate assessment period. If not measured in interval, then impute most recent measurement.
Serum Ferritin (ng/mL)	Most proximal ferritin value to the end of the time-varying covariate assessment period. If not measured in interval, then impute most recent measurement.
Concomitant Medications (including total number of concomitant medications)	
Intravenous Vitamin D use	Defined as a categorical variable, no use, low dose, and high dose. Low and high dose will be determined empirically by assessing the distribution of the data (e.g., determining the median) and using the content expertise of the research team.
Oral phosphate binder use	Defined as a categorical variable, no use, low dose, and high dose. Low and high dose will be determined empirically by assessing the distribution of the data (e.g., determining the median) and using the content expertise of the research team.
Other Covariates	
Current vascular access	Using access information, we will classify patients as having a catheter, fistula, or graft.
Acute Care Hospitalization, in days	This will be determined from the USRDS file institutional claims file.
Co-pay	Cost of cinacalcet prescription using Part D claims data.
Donut Hole status	Entrance into and out of donut hole will be categorized yes or no. Co-pay will be used to determine donut hole status.
Low Income Subsidy	Categorized yes or no based on cost-share variable (04-08 indicates Low Income Subsidy).

See Annex 5 for the detailed description of certain time-varying covariates.

9.3.3 Subgroups

For objectives 1 and 2, we will conduct select subgroup analyses in the following categories: age, gender, race, dialysis vintage, and ESRD cause.

For objective 3, we will also examine trends in lab values after first discontinuation (rather than all discontinuations) and trends in lab values stratified by Vitamin D dose (high vs. low).

9.4 Data Sources

The data source for this study will be 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.

9.4.1 Data Quality

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 should not be a major concern. We anticipate no data editing for the data within the merged DaVita-Medicare database.

9.4.2 Validity and Reliability

The validity, completeness and reliability of the USRDS data have been examined by two early studies conducted by the USRDS (23). 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% (24). 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 (23). Prospective validation of the data, however, is not performed on a continuous basis.

9.5 Study Size

Based on a preliminary analysis, from 01 July 2006 to 31 December 2010, there were 1,879,367 Medicare Part D claims. Among these claims, 1,285,879 patients had Medicare Part A, B, and D coverage during a 6 month baseline period and were receiving in center hemodialysis. After excluding cinacalcet use in the prior 6 months, there were 86,807 new users who received an initial prescription of 30 days between 01 July 2006 and 31 December 2010. Of these new users, 47% were DaVita patients.

Margin of error for absolute risk reduction by risk factor prevalence and effect size:

Margin of error is half the width of the 95% confidence interval and is estimated as 1.96*sqrt((p1*(1-p1)/n1) + (p2*(1-p2)/n2)), where sqrt is the square root function, p1 is the probability of the outcome in the absence of the risk factor, n1 is the number of people without the risk factor, p2 is the probability of the outcome in the presence of the risk factor, and n2 is the number of people with the risk factor. Estimates are based on a sample size of 44,000 and a probability of 0.1 that the outcome will occur in the absence of the risk factor.

The results below suggest that for risk factors with a prevalence >=%5 we will be able to estimate changes in risk of discontinuation with fairly high precision.

TABLE 3: MARGIN OF ERRORS

	Absolute increase in risk due to risk factor			
Risk factor prevalence	**0.01**	**0.02**	**0.05**	**0.10**
0.01	0.029	0.030	0.033	0.037
0.05	0.013	0.014	0.015	0.017
0.10	0.010	0.010	0.011	0.012

9.6 Data Management

9.6.1 Obtaining Data Files

The merged DaVita-Medicare database is housed at UNC and will not be accessed remotely by Amgen. These files do not contain any protected health information (with the exception of ZIP code of patient residence and visit dates) and qualify as a Limited Data Set.

9.6.2 Data Collection

All data were pre-collected through CMS reimbursement systems and DaVita dialysis facilities. We will complete all analyses using one analysis set that will be derived once we apply the inclusion / exclusion criteria to the merged DaVita-Medicare database. All data are currently maintained using SAS 9.2.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Primary Analysis

We will initiate all analyses after inclusion criteria have been applied to the merged DaVita-Medicare database and the analytic set has been derived. We will not conduct separate interim or final analyses.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

For this study, we plan to create cohorts that will address the objectives of this study and allow a transition into the marginal structural modeling approach that will be used in a subsequent cinacalcet study.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

The percentage of missing data for the proposed variables of this study is minimal (<5%) based on preliminary data exploration. For missing laboratory values we will be using the carry forward method, considered to be synonymous with clinical practice. For other covariates, we will conduct a complete case analysis and remove patients for whom not all data are available.

