Summary Table of Study Protocol

Title	Cinacalcet Use and the Risk of Gastrointestinal (GI) Bleeding Among Hemodialysis Patients with Secondary Hyperparathyroidism (SHPT) in DOPPS
Protocol version identifier	20170665
Date of last version of the protocol	06 March 2018
EU Post Authorisation Study (PAS) Register No	NA
Active Substance	Cinacalcet Hydrochloride
Medicinal Product	Cinacalcet (Sensipar®/Mimpara®)
Product Reference	
Procedure Number	
Marketing Authorisation Holder(s)	Amgen
Joint PASS	No
Objectives	1. Estimate the association between exposure to cinacalcet and the risk of hospitalization from GI bleeding, by region (US, Other) and overall. 2. Estimate the association between exposure to cinacalcet and the risk of death from GI bleeding, by region (US, Other) and overall. 3. Estimate the rate of hospitalization from GI bleeding and the rate of death from GI bleeding, by region (US, Other) and overall.
Country(-ies) of Study	United States, France, Germany, Italy, Spain, United Kingdom, Belgium, Sweden, Russia, Australia, New Zealand, Canada, and Japan
Author(s)	PPD PPD PPD PPD

Marketing Authorisation Holder

Marketing authorisation holder(s)	
MAH Contact	PPD Observational research manager, CfOR PPD

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Study Design Schema

Figure 1. Study Design Schematic for the Cohort Study

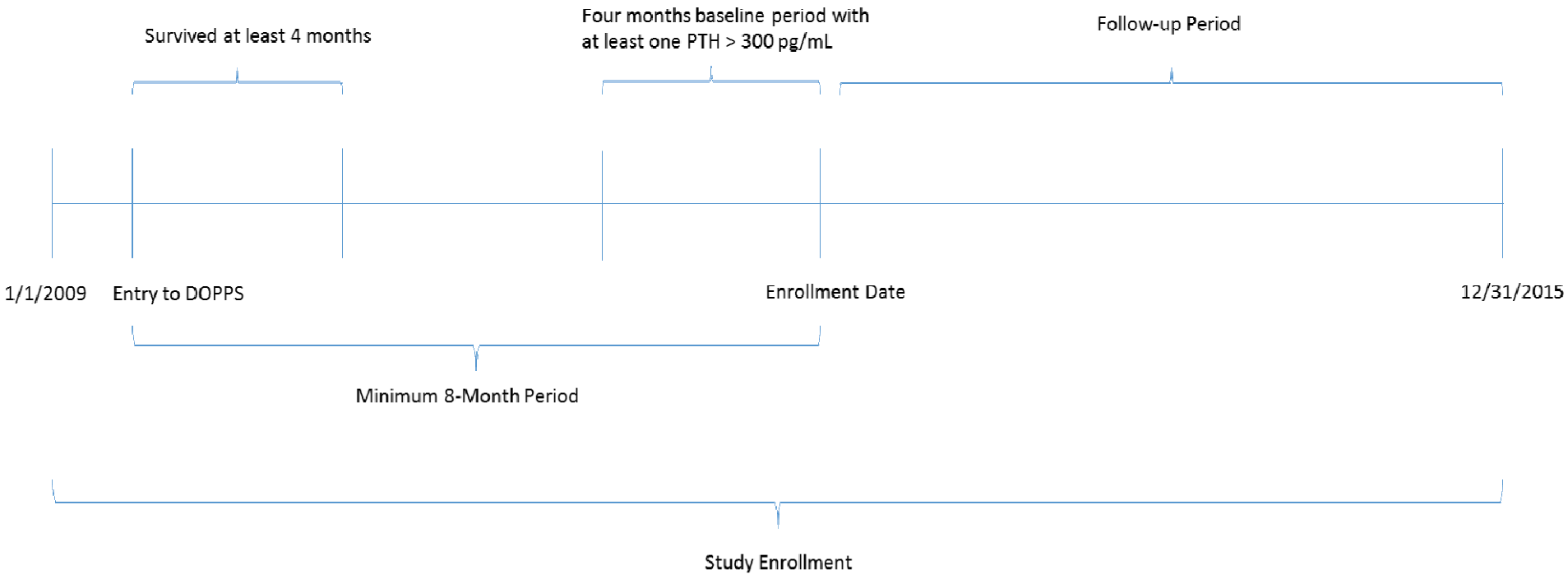
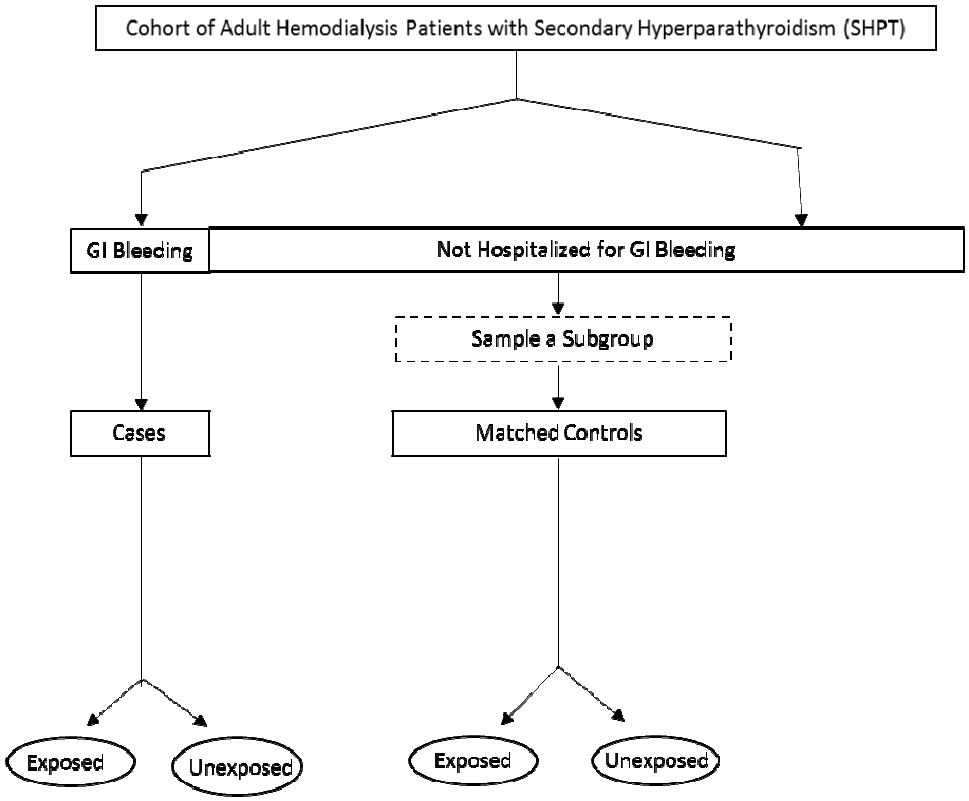


Figure 2. Study Design Schematic for the Nested Case-Control Study



Note: Case-control study begins by selecting cases (those hospitalized for GI bleeding) and matched controls (1:4 matching ratio) from a cohort of SHPT patients. Controls are sampled from the same SHPT population that gave rise to the cases and are matched on the following criteria: (1) duration of follow-up (exact match on number of days)), (2) time on dialysis (≤ 1 year, >1 year), (3) age (±1 year), (4) gender, and (5) race (U.S. only). Exposure status and time-varying covariates are evaluated at two months and four months prior to index date.

