Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): Rationale and Design Overview

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Background and Objectives: The dramatically high rates of mortality and cardiovascular morbidity observed among dialysis patients highlights the importance of identifying and implementing strategies to lower cardiovascular risk in this population. Results from clinical trials undertaken thus far, including trials on lipid reduction, normalization of hematocrit, and increased dialysis dosage, have been unsuccessful. Available data indicate that abnormalities in calcium and phosphorus metabolism, as a result of either secondary hyperparathyroidism alone or the therapeutic measures used to manage secondary hyperparathyroidism, are associated with an increased risk for death and cardiovascular events. However, no prospective trials have evaluated whether interventions that modify these laboratory parameters result in a reduction in adverse cardiovascular outcomes.

Design, Setting, Participants, & Measurements: Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events is a global, phase 3, double-blind, randomized, placebo-controlled trial evaluating the effects of cinacalcet on mortality and cardiovascular events in hemodialysis patients with secondary hyperparathyroidism. Approximately 3800 patients from 22 countries will be randomly assigned to cinacalcet or placebo. Flexible use of traditional therapies will be permitted. The primary end point is the composite of time to all-cause mortality or first nonfatal cardiovascular event (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular disease, including lower extremity revascularization and nontraumatic amputation).

Results: The study will be event driven (terminated at 1882 events) with an anticipated duration of approximately 4 yr.

Conclusions: Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events will determine whether management of secondary hyperparathyroidism with cinacalcet reduces the risk for mortality and cardiovascular events in hemodialysis patients.

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Mortality and cardiovascular morbidity are unacceptably high in dialysis patients despite substantial improvements in dialysis technology and multiple efforts to standardize and improve practice (1). A large portion of the increased mortality in the dialysis population is the result of premature cardiovascular disease (2). To date, prospective clinical trials in large dialysis populations have failed to demonstrate a meaningful benefit from hepatic hydroxymethyl glutaryl–CoA reductase inhibitors (statins), normalized hematocrit, or higher dialysis dosage, expressed as Kt/V_{urea} (3–5). Other metabolic abnormalities associated with uremia might be fruitful areas for potential interventions.

Elevations in biochemical markers of secondary hyperparathyroidism (sHPT) are associated with the risk for all-cause mortality and cardiovascular morbidity in the dialysis popula-

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tion, potentially mediated through vascular calcification, hypertension, and left ventricular hypertrophy (6–11). As modifiable cardiovascular risk factors, interventions that target biochemical markers of chronic kidney disease–mineral and bone disorder (CKD-MBD) (12) are therefore excellent candidates for clinical investigation in the dialysis population. However, no prospective trials have evaluated whether interventions that modify these laboratory parameters result in a reduction in adverse cardiovascular outcomes.

Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) is a randomized clinical trial (RCT) designed to test the hypothesis that cinacalcet reduces the risk for mortality and cardiovascular morbidity compared with placebo in patients who receive maintenance hemodialysis and traditional therapy for sHPT. The purpose of this article is threefold: (*1*) To review the putative role of sHPT and the conventional approaches used to manage sHPT as potential contributors to mortality and cardiovascular disease among patients who receive maintenance hemodialysis, (*2*) to provide the rationale for conducting an RCT to test the hypothesis that treatment with cinacalcet reduces the risk for mortality and cardiovascular morbidity in patients who receive maintenance hemodialysis, and (*3*) to review the design of EVOLVE.

Challenges in Controlling sHPT Using Traditional Therapies

sHPT is a common and serious disease that develops relatively early in the course of CKD, often when the GFR drops below approximately 60 ml/min per 1.73 m^2 and long before the initiation of dialysis (13). Several factors contribute to the pathogenesis of sHPT, including reduced synthesis of 1,25-dihydroxy vitamin D, hypocalcemia, and skeletal resistance to the calcemic action of parathyroid hormone (PTH). As CKD progresses toward end stage, the prevalence of sHPT increases, affecting nearly all patients who receive dialysis therapy. In addition, increases in serum calcium may occur as a result of traditional therapy (*e.g.*, vitamin D derivatives, phosphate binders), together with hyperphosphatemia and increased levels of the calcium-phosphorus ion product. Traditional therapies fail to control simultaneously PTH and abnormalities of divalent ion metabolism in many patients with CKD and have the potential to aggravate complications of the disease. For example, although vitamin D derivatives (including calcitriol, alfacalcidol, doxercalciferol, and paricalcitol) efficiently reduce PTH concentrations, these agents can lead to hyperphosphatemia and relative hypercalcemia as a result of enhanced gastrointestinal absorption of phosphorus and calcium. Calcium-based phosphate binders do not efficiently control sHPT when used alone and contribute to hypercalcemia in up to 40% of patients (14), particularly when administered in conjunction with vitamin D derivatives. Calcium-free phosphate binders tend not to raise serum calcium concentrations but generally do not adequately control sHPT when used alone. Indeed, epidemiologic evidence suggests that despite the aggressive use of vitamin D derivatives and phosphate binders, fewer than 10% of hemodialysis patients achieve target concentrations for all four of the biochemical parameters recommended by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (10).