9.7.3 Descriptive Analysis/Analyses

9.7.3.1 Description of Study Enrollment

We will construct a STROBE diagram to illustrate how the study population was derived from the source population. Excluded patient counts will be provided for each inclusion criteria applied, as specified in Section 9.2.2.1 and 9.2.2.2.

9.7.3.2 Description of Subject/Patient Characteristics

We will tabulate subject characteristics and a comorbidity profile of new users of cinacalcet during a 6-month baseline period. For these descriptive analyses, the mean and standard deviation will be provided for continuous variables, and the frequency and percent will be provided for categorical variables.

9.7.4 Analysis of the Primary Endpoints

9.7.4.1 Objective 1

For objective 1, the probability of drug discontinuation will be estimated at 30-day intervals after the start of follow-up. At the end of each 30-day interval, it will be determined if the patient discontinued cinacalcet or continued treatment. Patients will be defined as discontinuing cinacalcet if there is greater than a 15-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 will create and fit a logistic model for drug discontinuation. The model will be based on various time-varying covariates determined at the end of each 30-day interval during follow up. Because we will not know the exact time of discontinuation in a given interval, using the 30-day interval prior to the discontinuation interval for the identification of time-varying covariates in our probability estimate will decrease the chance that we are using variables that occur following the discontinuation of cinacalcet. Although each patient may contribute multiple 30-day intervals to the analysis dataset, we will not need to adjust for repeated measures since each patient can only discontinue once. In addition, a pooled logistic regression will be used and the average effects of covariates across the 30-day intervals will be reported.

9.7.4.2 Objective 2

For objective 2, the probability of drug reinitiation will be estimated at each 30-day interval following the discontinuation interval. For each 30-day interval, it will be 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 will be estimated using logistic regression. Logistic regression will then be 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 contribute multiple 30-day intervals to the analysis dataset, we will not need to adjust for repeated measures since each patient can only reinitiate once. In addition, a pooled logistic regression will be used and the average effects of covariates across the 30-day intervals will be reported.

9.7.4.3 Censoring for Objectives 1 and 2

For objectives 1 and 2, patients will be censored during follow-up for death, loss of Medicare coverage, kidney transplant, switches to another dialysis modality, filling a >30 day prescription (Objective 1), parathyroidectomy, or administratively. In the case where laboratory values are not available in a 30-day interval being used to predict

discontinuation or reinitiation, available labs from the prior 30-day interval will be carried forward. This carry forward method is congruous to clinical practice, as these labs would be the labs available to the physician making medication decisions.

9.7.4.4 Objective 3

For objective 3, follow-up will begin at the end of the days supply of the 1st prescription fill for new users. Laboratory values (timing and values) will be determined until another fill of cinacalcet is documented at which time the patient will be censored. Follow-up will begin again following the end of subsequent fills of cinacalcet, and laboratory values will be determined until the patient is censored at the next fill of cinacalcet or the administrative end of follow-up. Laboratory values immediately preceding discontinuation will be used as the anchor point for the calculations of trajectories. Laboratory values following discontinuation as a function of time (up to one year) will be modeled using cubic smoothing splines (26). 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 (27). 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 will let the smoothing parameter be set by the cross-validation approach that attempts to minimize the mean-squared error of the resulting fit. Population-level averages of laboratory values as a function of time since discontinuation will be presented numerically and graphically. GEE methods will be used to account for any repeated measures.

9.7.5 Sensitivity Analyses

Several sensitivity analyses are planned. See Annex 7 for Objectives 1 and 2 sensitivity analysis schemas.