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1. List of Abbreviations

Abbreviation or Term	Definition/Explanation
CI	Confidence Interval
CHC	Cumulative Hemodialysis Census
CKD	Chronic Kidney Disease
DOPPS	Dialysis Outcomes and Practice Patterns Study
ESRD	End-stage Renal Disease
GI	Gastrointestinal
HR	Hazard Ratio
IS	Interval Summary
MedDRA	Medical Dictionary for Regulatory Affairs
MQ	Medical Questionnaire
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
PQ	Patient Questionnaire
PTH	Parathyroid hormone
PYs	Patient-years
SHPT	Secondary Hyperparathyroidism
SMQs	Standardised MedDRA Queries
USRDS	United States Renal Data System

2. Abstract

- Study Title

  Cinacalcet Use and the Risk of Gastrointestinal (GI) Bleeding Among Hemodialysis Patients with Secondary Hyperparathyroidism (SHPT)

- Study Background and Rationale

  The rate of GI bleeding in the 2013 US Medicare hemodialysis population was 23 per 1,000 patien-years (PYs), while the mortality rate from GI bleeding was 0.91 per 1,000 PYs. In placebo-controlled trials, the rate of GI bleeding in hemodialysis patients was similar in the etelcalcetide group (2.0%) and the placebo group (2.1%). We will conduct an observational study to address the possibility of a potential association between calcimimetics and fatal and non-fatal GI bleeding in a population of hemodialysis patients.

- Objective(s)

  1: Estimate the association between exposure to cinacalcet and the risk of hospitalization from GI bleeding, by region (US, Other) and overall.

  2. Estimate the association between exposure to cinacalcet and the risk of death from GI bleeding, by region (US, Other) and overall.

  3: Estimate the rate of hospitalization from GI bleeding and the rate of death from GI bleeding, by region (US, Other) and overall.

- Study Design/Type

  A retrospective cohort study design will be employed to estimate background rates of hospitalization from GI bleeding and death from GI bleeding, by region (US, Other) and overall. And, nested within the cohort, a matched case-control study design will be used to estimate the risk of GI events associated with cinacalcet use.

- Study Population

  The study population will be comprised of individuals from the Dialysis Outcome and Practice Patterns Study (DOPPS), an international prospective cohort study of a random sample of patients from dialysis facilities in more than 20 countries, for the time period 2009-2015 (DOPPS phases IV & V). All patients are required to survive at least four months afer entry into DOPPS, a requirement that is consistent with prior studies in this therapeutic area. After patients have surived four months in DOPPS, a four month baseline period will begin, during which there must be at least one occurrence of a PTH lab > 300 pg/mL. The enrollment date will be the first date after the 4-month baseline period has elaspsed.

- Summary of Patient Eligibility Criteria

Inclusion Criteria (evaluated on the enrollment date)

(1) Ages ≥ 18 years of age.
(2) Received in-center hemodialysis at a DOPPS facility, in the following countries: United States, France, Germany, Italy, Spain, United Kingdom, Belgium, Sweden, Russia, Australia, New Zealand, Canada, and Japan.

Exclusion Criteria
Patients will be excluded from the analysis if there is evidence of any of the following events at any point prior to the enrollment date:

(1) Parathyroidectomy
(2) Kidney transplant
(3) Cinacalcet use.

- Follow-up

  Follow-up will begin on the enrollment date. Subjects entering the study cohort will be followed from the enrollment date until the date of the first occurrence of the following events: (1) hospitalization for GI bleeding, and, separately, death from GI bleeding; (2) kidney transplantation; (3) parathyroidectomy, (4) death from causes other than GI bleeding, (5) termination of enrollment in DOPPS, and (6) administrative end of follow-up.

- Variables

  – Outcome Variables
  We will separately evaluate two outcomes in this study: GI bleeding in a hospital setting and death from GI bleeding. Only the first GI bleeding event occurring during the follow-up period in a hospital setting, where GI bleeding is the primary cause of hospitalization (if available), will be considered for this analysis. Similar to methods used by DOPPS in previous studies, we will consider the hospital

admission rate as the date of the GI bleeding event. In addition, death from GI bleeding will be assessed from both hospitalization/discharge records and from national death registries linked to DOPPS.

- Exposure Variable
  The main exposure of interst is the use of cinacalcet. In DOPPS, medication usage is abstracted from the medical record via the 4-month Interval Summary and Medications Inventory questionnaires. In the cohort study, use of cinacalcet (ever vs. never) will be evaluated in the total study population. In the case-control study, we will assess cinacalcet exposure in the two months prior to the case event, and, as a sensitivity analysis, four months prior to the case event.
- Other Covariate(s)
  For the case/control study, controls will be matched to cases on the following variables (all of which are evaluated on the index date): duration of follow-up exact match on number of days), time on dialysis (≤ 1 year, > 1 year), age (±1 year), gender, and, for the U.S. only, race (black vs. other). The following baseline, pre-index risk factors for GI bleeding will be evaluated as potential confounders in the case/control study: previous GI bleeding, peptic ulcer disease, diabetes mellitus, hypertension as the cause of ESRD, cirrhosis, cardiovascular disease, coronary artery disease, use of non-steroidal anti-inflammatory drugs (NSAIDs), current smoking status, PTH, calcium, and phosphorous. Time-varying medications (NSAIDs, anti-coagulants, proton pump inhibitors), which will be assessed monthly after the start of follow-up, will also be considered as potential confounders.