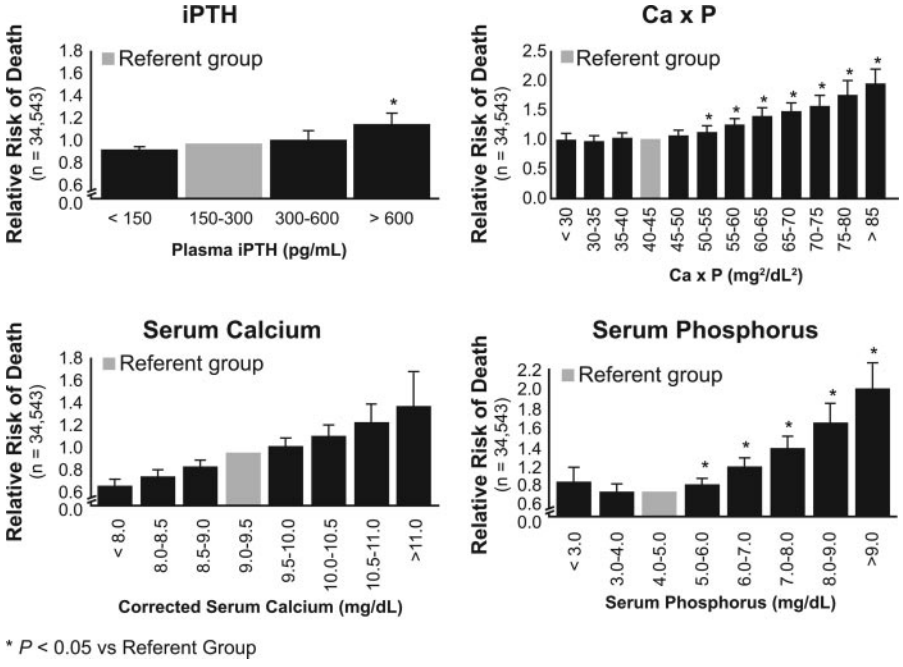

Figure 1. Associations between elevations in phosphorus, calcium, calcium-phosphorus product, and parathyroid hormone (PTH) with risk for mortality. Abbreviations: iPTH, intact PTH, Ca × P, calcium-phosphorus product. Adapted from reference (9), with permission.

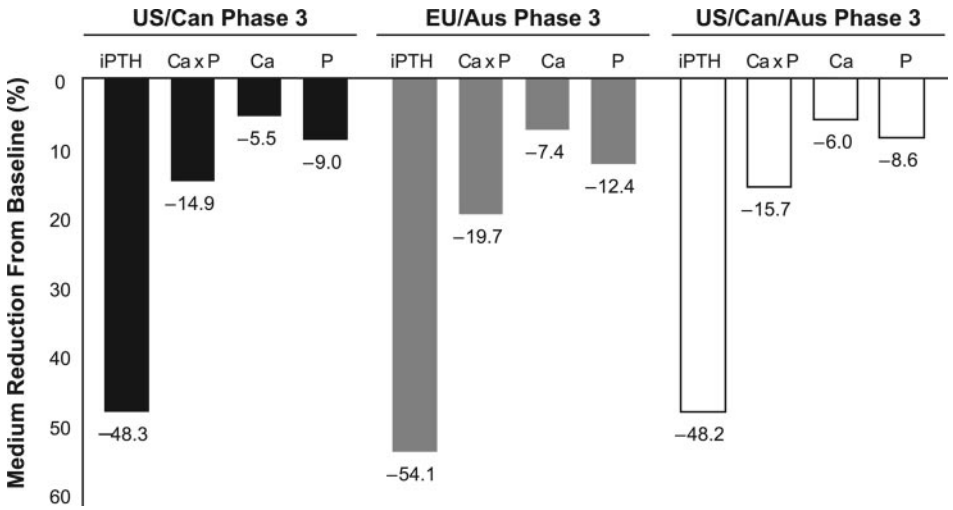

Figure 2. Effect of cinacalcet on PTH, Ca, P, and Ca × P in phase 3 clinical trials (21,22). US, United States; EU, Europe; Aus, Australia.