For objectives 1:

- Varying the length of the time-varying covariate assessment to include both the interval prior to discontinuation and the actual discontinuation interval (up until the midpoint of the actual discontinuation interval)

- Varying the allowable gap (30 and 60 days) between a patient's last pill day (calculated from the days supply dispensed) and the date of the next fill of cinacalcet used to determine if a patient is a discontinuer

For objective 2:

- Varying the length of the time-varying covariate assessment to include both the interval prior to reinitiation and the actual reinitiation interval (up until the midpoint of the actual reinitiation interval)
- Varying the allowable gap (30 and 60 days) between a patient's last pill day (calculated from the days supply dispensed) and the date of the next fill of cinacalcet used to determine if a patient is a discontinuer

For objective 3:

- Categorize outcome laboratory values according to KDIGO guidelines and report:
    - Time to critical laboratory values following cinacalcet discontinuation
    - Percent change over time from reference laboratory values following cinacalcet discontinuation

9.7.5.1 Subgroup Analyses

Section 9.3.2 defines the clinical variables that we may consider examining for subgroup analyses. We may modify clinical variables to use in the stratified analyses once final sample sizes have been determined (to avoid subgroup analyses with poor precision). In addition, for Objective 3 we will we will also examine trends in lab values after first discontinuation (rather than all discontinuations) and stratified by Vitamin D dose (high vs. low) and length of time on cinacalcet. For objective 3, we will also stratify by pre-discontinuation control of laboratory values through the creation of an indicator variable for control. The decision of what constitutes biochemical control will be based on the data and input from the collaborating physician. This indicator variable will be created to best discriminate between control and loss of control.

9.8 Quality Control

Clinician-informed trimming rules for lab values and doses of medications will be used during the construction of the analytic data file. We anticipate no data editing for this study after construction of the analytic file.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

Threats to internal validity include misclassification/misidentification of prescriptions in claims data and survival bias (as subjects will be required to have a minimum of 90 days of dialysis care prior study inclusion).

9.9.2 Measurement Error(s)/Misclassification(s)

For objectives 1 and 2, the exact discontinuation and reinitiation dates will not be known, but a time frame of discontinuation and reinitiation will be. In order to ensure that we are obtaining risk factor variables prior to the actual discontinuation and reinitiation dates, we will be using variables obtained at the end of the prior 30-day time interval. More proximal variables identified during the actual discontinuation and reinitiation intervals could be missed. However, identifying variables from the actual discontinuation and reinitiation intervals, when the exact dates are unknown, risks obtaining information that occurs following discontinuation or reinitiation and biasing our results. Likewise, conditioning on future events, such as not refilling, would impose selection effects in the analysis that could bias results. We will explore this potential measurement error through sensitivity analyses that vary the time-varying covariate assessment interval and the allowable gap between prescription fills used to identify discontinuers.

9.9.3 Information Bias

Considering the study design and study objectives, information bias is not a likely source of bias in this study.

9.9.4 Selection Bias

Although the study will not describe discontinuation for all cinacalcet users, it is unlikely the distribution of factors associated with discontinuation and reinitiation will be different in patients included in the study compared to patients excluded from the study. As a result, selection bias is not a likely source of bias in this study.

9.9.5 Confounding

For our final results, we will report risk factors of discontinuation and factors associated with reinitiation independent of other covariates. We will adjust for possible confounding of the association between the individual factors and discontinuation and reinitiation.

9.9.6 External Validity of Study Design

Based on the selection of the database for this study, patients must have been receiving HD from a DaVita facility. 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 HD in non-DaVita facilities.

9.10 Other Aspects

9.10.1 Analysis Limitations

Analyses using DaVita data will be limited to years 2006-2010. Based on prior experience with analysis of the USRDS data, missing data will be minimal and will not likely impact interpretation of the results.

As noted in section 9.9.2, we will not know the exact discontinuation or reinitiation dates, and we may not obtain the risk factors most proximal to the discontinuation or reinitiation dates. However, our primary analysis methods will ensure that we are not biasing results by initially limiting our risk factors to intervals prior to discontinuation or reinitiation. We will further explore our results in sensitivity analyses that vary the time-varying covariate assessment interval and the allowable gap between prescription fills used to identify discontinuers.

Another limitation of the study will be the lack of data on all predictors (e.g., nausea and vomiting) of discontinuation and reinitiation. In addition, adverse events are important predictors of discontinuation and that a limitation of the study is the inability to directly identify adverse events. We will have calcium laboratory values and will be able to identify occurrences of hypocalcemia, but our ability to capture other adverse events (e.g., nausea and vomiting) will be limited. Given the structure of the data, we also will be unable to attribute adverse events to cinacalcet.