- Study Sample Size

  Based on preliminary data, there were approximately 10,000 hemodialysis patients with SHPT in DOPPS during 2009-2015. Assuming that the rate of hospitalization for GI bleeding is similar to prevous studies (~2.0 per 100 PYs), the half-width of the 95% confidence interval (CI) for the incident rate would be 0.2774. Under this scenario, we would have 200 cases and 800 matched controls for the case-control study. Setting the Type 1 error α=0.05 and assuming a 20% background prevalence of cinacalcet use, we would have >0.80 power to detect an odds ratio of 1.75 or greater for the association between exposure to cinacalcet use and hospitalization for GI bleeding. When estimating the death rate due to GI bleeding, assuming a rate of ~0.2 per 100 PYs (based on preliminary data from DOPPS), the half-width of the 95% confidence interval would be 0.0884. The equivalent case-control study, under the same assumptions as above, would have 20 cases and 80 controls and >0.80 power to detect an odds ratio of 4.25 or greater for the association between cinacalcet use and death from GI bleeding.

- Data Analysis

  Descriptive statistics using mean and standard deviation (SD) or median and $25^{th}/75^{th}$ percentile estimates for continuous variables (as appropriate) and number and percentages (n, %) for categorical variables will be used to examine patient characteristics in a cohort of subjects with SHPT who are on dialysis.

  We will estimate the hazard ratio (HR) and 95% CI for the association of cinacalcet exposure and risk of an inpatient hospitalization for GI bleeding (or death from GI bleeding), implemented using conditional logistic regression analysis for standard matched case-control studies.

We will estimate the crude incidence rates of hospitalization for GI bleeding or crude death rates from GI bleeding and associated 95% CIs using the Poisson model.

3. Amendments and Updates

Amendments must be made only with the prior approval of Amgen. Agreement from the collaborator must be obtained for all amendments. Both Amgen and the investigators reserve the right to terminate participation in the study according to the study contract.

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
None				

4. Milestones

Milestone	Planned date
Expedited Review by Study Authors	4/30/2017
ORRG Review	10/26/2017
Feasibility Assessment for FDA Review	6/30/2018
Manuscript Submission	12/31/2018

5. Rationale and Background

5.1 Disease and Therapeutic Area

Secondary hyperparathyroidism (SHPT) among patients with chronic kidney disease (CKD) results from decreased active vitamin D and is manifested by low serum calcium and elevated levels of phosphorus and parathyroid hormone (PTH) [1, 2]. Treatment options to control the mineral/bone disorders associated with CKD include modulation of calcium and phosphorous balance through dietary intake and dialysis, and use of active vitamin D compounds and phosphate binders [3]. Cinacalcet (Sensipar®/Mimpara®, Amgen Inc., Thousand Oaks, CA), an oral calcimimetic agent, is approved for the treatment of SHPT in patients with CKD on dialysis. Cinacalcet directly lowers PTH, and subsequently, calcium and phosphorus [4, 5]. After receiving marketing authorization in 2004, the use of cinacalcet has steadily increased in the dialysis-dependent CKD population to recent estimates of approximately 28% in 2015 in the US, 16% in Germany, and 7% in Canada in 2014-2015 [6]. Etelcalcetide, a recently approved IV

calcimimetic agent, has also demonstrated efficacy in the treatment of SHPT, with a greater reduction in serum PTH over 26 weeks when compared to placebo [7, 8].

5.2 Rationale

Gastrointestinal (GI) bleeding is a frequent complication for hemodialysis patients with chronic kidney disease (CKD) [9], with up to a five-fold higher risk as compared with those without CKD [10, 11]. Based on hospitalization records from the 2013 US Medicare hemodialysis population, the hospital admission rate for GI bleeding was 23 per 1,000 patient-years [PYs] [12]. The mortality rate from GI bleeding in the same 2013 US Medicare hemodialysis patients was estimated to be 0.91 per 1,000 PYs [12]. In a large study of United States Renal Data System (USRDS) data on patients receiving long-term dialysis, chronic gastric ulcer and colonic diverticulosis were the most frequently defined risk factors for upper and lower GI bleeding. Additional risk factors included age greater than 49 years, female gender, previous GI bleeding, peptic ulcer disease, diabetes mellitus, hypertension as the cause of ESRD, cirrhosis, cardiovascular disease, coronary artery disease, use of non-steroidal anti-inflammatory medications, current smoking status, and black race [13, 14].

In a recent placebo-controlled randomized study evaluating the efficacy of etelcalcetide, the incidence rates of GI bleeding (defined using the standardized Medical Dictionary for Regulatory Affairs [MedDRA] query for Gastrointestinal Haemorrhage) were balanced between the etelcalcetide group (2.0%) and placebo group (2.1%) [7]. No clinically meaningful differences were noted in an active-controlled study (Study 20120360), where incidence rates of events associated with GI bleeding were 2.7% in the etelcalcetide groups versus 1.5% in the cinacalcet group. Notably, the rate of GI bleeding in the randomized and open-label extension studies were consistent with the background rate of GI bleeding in the US Medicare hemodialysis population.

Despite earlier evidence from randomized studies, we will undertake a nested case-control study to address safety concerns of a potential association between calcimimetics and fatal and non-fatal GI bleeding. The challenges in conducting such an observational study include the low number of fatal and non-fatal GI bleeding events, the concomitant use of anti-coagulant agents and NSAIDs, and the presence of severe co-morbid conditions in the study population.

6. Research Question and Objectives

6.1 Primary

For the first objective, we will test the null hypothesis of no association between cinacalcet use and hospitalization for GI bleeding (and, separately, death from GI bleeding) in adult hemodialysis patients with secondary hyperparathyroidism (SHPT).

6.2 Secondary

For the second study objective, no formal hypothesis will be tested. We will estimate the incidence rate of hospitalization from GI bleeding (and, separately, death from GI bleeding) in adult hemodialysis patients with SHPT, overall, and by patient characteristics.

7. Research Methods

7.1 Study Design

We will conduct a retrospective cohort study among hemodialysis patients with SHPT for the purpose of estimating the rate of hospitalization from GI bleeding, and, separately, for estimating the rate of death from GI bleeding, overall, and by patient characteristics. Nested within the cohort, we will then conduct a matched case-control study to estimate the association between cinacalcet use and hospitalization for GI bleeding, and, separately, another matched case-control study to estimate the association between cinacalcet use and death from GI bleeding. The cohort of hemodialysis patients with SHPT will represent the source population that gave rise to the cases who were hospitalized for GI bleeding or died from GI bleeding. Matched controls will be sampled independently of their exposure to cinacalcet from this cohort for the purpose of determining the relative size of the exposed and unexposed components of the source population.

7.2 Setting and Study Population

7.2.1 Study Period

The study period will be 01 January 2009 – 31 December 2015, encompassing Dialysis Outcomes and Practice Patterns Study (DOPPS) Phase 4 (time period: 2009 – 2011) and DOPPS Phase 5 (time period: 2012 – 2015).