sHPT, Mortality, and Cardiovascular Disease in Dialysis Patients

The clinical outcome most frequently associated with sHPT is the development of abnormal bone that can progress to osteitis fibrosa cystica, which is one of the histologic findings referred to as renal osteodystrophy (15–17). However, recent epidemiologic data demonstrate that sHPT (and more generally the biochemical abnormalities of CKD-MBD) is a risk factor for mortality and cardiovascular morbidity and therefore can be considered a nontraditional cardiovascular risk factor (12,18), which may predispose to vascular calcification (7), increased arterial stiffness, and left ventricular hypertrophy (6,8). Analyses from multiple large dialysis databases suggest that elevated serum calcium, phosphorus, calcium-phosphorus product, and PTH are associated with increased risk for all-cause and cardiovascular mortality (9–11,19) (Figure 1). Whether improvements in the control of the biochemical parameters that are associated with sHPT and the therapeutic measures that are used to manage sHPT will reduce the burden of cardiovascular disease and adverse clinical outcomes in patients who receive dialysis warrants further investigation.

Traditional risk factor modification has been unsuccessful in improving clinical outcomes (3). Therefore, there is a need to investigate other therapeutic interventions, particularly those targeted toward selected uremia-related risk factors, to test their ability to reduce the burden of cardiovascular disease and adverse clinical outcomes in patients who receive dialysis.

Rationale for an RCT Using the Calcimimetic Cinacalcet

The calcimimetics, which include cinacalcet, are a novel class of small molecules that act as allosteric modulators of the calcium sensing receptor on the surface of parathyroid cells and cells of numerous other tissues (20). Three clinical trials that studied 1136 dialysis patients with uncontrolled sHPT (defined as PTH ≥300 pg/ml despite conventional therapy) demonstrated that treatment with cinacalcet resulted in simultaneous reductions in serum concentrations of PTH, calcium, phosphorus, and calcium-phosphorus product (21,22) (Figure 2).

Post hoc analyses of data from four placebo-controlled RCTs, with follow-up times varying from 6 to 12 mo, showed that treatment with cinacalcet led to significant reductions in the risk for parathyroidectomy, fracture, and hospitalizations related to cardiovascular disease (Table 1) (23). Although the RCTs that were pooled in this analysis were neither designed nor powered to assess clinical outcomes, these pooled data support the safety of cinacalcet in clinical practice and generate the hypothesis that the use of cinacalcet may result in a reduction in important clinical events.

Consensus clinical practice guidelines, including the NKF-

Table 1. Key clinical event rates from *post hoc* analysis of phase 3 cinacalcet studies (24)

Clinical Outcome	Cinacalcet (Events per 100 Patient-Years)	Control (Events per 100 Patient-Years)	HR (95% CI)[a]	*P* for HR
Parathyroidectomy	0.3	4.1	0.07 (0.01 to 0.55)	0.009
Fracture	3.2	6.9	0.46 (0.22 to 0.95)	0.040
Cardiovascular hospitalization	15.0	19.7	0.61 (0.43 to 0.86)	0.005
Mortality	5.2	7.4	0.81 (0.45 to 1.45)	0.470

[a]Control is used as the reference group. CI, confidence interval; HR, hazard ratio.

K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease (24), identify the need for a robust RCT designed to provide definitive evidence that correction of the biochemical parameters associated with sHPT exert a meaningful, beneficial effect on clinical end points in hemodialysis patients. Such information has yet to be reported with traditional therapeutic approaches, which include phosphate binders and vitamin D derivatives. In addition to clinical outcomes data, large simple pragmatic trials may provide important health economic information and valuable insights into geographic variability in patient demographics and the management of this disease state.