We acknowledge patients that discontinue short-term, or repeatedly stop and start cinacalcet, may have different predictors of discontinuation compared to patients who stop cinacalcet indefinitely. Our reasons for selecting a 15 day gap include: 1) 30-day fill being the most common prescription days supplied; 2) the rapid changes in PTH that occur when cinacalcet is taken or withdrawn, and thus, our need to incorporate a relatively narrow window otherwise we will miss the changes; and 3) the need to assess confounding and misclassification in a narrow window for our next project related to persistence of cinacalcet and clinical outcomes (which will be using a marginal structural model approach). We will attempt to address this difference by conducting sensitivity analyses extending the allowable gap between refills. We will assess if the use of 30 day and 60 day gaps impact our results.

10. Protection of Human Subjects

10.1 Institutional Review Board/Independent Ethics Committee

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. The UNC Chapel Hill Office of Human Research Ethics reviewed this study and it was determined to be exempt from further review according to the regulatory category cited under 45 CFR 46.101(b), exemption category 4; existing data, public or de-identified. See Annex 6.

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 information on adverse events, nor do they 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 adverse reactions reporting is not required.

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 adverse reactions reporting is not required.

11.2.2 Definition of Other Safety Findings

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

11.2.3 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 relevant nephrology, epidemiology, and general medicine journals. Results will also be presented at highly frequented professional conferences including the American Society of Nephrology (ASN) and International Society of Pharmacoepidemiology (ISPE) annual meetings.

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 (eg, 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.

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14. Annexes

Annex 1. List of Stand-alone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

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

Study reference number:
N/A

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
1.1.2 End of data collection[2]	☒	☐	☐	7
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	7
1.1.6 Final report of study results.	☒	☐	☐	7

Comments:

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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)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	10
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	10

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**

[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)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	10
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	15
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)	☒	☐	☐	10

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	13
4.2 Is the planned study population defined in terms of:				13
4.2.1 Study time period?	☒	☐	☐	13
4.2.2 Age and sex?	☒	☐	☐	13
4.2.3 Country of origin?	☒	☐	☐	13
4.2.4 Disease/indication?	☒	☐	☐	15
4.2.5 Co-morbidity?	☒	☐	☐	
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)	☒	☐	☐	13

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)	☒	☐	☐	13
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)	☒	☐	☐	25
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	13
5.4 Is exposure classified based on biological				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
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?	☒	☐	☐	24

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?	☒	☐	☐	15
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)	☒	☐	☐	22

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)	☒	☐	☐	15-17, 25
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	24

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.)	☒	☐	☐	18
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.)	☒	☐	☐	18
8.1.3 Covariates?	☒	☐	☐	18
8.2 Does the protocol describe the information				

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	18
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	18
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	18
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	15
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)	☒	☐	☐	43
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	19

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	20

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?	☒	☐	☐	21
10.3 Are descriptive analyses included?	☒	☐	☐	21
10.4 Are stratified analyses included?	☒	☐	☐	24
10.5 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	25
10.6 Does the plan describe methods addressing effect modification?	☒	☐	☐	24

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)	☒	☐	☐	21
11.3 Are methods of quality assurance described?	☒	☐	☐	19
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	19
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?	☒	☐	☐	25
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)	☒	☐	☐	25
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13
12.3 Does the protocol address other limitations?	☒	☐	☐	25

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?	☒	☐	☐	26
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	26

Comments:

There were no ethical issues upon IRB review of the protocol.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**

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?	☒	☐	☐	7

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)?	☒	☐	☐	27
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	27

Comments:

Annex 3. Sample Safety Reporting Form

Not applicable.

Annex 4. Pregnancy and Lactation Notification Worksheets

Not applicable.

Annex 5.