7.2.2 Patient Eligibility

The study population will be derived from a source population of adult patients (≥18 years of age) with ESRD, receiving center-based hemodialysis and enrolled at a Dialysis Outcomes and Practice Patterns Study (DOPPS) participating facility. The study population for our analysis will include patients from the DOPPS phases IV (2008-2011) and V (2012-2015) who survived at least 4 months after entry in their respective DOPPS phase from the following countries (exceptions noted in parentheses): Australia and New Zealand (DOPPS 4 only), Belgium (DOPPS 4 only), Canada, France, Germany, Italy, Spain (through 2014), Sweden (DOPPS 4 only), Japan, the UK and the US. The requirement to survive at least 4 months is consistent with prior studies in this therapeutic area [15, 16], and was chosen to ensure patients are at risk of having SHPT [17, 18], and, therefore, eligibile to receive cinacalcet therapy. A 4-month baseline period will begin when patients have survived at least four months following entry into DOPPS and had at least one occurrence of a PTH lab > 300 pg/mL. The enrollment date will be the first date after the 4-month baseline period has elaspsed.

7.2.2.1 Inclusion Criteria

The following inclusion criteria will be applied to DOPPS participants on the enrollment date:

- Ages ≥18 years of age
- Received in-center hemodialysis at a DOPPS facility

7.2.2.2 Exclusion Criteria

Information pertaining to medical history and medication usage prior to entry in DOPPS is captured in the Medical Questionnaire (MQ) form in a Yes/No format, but often without accompanying date information. Consequently, patients will be excluded from the

analysis if there is evidence of any of the following events at any time prior to the enrollment date:

- Parathyroidectomy
- Kidney transplant
- Cinacalcet Use

7.2.3 Baseline Period

The baseline period will be the 4 months prior to the enrollment date, during which laboratory measurements will be evaluated. Co-morbidities and medication usage will be evaluated using all data prior to the enrollment date.

7.2.4 Study Follow-up

For the cohort study, follow-up will begin on the enrollment date. Subjects entering the study cohort will be followed from the enrollment date until the date of the first occurrence of the following events: (1) hospitalization for GI bleeding, and, separately, death from GI bleeding; (2) kidney transplantation; (3) parathyroidectomy, (4) all-cause mortality, and, separately, death from causes other than GI bleeding, (5) termination of enrollment in DOPPS, and (6) administrative end of follow-up.

Follow-up time is not applicable for the nested case-control study. The date of admission for the first hospitalization for GI bleeding or death from GI bleeding will be assigned as the index date for cases. The corresponding matched date will be assigned as the index date for the controls.

7.2.5 Controls

Controls will be selected from the SHPT cohort (the source population of dialysis patients that gave rise to the cases), and will be selected independent of their exposure status. All controls will be selected using risk-set sampling (i.e., controls selected randomly from those without a relevant GI event and still under follow-up at the time a case is diagnosed) using a 1:4 (cases:controls) matching ratio and matched on the following variables on the index date:

- Duration of follow-up (time at risk) in SHPT cohort (exact match on number of days)

- Time on dialysis (≤ 1 year, > 1 year)
- Age (± 1 year)
- Gender
- Race (black vs. other, U.S. only)

Patients can be sampled as controls for more than one case and patients sampled as controls may subsequently become cases.

We will guard against overmatching by making sure that each of the matching variables are related to the exposure under study (use of cinacalcet) and are independent risk factors for the outcome (i.e., each matching factor is a confounder).

7.3 Variables

7.3.1 Exposure Assessment

The primary exposure of interest in the nested case-control study is the use of cinacalcet and is collected via the Medication Inventory questionnaire in DOPPS. Because GI bleeding during hospitalization and death from GI bleeding are considered to be acute events, we will only consider cinacalcet use occurring within 2 months prior to the index event. We will also conduct sensitivity analyses examining cinacalcet exposure occurring within 4 months prior to the index date.

7.3.2 Outcome Assessment

Only the first GI bleeding event occurring during the follow-up period in a hospital setting, where GI bleeding is the primary cause of hospitalization (if available), will be considered for this analysis. Similar to methods used by DOPPS in previous studies, we will consider the hospital admission date as the date of the GI bleeding event.

In addition, death from GI bleeding will be assessed from both hospitalization/discharge records and from national death registries linked to DOPPS.

7.3.3 Covariate Assessment

Covariates

Below we describe the categorization of a set of baseline and time-varying covariates that will be used to describe the study population, including covariates that are potential confounders of the association between cinacalcet use and GI bleeding outcomes.

Table 1. Baseline covariates.

Variable	Measurement
Demographics	
Patient age	Continuous; categories in 4-year age groups (18-44, 45-64, 65-74, 75+)
Patient sex	0/1 indicator (male)
Patient race	Black race (US only)
Dialysis vintage	Categories: ≤1 year, >1 year
Cause of end-stage renal disease	Categories (diabetes, GN, hypertension, other)
Body mass index	Continuous
Laboratory Values	
Serum Parathyroid Hormone(pg/mL)	Continuous; Categories: - Low <150 pg/mL - Normal 150 - ≤ 300 pg/mL - High Normal >300-600 pg/mL - High >600 pg/mL
Corrected serum calcium level (mg/dL)	Continuous; Categories: - Critically Low <7.5 mg/dL - Low 7.5 - <8.4 mg/dL - Normal 8.4-10.2 mg/dL - High >10.2 mg/dL
Serum phosphorus level (mg/dL)	Continuous; Categories: - Low <3.5 mg/dL - Normal 3.5-5.5 mg/dL - High >5.5 mg/dL
Serum Albumin (g/dL)	Continuous; Categories: - Low <3.2 g/dL - Normal ≥3.2 g/dL
Comorbidities	
Diabetes mellitus	0/1 indicator at study entry
Cardiovascular disease	0/1 indicator at study entry
Coronary artery disease / Atherosclerosis	0/1 indicator at study entry

Variable	Measurement
Cerebrovascular disease	0/1 indicator at study entry
Myocardial infarction	0/1 indicator at study entry
Malignancy (Other Than Skin)	0/1 indicator at study entry
Congestive heart failure	0/1 indicator at study entry
Chronic obstructive pulmonary disease	0/1 indicator at study entry
History of fracture	0/1 indicator at study entry
History of GI Bleeding	0/1 indicator at study entry
Hyperlipidemia	0/1 indicator at study entry
Hypertension	0/1 indicator at study entry
Liver disease / Cirrhosis	0/1 indicator at study entry
Peripheral vascular disease	0/1 indicator at study entry
Peptic ulcer disease	0/1 indicator at study entry
Current smoking status	0/1 indicator at study entry
Ability to ambulate	0/1 indicator at study entry
Concomitant Medications	
Vitamin D	Categories (IV, oral, both), evaluated during 4-month baseline period
Oral phosphate binder use	Categories (none, Ca-based, non-Ca-based, both), evaluated during 4-month baseline period
Proton pump inhibitors	0/1 indicator, evaluated using all baseline history information
NSAIDs	0/1 indicator, evaluated using all baseline history information
Anti-coagulants	0/1 indicator, evaluated using all baseline history information
Vascular Access	
Acess Type	Categories (arteriovenous fistula, arteriovenous graft, venous catheter)

Table 2 displays the included time-varying covariates that will be measured at 1 month intervals following the start of follow-up.