EVOLVE

Study Design, Participants, and Setting

EVOLVE is a multicenter, randomized, double-blind, placebo-controlled trial designed to determine the efficacy of cinacalcet compared with placebo in patients who receive maintenance hemodialysis and traditional therapy for sHPT on the primary composite end point of time to all-cause mortality or first nonfatal cardiovascular event (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular disease, including lower extremity revascularization and nontraumatic amputation). EVOLVE is a global study carried out in approximately 500 sites in 22 countries: United States, Canada, Argentina, Brazil, Mexico, Australia, Austria, Belgium, Denmark, France, Germany, Hungary, Ireland, Italy, Netherlands, Poland, Portugal, Russia, Spain, Sweden, Switzerland, and United Kingdom. A study schema is provided in Figure 3. EVOLVE is conducted by a collaborative network as outlined in Table 2.

Justification for an RCT with Cinacalcet

The importance of validating therapeutic hypotheses from longitudinal studies of risk factors with RCT is exemplified by studies that have reexamined and ultimately changed standards of care. Notable examples include the Women's Health Initiative, the Hemodialysis (HEMO) Study, the Deutsche Diabetes Dialyze Studie (4D Study), and, more recently, the Homocysteine Lowering with Folic Acid and B Vitamins in Vascular Disease (HOPE 2) trial (3,5,25,26). The Women's Health Initiative was a large, randomized, placebo-controlled study that examined the effect of hormone replacement therapy (HRT) with estrogen and progestin on cardiovascular risk in postmenopausal women (25). Many questioned the ethics of this study at the time it was initiated, because HRT was part of standard of care for management of cardiovascular risk in women, based on conclusions from observational data. However, the Women's Health Initiative was stopped early because women who were randomly assigned to HRT were found to have a higher risk for cardiovascular disease than women who were randomly assigned to receive placebo.

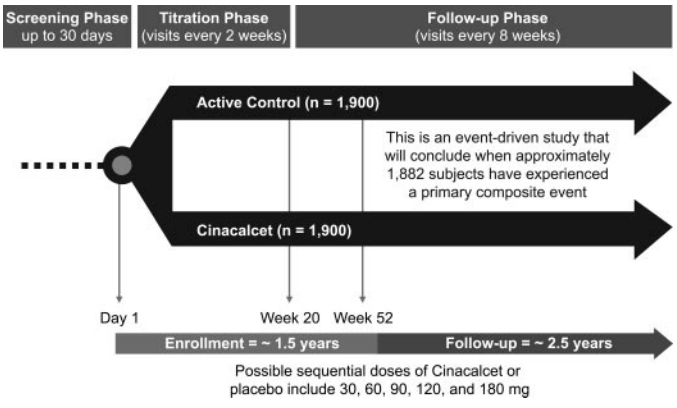

Figure 3. Schematic diagram of the Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE) study design.

Justification for the Use of a Placebo

The principal reason for providing placebo tablets to patients in the control arm is to ensure study blinding with regard to both investigators and patients. However, the use of a placebo control group in EVOLVE does not suggest that the control group is untreated. All EVOLVE study participants are expected to receive standard pharmacologic therapy (as tolerated) with currently available agents for the management of sHPT. EVOLVE is designed to address the question of whether cinacalcet, used in conjunction with conventional treatment, offers a meaningful benefit compared with usual therapy for sHPT. These standard therapies (*e.g.*, vitamin D derivatives, phosphate binders) will be used in both treatment groups with flexibility, allowing the physician unrestricted ability to treat the disease in accordance with national or international relevant guidelines (24).

Inclusion and Exclusion Criteria

Eligible EVOLVE participants will be ≥18 yr of age, have stage 5 CKD treated with maintenance hemodialysis (including hemodiafiltration) three times a week for ≥3 mo before randomization, have intact PTH (iPTH) ≥300 pg/ml (31.8 pmol/L), and have calcium-phosphorus product ≥45 mg^2/dl^2 (3.63 $mmol^2/L^2$). In addition, eligible participants must have a serum calcium ≥8.4 mg/dl (2.1 mmol/L) and be likely to remain available during the follow-up phase of the study. Participants should agree to follow-up for the duration of the study and sign the appropriate written informed consent form before any study-specific procedure. There will be no upper limit for inclusion with regard to PTH values because there is no global consensus on what such an upper limit should be. If a parathyroidectomy is indicated for a patient according to investigator's opinion, then the patient should not be enrolled into the study. If a patient is enrolled into the study and undergoes parathyroidectomy, then the patient will no longer receive study drug but will continue to be followed.