TABLE 4: CODES AND DATASETS

VARIABLE	DESCRIPTION	DATA SOURCE
Demographics		
Age Categories (years)	18-44 45-64 65-74 ≥75	USRDS Patient File
Sex Categories	Male Female	USRDS Patient File
Black	Patients of Black race	Medicare enrollment data (USRDS)
Non-Black	Patients of White or Other race	Medicare enrollment data (USRDS)
Hispanic	Patient of Hispanic ethnicity	Medicare enrollment data (USRDS)
Non-Hispanic	Patient of Non-Hispanic ethnicity	Medicare enrollment data (USRDS)
Dialysis Vintage Categories (years)	≤1 <1-3 <3-5 ≥5	USRDS Patient File
ESRD Cause	Diabetes Hypertension Glomerulonephritis Other	USRDS Medical Evidence Form
Laboratory Values		
Parathyroid hormone (pg/mL)	Serum parathyroid measured in pg/mL Low <150 pg/mL Normal 150-300 pg/mL High >300 pg/mL	DaVita Clinical Data
Calcium (mg/dL)	Serum calcium measured in Low <8.4 mg/dL Normal 8.4-9.5 mg/dL High >9.5 mg/dL	DaVita Clinical Data
Phosphorus (mg/dL)	Serum phosphorus measured in Low <3.5 mg/dL Normal 3.5-5.5 mg/dL High 5.5 mg/dL	DaVita Clinical Data
Intravenous Vitamin D		
Calcitriol	J0635	DaVita Clinical Data
Calcitriol	J0636	DaVita Clinical Data
Paricalcitol	J2500	DaVita Clinical Data
Paricalcitol	J2501	DaVita Clinical Data

Doxercalciferol	J1270	DaVita Clinical Data
Oral Phosphate Binders		
Renagel® (sevelmar)	NDC	Medicare Part D
Phoslo® (calcium acetate)	NDC	Medicare Part D
Cinacalcet		
30mg cinacalcet hydrochloride, oral coated tablet	NDC 55513-0073-30	Medicare Part D
60mg cinacalcet hydrochloride, oral coated tablet	NDC 55513-0074-30	Medicare Part D
90mg cinacalcet hydrochloride, oral coated tablet	NDC 55513-0075-30	Medicare Part D
Comorbidities		
Congestive Heart Failure	ICD-9-CM diagnosis codes during baseline: 428.xx, 40211,40291,40411,40413,40491,40493	Medicare Part A and B
Diabetes	ICD-9-CM diagnosis codes during baseline 250.xx, 648.00-648.04, 249.00-249.31, 249.40-249.91, 775.1	Medicare Part A and B
History of Cardiovascular Disease (Hosptialization for stroke or myocardial infarction, or revascularization during the baseline period)	History of MI: ICD-9-CM codes 410 as a primary or secondary diagnosis in the discharge summary and with length of stay > 1 days (unless the patient died) and <180 days; History of stroke: Hospitalization for stroke will be defined as an admission with ICD-9-CM code 433.x1, 434.x1, 435, 436, 437.1x, or 437.9x in the first position. Revascularization will be identified with CPT codes and ICD-9-CM Procedure Codes	Medicare Part A and B
Chronic obstructive pulmonary disease	ICD-9-CM codes during baseline period: 490-492.8, 493.00-493.92, 494-494.1, 495.0-505.xx, 506.4	Medicare Part A and B

ANNEX 6. IRB EXEMPTION

Email from UNC IRB forward to Paul Dluzniewski on 8/1/13

To: M. Brookhart
Epidemiology

From: Office of Human Research Ethics

Date: 7/23/2013

RE: Notice of IRB Exemption
Exemption Category: 4.Existing data, public or deidentified
Study #: 13-2584

Study Title: Patterns of Use of Cinacalcet Among Patients with End-Stage Renal Disease

This submission has been reviewed by the Office of Human Research Ethics and was determined to be exempt from further review according to the regulatory category cited above under 45 CFR 46.101(b).

Study Description:

Purpose: The primary objective of this study is to examine the patterns of use of cincalcet since its launch in 2004 in an end-stage renal disease (ESRD) population. Cinacalcet, an oral calcimimetic agent, was approved by the Food and Drug Administration in 2004 for the treatment of secondary parathyroidism in patients with dialysis dependent kidney failure.

Participants: Adult patients (18 years and older) with ESRD who received center-based hemodialysis at a DaVita facility in the United States and had Medicare as their primary insurer between 2004 and 2010.