Table 2. Time-varying covariates.

Variable	Measurement
Laboratory Values	
Serum Parathyroid Hormone (pg/mL)	Continuous; Categories: - Low <150 pg/mL - Normal 150-300 pg/mL - High Normal >300-600 pg/mL - High >600 pg/mL
Corrected serum calcium level (mg/dL)	Continuous; Categories:

Variable	Measurement
	- Low <8.4 mg/dL - Normal 8.4-10.2 mg/dL - High >10.2 mg/dL
Serum phosphorus level (mg/dL)	Continuous; Categories: - Low <3.5 mg/dL - Normal 3.5-5.5 mg/dL - High >5.5 mg/dL
Serum Albumin (g/dL)	Continuous; Categories: - Low <3.2 g/dL - Normal ≥3.2 g/dL
Medications	
Vitamin D use	Categories (IV, oral, both); active or analog
Oral phosphate binder use	Categories (none, Ca-based, non-Ca-based, both)
Proton Pump inhibitors	0/1 indicator
NSAIDs	0/1 indicator
Anti-coagulants	0/1indicator
Cardiovascular Events	
Acute myocardial infarction	0/1 indicator
Congestive heart failure	0/1 indicator
Stroke	0/1 indicator
Peripheral vascular disease event	0/1 indicator
Cardiovascular mortality	0/1 indicator
Other Covariates	
Time	Day and month
Vascular Access Type	Categories (arteriovenous fistula, arteriovenous graft, venous catheter)
In-patient Hospitalization (# days)	Count
Dialysate calcium	Continuous
DOPPS 4 or 5	0/1 indicator

7.3.4 Validity and Reliability

Although validity and reliability of the study questionnaries and data collection in DOPPS phases IV & V have not been evaluated, earlier versions of DOPPS data have been

shown to be representative of the hemodialysis population [9, 19]. Robinson et alcompared data from the Centers for Medicare & Medicaid Services (CMS) with data from 66 facilities participating in US DOPPS Phase III (2005–2008) [20]. The authors reported that the differences in patient characteristics were small and not statistically significant ($p > 0.10$). To assess whether the DOPPS random sampling methodology provided a sample that was representative of the United Kingdom hemodialysis population, Rayner et al compared several measures in the DOPPS II (2002-2003, n=565) sample and the United Kingdom Renal Registry populations (2003, n=24,463) [21]. They reported that the results for all patient laboratory and comorbidity measures were highly comparable, despite differences in regions covered in both data sources. Finally, previous analyses of US DOPPS data have provided mortality estimates comparable to those obtained from the US Renal Data System [22].

7.4 Data Source

The data source for this study is the Dialysis Outcomes and Practice Patterns Study (DOPPS), Phases IV & V. DOPPS is an international prospective cohort study of hemodialysis practices, based on observational longitudinal data from a random sample of patients from dialysis facilities in more than 20 countries. Within each country, facilities were randomly selected in strata of geographical region and facility type according to the frequency of facilities within each stratum. Facilities treating fewer than 20 hemodialysis patients were excluded from DOPPS for reasons of study efficiency. Within each remaining facility, a random sample of 20 to 40 patients were chosen from all patients receiving long-term, maintenance hemodialysis therapy, to represent the prevalent hemodialysis patient population. The sampling method used to select dialysis units and the random sampling of patients provided a nationally representative sample of prevalent and incident hemodialysis patients. Sample replenishment protocols varied by phase. For example, DOPPS Phase 4 used a thrice-annual replenishment strategy in which sampled patients who died or otherwise departed the facility were replaced (on average) every 4 months during the study via random selection among patients who started dialyzing in the facility since the previous selection.

DOPPS applies a common protocol with standardized questionnaires to capture detailed longitudinal patient-level information, as well as dialysis facility practices and process of

care. A number of questionnaires are used to obtain information on baseline characteristics and follow-up data. The Cumulative Hemodialysis Census (CHC) is a roster of all chronic hemodialysis patients actively dialyzing in a facility which is updated continuously, and serves as the sampling frame. From the Medical Questionnaire (MQ) demographic information, including age, race, sex, and cause of ESRD, is collected at baseline for all patients greater than 17 years of age. In addition, information about pre-ESRD care, history of comorbid conditions, aspects of prescribed and delivered hemodialysis therapy, recent laboratory values, medications use, and detailed information on hospitalizations, is captured.

At baseline, and approximately every 4 months thereafter, data relating to each DOPPS participant's medical history, dialysis prescription, laboratory data, and prescribed medications are abstracted from the medical record via the Interval Summary (IS) and Medications Inventory questionnaires. The 4-month interval summary also records any interval occurrence of hospitalizations, outpatient events and medical interventions, vascular access events, and departures.

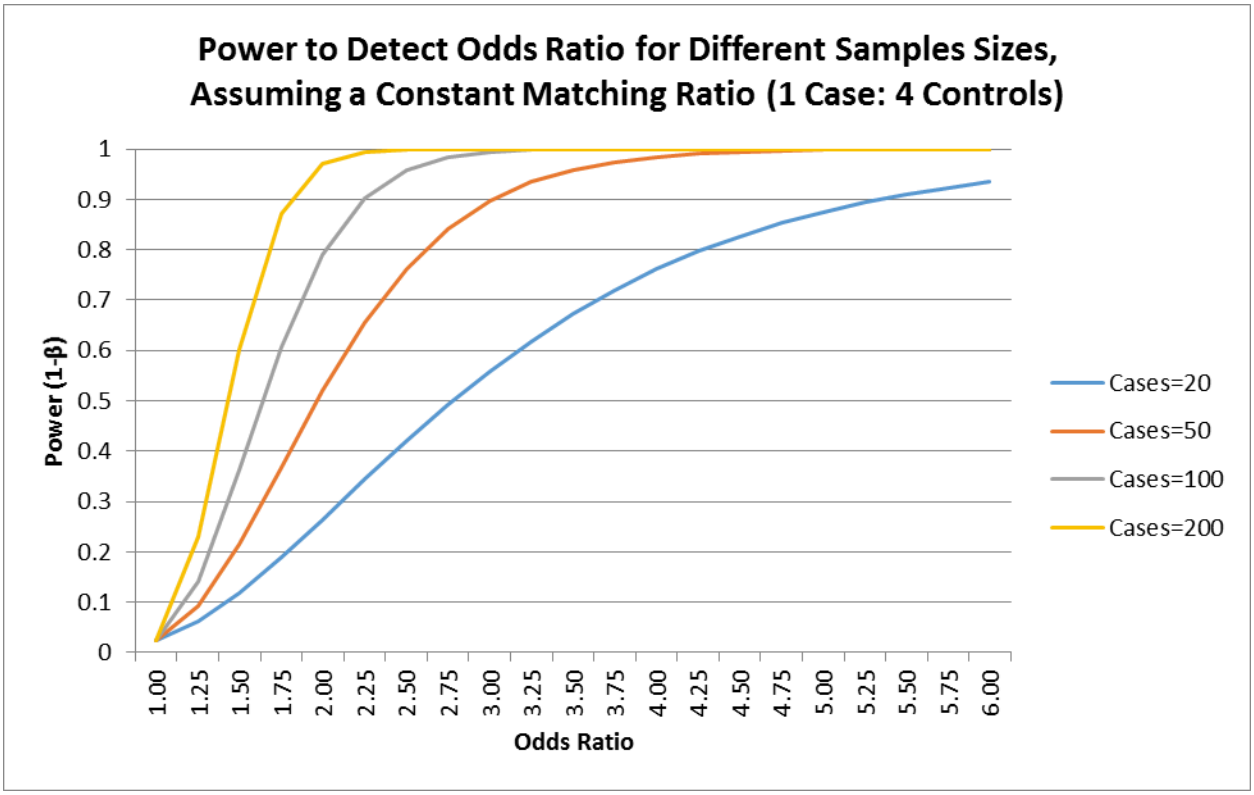
The baseline medical form is used to capture information on patient comorbidities. DOPPS has collapsed responses to 47 questions describing various aspects of the patient's medical history, including coronoary artery disease, cancer other than skin, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, GI bleeding, HIV/AIDS, hypertension, lung disease, neurologic disease, psychiatric disorder, and peripheral vascular disease into 14 summary comorbid conditions [19]. The prevalence and prognostic importance of these 14 comorbid conditions has been shown repeatedly over time in studies using the DOPPS data [22, 23].

The primary exposure of interest in the current analysis (i.e. exposure to oral cinacalcet use) will be collected from the Medication Inventory questionnaire. Data on the outcome of interest, GI bleeding and death from GI bleeding, will be collected from hospitalization / discharge records, as well as from national death registries linked to DOPPS. Analyses will be conducted only for patients with follow-up data.

7.5 Study Size

Objective 1

We consider the statistical power on a binary predictor (exposure to cinacalcet) on the outcome (hospitalization for GI bleeding or death from GI bleeding), setting the type I error α=0.05. Under a 1:4 matched case-control study, a background prevalence of cinacalcet use of 20%, and a total sample size of 1,000 patients (i.e., 200 cases and 800 controls), we would have > 0.80 power to detect an odds ratio of 1.75 or greater (see figure below). We anticipate having approximately 250 cases hospitalized for GI bleeding and approximately 20 cases who died from GI bleeding.



Objective 2

Based on preliminary data, there is a total of approximately 10,000 (6,000 in the U.S. and 4,000 in other countries) hemodialysis patients with SHPT in DOPPS during 2009 – 2015. In this population, preliminary data from DOPPS suggests that the rate of hospitalization for GI bleeding is approximately 2 per 100 person-years and the rate of death from GI bleedings is approximately 0.20 per 100 person-years. In the table below we present precision estimates for a hypothetical range of incidence rates, by sample size. As an example, for an estimated GI bleeding rate of 2 per 100 person-years, the

half-width of the 95% CIs is 0.2774, assuming a sample size of 10,000 study participants.

Precision Estimates for Estimated Incidence Rates.

Outcome	Sample Size (N)	Estimated Incidence Rates (/ 100 Person-Years)	Precision (Half-Width of Confidence Interval)
Hospitalization for GI Bleeding	5,000	1.0	0.2781
	5,000	2.0	0.3927
	5,000	3.0	0.4806
	10,000	1.0	0.1963
	10,000	2.0	0.2774
	10,000	3.0	0.3397
Death from GI Bleeding	5,000	0.1	0.0906
	5,000	0.2	0.1261
	5,000	0.3	0.4806
	10,000	0.1	0.0630
	10,000	0.2	0.0884
	10,000	0.3	0.1080

7.6 Data Management

7.6.1 Linking Data Files

The Arbor Research DOPPS databases are constructed from a combination of electronic health record extracts, web-based questionnaire collection, and, for a limited number of study sites, manual key punching data entry. No additional linkage to external data sources are required for this study.

7.6.2 Review and Verification of Data Quality

The DOPPS data management and analytical programs undergo institutional quality control processes, increasing the accuracy and minimizing the risk of compromised data integrity and vulnerability. Arbor Research Collaborative for Health will manage data quality, including both production and quality control programming. A primary programmer will construct the analytic files from the various DOPPS questionnaires, and these analytic files will subsequently be validated by an independent programmer. Once completed, the final analysis data sets will then be available for analysis.

7.7 Data Analysis

7.7.1 Planned Analyses

7.7.1.1 Primary Analysis

Descriptive statistics using mean and standard deviation (SD) or median and 25th/75th percentile estimates for continuous variables (as appropriate) and number and percentages (n, %) for categorical variables will be used to examine patient characteristics in a cohort of subjects with SHPT who are on dialysis (Appendix Table 1). Medications and laboratory parameters will be assessed during the baseline period (within 4 months prior to the enrollment date), while medical history items will be evaluated using all available data prior to the enrollment date.

Objective # 1

We will estimate the hazard ratio (HR) and 95% CI for the association of cinacalcet exposure and risk of an inpatient hospitalization for GI bleeding (or death from GI bleeding), implemented using a proportional hazards model with a modification to the partial likelihood used in full-cohort studies [24]. The analysis of data arising from a nested case-control study derives from the analysis of a prospective cohort study in which we have collected exposure and other covariate data and observed either a survival time, or event time, or a censoring time for all those in the cohort. Conditional logistic regression is required with this type of analysis because controls will be matched to cases on multiple factors that are related to the outcome of interest (i.e., the cases and controls are not independent). We will use conditional logistic regression analysis for standard matched case-control studies. All of the matching factors will be included in the Cox model (base case). The main exposure of interest in this analysis will be receipt of cinacalcet (yes vs. no) 2 months preceding the index date.