Procedures (methods): The specific aims are as follows: 1. To describe risk factors for discontinuation of cinacalcet among dialysis-dependent patients. Possible risk factors include: Lab values (calcium, parathyroid hormone, phosphorus), hospitalizations, quality of life, measures of health status, concomitant medications (vitamin D), facility-level characteristics, variations across facilities, and vascular access. 2. To describe risk factors for re-initiation of cinacalcet among dialysis-dependent patients. Possible risk factors, as above. 3. To describe the trajectory of laboratory values, such as calcium, phosphorus, and parathyroid hormone, following the discontinuation of cinacalcet. 4. Using the models developed in the above aims, describe results from aims 1-3 across subgroups, such as race, gender, and type of access.

Investigator's Responsibilities:

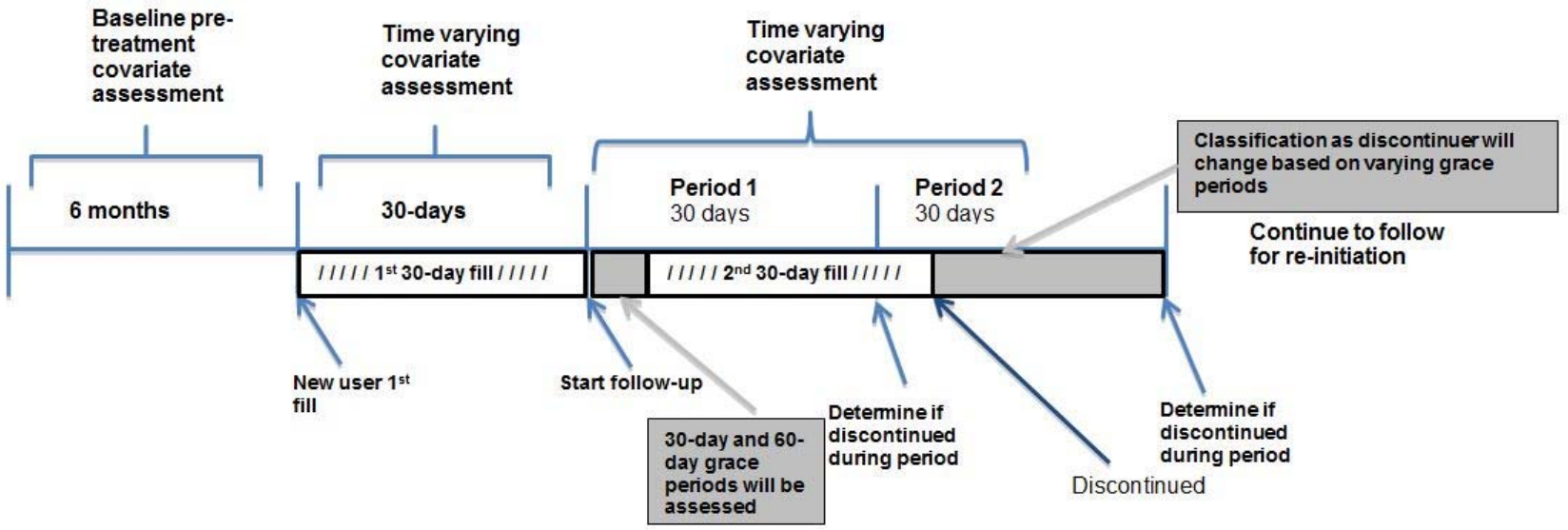
If your study protocol changes in such a way that exempt status would no longer apply, you should contact the above IRB before making the changes. The IRB will maintain records for this study for 3 years, at which time you will be contacted about the status of the study.

Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., principals, facility directors, healthcare system).

CC:
Diane Reams, SHEPS Center for Health Services Research

IRB Informational Message—please do not use email REPLY to this address

Annex 7. Study Design Schema: Objective 1 Sensitivity Analyses

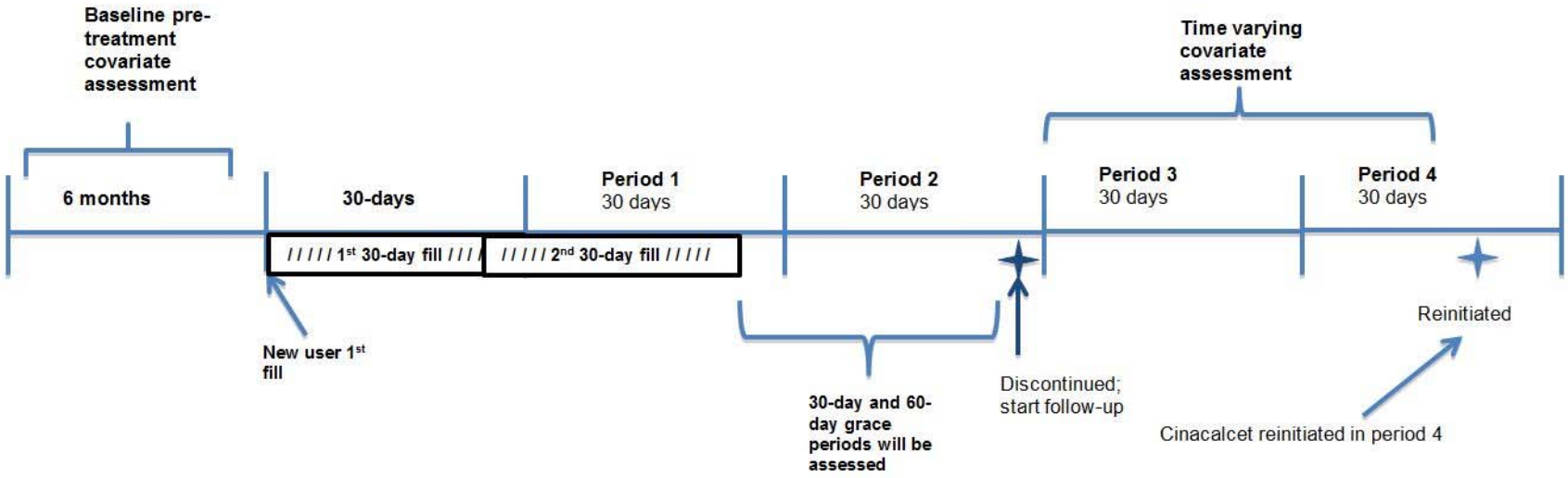


OBJECTIVE 1: To describe risk factors for discontinuation of cinacalcet among dialysis-dependent patients

OBJECTIVE 1 SENSITIVITY ANALYSES DETAILS

- New users of cinacalcet, defined as no other use of cinacalcet during the prior 6 months
- Follow-up begins at the end of the first 30-day fill and at this point patients are at risk for discontinuation
- Patient is a discontinuer if there is no refill within 15 days from last available pill, classified as a discontinuer regardless of any later fills
- Determine if a patient has discontinued for each 30-day period
- Based on days supply available and application of the grace period, impute the estimated day of discontinuation during period 2.
- Use baseline covariates and time varying covariates from the interval prior to the discontinuation interval to estimate the effect of covariates and laboratory values on risk of cinacalcet discontinuation. Use laboratory values from the interval prior to the discontinuation interval that is most proximal to the discontinuation period.
- Vary the length of the time-varying covariate assessment to include the interval prior to discontinuation and up until the midpoint of the actual discontinuation interval and a separate analysis varying the allowable gap between prescription fills used to identify discontinuers

Study Design Schema: Objective 2 Sensitivity Analyses



OBJECTIVE 2: To describe factors associated with reinitiation of cinacalcet among dialysis-dependent patients

OBJECTIVE 2 SENSITIVITY ANALYSES DETAILS

- New users of cinacalcet, defined as no other use of cinacalcet during the prior 6 months
- Follow-up begins after first discontinuation, as defined in Objective 1, of cinacalcet and at this point patients are eligible to reinitiate cinacalcet
- Determine if patient reinitiated cinacalcet at the end of each 30-day period following a discontinuation
- Use baseline covariates and time varying covariates from the interval prior to the reinitiation interval to estimate the effect of covariates and laboratory values on risk of cinacalcet reinitiation. Use laboratory values from the interval prior to the reinitiation interval that is most proximal to the reinitiation period.
- Vary the length of the time-varying covariate assessment to include the interval prior to reinitiation and up until the midpoint of the actual discontinuation interval and a separate analysis varying the allowable gap between prescription fills used to identify discontinuers