We will identify potential confounders based on *a priori* subject matter knowledge and all of the candidate confounders will be included in the final adjusted model. Multi-collinearity among the candidate confounders will also be examined. If multi-collinearity is identified between two variables, the variable determined to be the more important confounder (based on confounding influence, convention, or prevalence in the population) will remain in the model. All statistical analyses will be performed using SAS version 9.3 (Cary, NC) (see Appendix Table 4).

Objective # 2

We will estimate the crude incidence rates of hospitalization for GI bleeding or crude death rates from GI bleeding and associated 95% CIs. Rates will be calculated as the number of incident events during the follow-up period divided by the total person-time at risk. We will also estimate the incidence rates within strata of select matching criteria (e.g., age and gender) and within strata of other baseline covariates. Confidence intervals will be calculated using the Poisson distribution when the number of events is large (≥ 20); otherwise, approximations of the Poisson distribution that are appropriate when the number of events are small (such as Byar's asymmetric confidence intervals) will be used (Appendix Table 2).

7.7.2 Planned Method of Analysis

7.7.2.1 Missing or Incomplete Data

A complete case analysis will be used for missing repeated and static variables (e.g. age, race), when the overall missing observations represent less than five perecent of the data. If any covariate is missing more than 5%, we will adopt a multiple imputation strategy. Under this strategy, we assume that data is missing at random (i.e., the probability of 'missingness' is independent of the unobserved true value of the data) and that missing data can be modeled as a function of the other covariates in the analysis data set. Under these conditions, multiple imputation allows for valid statistical inferences that reflect the uncertainty due to missing data. Briefly, the steps involved in multiple imputation will be as follows: (1) The missing data will be filled in *m* times to generate *m* complete data sets, based on the model for 'missingness' (we will set m=5), (2) The *m* complete data sets will be analyzed by using the the proportional hazard approach for the outcome model, as described earlier, and (3) The results from the *m* analyses will be combined for inference in the final analysis.

7.7.2.2 Sensitivity Analysis

A sensitivity analysis will be performed to determine if altering the exposure criteria of cinacalcet use occurring within 2 months prior to the case event to 4 months prior to the case event greatly affects the results.

7.7.2.2.1 Subgroup Analysis

All analyses will be conducted separately for the United States and Europe.

7.8 Quality Control

DOPPS data goes through scheduled tests for integrity, outliers, and additional checks for impossible or unlikely values according to standard procedures. We anticipate no data editing for this study after construction of the analytic files.

7.9 Limitations of the Research Methods

7.9.1 Internal Validity of Study Design

No validation studies are planned. There are a few sources of potential bias in this study, as noted below.

7.9.1.1 Measurement Error(s)/Misclassification(s)

Threats to internal validity include misclassification of cinacalcet use in reported data. Medication use information will be abastracted from prescriptions recorded on the medical chart, which are an imperfect measure of actual medication consumed. Data on medication usage is collected in 4-month intervals via the Interval Summary form and monthly via the Medications Inventory questionnaire. For cinacalcet use, indicators of ever used / never used are provided at the end of each facilities reporting month during follow-up. We assume that cinacalcet is used for every day in the month where 'Ever Used' for cinacalcet is equal to 'Yes.' Consequently, we cannot precisely determine the duration of treatment. This approach could potentially result in misclassification error, but any error will likely be non-differential with respect to case/control status and lead to an under-estimation of the relative risk estimates related to the use of cinacalcet. We will use simple bias analysis tools to correct for potential misclassification of our binary exposure, assuming a range of sensitivities and specificities for the measured cinacalcet exposure.

7.9.1.2 Confounding

We will use assess balance in covariates between cases and controls. The variables of interest will include demographic characteristics, co-morbidity information, lab parameters and time-varying medication use. Information on candidate medication and lab confounders will be assessed during the four months preceding the index date, while potential medical history confounders will be evaluated using all available data prior to the index date. The specific variables are presented below.

Demographics (all matching factors evaluated at the index date)

- Duration of follow-up (number of days elapsed from enrollment date to index date)
- Time on dialysis (≤ 1 year, > 1 year)
- Age (continuous; <45, 45-64, 65-74, 75+ years)
- Gender (male vs. female)
- Race (black vs. other; U.S. only)

Co-morbidities (yes vs. no)

The following conditions will be assessed using information from the Medical Questionnaire:

- Previous GI Bleeding
- Peptic Ulcer Disease
- Diabetes Mellitus
- Hypertension as the case of ESRD
- Cirrhosis / Liver
- Coronary Artery Disease
- Current Smoking Status
- Vascular Access Type (Arteriovenous Fistula, Arteriovenous Graft, Venous Catheter)

Lab Paramters

- Serium Corrected Calcum
- Serum Phosphorus
- Serum PTH

Other factors

In addition to the baseline characteristics described above, we will also evaluate a limited number of time-varying candidate confounders that will be assessed within two months prior to the index date for the cases and their matched controls. These will include the following:

- Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)
- Use of Anti-cogulants
- Proton Pump Inhibitors

The relationship between cinacalet use and hospitalization for GI bleeding (or, death from GI bleeding) has not been well-studied. We rely of subject matter knowledge to include candidate confounding variables in our analyses, but residual confounding may exist as a result of unmeasured or unknown confounders. We will include even weak confounders in the final analysis, sacrificing precision of our final effect estimates by guarding against the potential bias that might be introduced by omission of the confounder. Finally , despite the large overall sample size for the proposed analysis examining hospitalization for GI bleeding as the outcome, it may be difficult to achieve distributional balance of covariates in the smaller study examining death from GI bleeding as the outcome.

7.9.2 External Validity of Study Design

The selection of patients for this study comprised adult patients with ESRD receiving center-based hemodialysis and enrolled at DOPPS facilities. Results from this study may not be completely generalizable to patients who receive hemodialysis in non-DOPPS facilities, however DOPPS is a representative sample of units internationally. The validity, completeness, and reliability of patients from DOPPS data from the US have been examined by studies published by Robinson et al [20] and Rayner [21].

7.9.3 Analysis Limitations

Analyses using DOPPS data will be limited to the years 2009-2015. Based on prior experience with analysis of the DOPPS data, missing data will be minimal and will not likely impact interpretation of the results.

As noted in section 8.9.1.1, we will not know the exact dates of cinacalcet use and hospitalization for GI bleeds to obtain the risk factors most proximal to these exposures and events. However, our primary analysis methods will ensure that we are not biasing results by initially limiting our risk factors to intervals prior to GI bleed-related hospitalization or death.

We use broad categories to capture use of cinacalcet (ever/never use), with no specfics on duration or intensity of use. Consequently, any potential association between cinacalcet use GI bleeding outcomes could be diluted.

We are including patients in our analyses irrespective of medication use, such as phosphate binders, and vitamin D, which affect CKD-MBD biochemical parameters. Although we will measure and adjust for use of these medications in our analyses, the potential for residual confounding still exists.

8. Protection of Human Subjects

8.1 Informed Consent

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy. At study entry, eligible patients are consented for clinical data abstraction. Consent may be withdrawn at any time. Separate consent is obtained for the collection and merging of data from patient-reported questionnaires.

8.2 Subject Confidentiality

Only aggregated data will be provided from DOPPS to Amgen. Arbor Research has ensured patient confidentiality has been maintained based on their standard processes.

9. Collection of Safety Information and Product Complaints

Reporting of individual adverse events is not applicable for secondary data collection studies.

10. Plans for Disseminating and Communicating Study Results

10.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the

work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.

- When a large, 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 corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

We intend to submit the results from the proposed analyses for publication.

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12. Appendices

Appendix Table 1. Characteristics of X,XXX subjects with secondary hyperparathyroidism (SHPT) receiving hemodialysis in the Dialysis Outcomes and Practice Patterns Study (DOPPS), by region, 2009-2015.

Baseline Characteristic	United States N (%) or Mean (S.D.)	Ex-United States N (%) or Mean (S.D.)
Total		
Demographics		
Age, years		
18 - 44		
45 - 64		
65 - 74		
75+		
Female		
Black Race		
Medical History		
Previous GI Bleeding		
Peptic Ulcer Disease		
Diabetes Mellitus		
Hypertension		
Hypertension as Cause of ESRD		
Cirrhosis / Liver Disease		
Cardiovascular Disease		
Coronary Artery Disease		
Ability to Ambulate		
Current Smoking Status		
Medication Use		
Vitamin D		

None

IV

Oral

Both

Phosphate Binders

None

Calcium Based

Non-Calcium Based

Both

NSAIDS

Proton Pump Inhibitors

Lab Parameters

Parathyroid Hormone (pg/mL)

<150 pg/mL

150 – 300 pg/mL

>300 – 600 pg/mL

>600 pg/mL

Calcium (mg/dL)

<8.4 mg/dL

8.4 – 10.2 mg/dL

>10.2 mg/dL

Phosphorus (mg/dL)

<3.5 mg/dL

3.5 – 5.5 mg/dL

>5.5 mg/dL

Appendix Table 2. Characteristics of cases hospitalized for GI bleeding and cases who died from GI bleeding, and their respective controls

	Hospitalization for GI Bleeding		Death from GI Bleeding	
	Cases	**Controls**	**Cases**	**Controls**
Baseline Characteristic	**N (%) or Mean S.D.)**	**N (%) or Mean S.D.)**	**N (%) or Mean S.D.)**	**N (%) or Mean S.D.)**
Total				
Follow-up (years)				
Demographics				
Age, years				
18 - 44				
45 - 64				
65 - 74				
75+				
Female				
Black Race				
Medical History				
Previous GI Bleeding				
Peptic Ulcer Disease				
Diabetes Mellitus				
Hypertension				
Hypertension as Cause of ESRD				
Cirrhosis / Liver Disease				
Cardiovascular Disease				
Coronary Artery Disease				
Ability to Ambulate				
Current Smoking Status				
Medication Use				

Vitamin D

None

IV

Oral

Both

Phosphate Binders

None

Calcium Based

Non-Calcium Based

Both

NSAIDS

Proton Pump Inhibitors

Lab Parameters

Parathyroid Hormone (pg/mL)

<150 pg/mL

150 – 300 pg/mL

>300 – 600 pg/mL

>600 pg/mL

Calcium (mg/dL)

<8.4 mg/dL

8.4 – 10.2 mg/dL

>10.2 mg/dL

Phosphorus (mg/dL)

<3.5 mg/dL

3.5 – 5.5 mg/dL

>5.5 mg/dL

Appendix Table 3. Risk of hospitalization for GI bleeding and death from GI bleeding in subjects with secondary hyperparathyroidism (SHPT) receiving hemodialysis who were exposed to cinacalcet two months prior and four months prior, using proportional hazards regression.

Exposure Period(s)	Hospitalization for GI Bleeding				Death from GI Bleeding		
	Cases (% Exposed)	Controls (% Exposed)	Hazard Ratio (95% C.I.)		Cases (% Exposed)	Controls (% Exposed)	Hazard Ratio (95% C.I.)
2 Months Prior (1:4 Matching)			†				†
Cinacalcet			‡				‡
History of GI Bleeding							
Coronary Artery Disease							
Hypertension							
Diabetes Mellitus							
Other Potential Confoudners							
4 Months Prior (1:4 Matching)			†				†
Cinacalcet			‡				‡
History of GI Bleeding							
Coronary Artery Disease							
Hypertension							
Diabetes Mellitus							
Other Potential Confoudners							

†Unadjusted hazard ratio.
‡Adjusted hazard ratio, adjusted for all indicated time-varying variables.

Appendix Table 4. Rates of Hospitalization for Gastro-Intestinal Bleeding and Death from Gastro-Intestinal Bleeding (per 100 Person-Years), Overall, by Baseline Characteristics and by Region.

Baseline Characteristic	**Hospitalization for GI[1] Bleeding (95% C.I.[1])**		**Death from GI[1] Bleeding (95% C.I.[1])**	
	United States	**Ex-United States**	**United States**	**Ex-United States**
Total	X.X (X.X, X.X)	X.X (X.X, X.X)	X.X (X.X, X.X)	X.X (X.X, X.X)
Demographics				
Age, years				
18 - 44				
45 - 64				
65 - 74				
75+				
Gender				
Males				
Females				
Race				
White				
Other				
Medical History				
Previous GI Bleeding				
Peptic Ulcer Disease				
Diabetes Mellitus				
Hypertension				
Hypertension as				
Cirrhosis / Liver				
Cardiovascular				
Coronary Artery				
Ability to Ambulate				
Current Smoking				

Medication Use

Vitamin D

None

IV

Oral

Both

Phosphate Binders

None

Calcium Based

Non-Calcium Based

Both

NSAIDS

Proton Pump Inhibitors

Lab Parameters

Parathyroid Hormone

<150 pg/mL

150 – 300 pg/mL

>300 – 600 pg/mL

>600 pg/mL

Calcium (mg/dL)

<8.4 mg/dL

8.4 – 10.2 mg/dL

>10.2 mg/dL

Phosphorus (mg/dL)

<3.5 mg/dL

3.5 – 5.5 mg/dL

>5.5 mg/dL