Patients will be excluded from participation in EVOLVE when they have an unstable medical condition (in the judgment of the investigator); have had a parathyroidectomy within 12 wk of informed consent and/or the investigator anticipates that the patient will need a parathyroidectomy within 6 mo after randomization; has a life-limiting concomitant disease; received therapy with cinacalcet within 3 mo of randomization;

Table 2. EVOLVE collaborative network and responsibilities[a]

Entity	Responsibilities
Amgen Inc. (study sponsor)	Develop operational strategy, oversee global study execution, and promote alignment among all regions; monitoring and site management in European Union and Australia
Executive Committee	Oversee the design, execution, and analysis of the study in conjunction with Amgen; report and communicate the study results in conjunction with Amgen
Clinical Endpoint Committee (Duke Clinical Research Institute)	Adjudicate study end points in an unbiased and consistent manner according to prespecified end point criteria
Data Monitoring Committee	Monitor accumulating efficacy and safety data; make recommendations to the Executive Committee and Amgen regarding study conduct
Independent Biostatistics Group (Frontier Science and Technology Research Foundation)	Support the study's Data Monitoring Committee through independent analyses of safety and efficacy study data
Clinical Research Organization (Quintiles Inc.)	Monitoring and site management in United States, Canada, Latin America, and Russia; data management and end point packages processing
Investigative sites	Recruitment of participants and ethical conduct of the study in accordance with the protocol and all applicable guidelines
Central laboratory (Covance Central Laboratory)	Specimen management; analysis and storage of laboratory samples
Interactive Voice Response System (ICOPhone)	Patient randomization, drug dispensation, and assignment of investigational product dosing and drug supply management
Dialysis Service Organizations	Facilitate site identification, contract approvals, and patient enrollment

[a]EVOLVE, Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events.

were hospitalized within 12 wk of randomization for myocardial infarction, unstable angina, heart failure (including any unplanned presentation to a health care facility that would require mechanical fluid removal therapy), peripheral vascular disease (other than for a dialysis vascular access), or stroke; had a seizure within 12 wk before randomization; have a scheduled date for kidney transplantation from a known living donor; or are currently enrolled in or have not completed at least 30 d since ending other investigational device or drug trial(s), or are receiving other investigational agent(s).

Primary Composite End Point

The primary end point is the composite of time to all-cause mortality or first nonfatal cardiovascular event (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular disease, including lower extremity revascularization and nontraumatic amputation). The components of this composite end point were chosen on the basis of the evaluation of appropriate pathophysiologic rationale, of the supportive observational and prospective clinical trials data, of the biologic plausibility that the rates of the events would be decreased after therapy with cinacalcet in addition to traditional therapies for sHPT, and that the expectation that all of the components would contribute similarly to the overall end point. Causes of death will be defined and categorized into cardiovascular or noncardiovascular. All deaths will be considered cardiovascular in nature unless a noncardiovascular cause can be clearly identified. Adjudication of myocardial infarction and hospitalization for unstable angina will be based on markers of cardiac muscle damage, including troponin, creatine kinase, and creatine kinase-MB (CKMB), as well as electrocardiographic and clinical data. The main distinction between the definitions of myocardial infarction and hospitalization for unstable angina are based on the thresholds for markers of cardiac muscle damage (troponin or creatine kinase-MB more than two times laboratory upper limits of normal [ULN] for myocardial infarction and greater than ULN but less than two times ULN for unstable angina). Heart failure will be defined as an unplanned

presentation to a hospital or dialysis facility with acute symptomatic pulmonary edema and the need for mechanical ultrafiltration. Requirements for symptomatic pulmonary edema include dyspnea with at least two of the following: (*1*) Bilateral basilar rales on physical examination, (*2*) raised jugular venous pressure, (*3*) interstitial edema findings on chest radiography, (*4*) increased upper pulmonary vessel diameter noted on chest radiography, and (*5*) elevated left ventricular end diastolic pressure or pulmonary capillary wedge pressure. Peripheral vascular events will be assessed on the basis of hospitalization as a result of signs and symptoms of lower limb peripheral vascular disease, with documentation of tissue necrosis or the need for a therapeutic intervention (*e.g.*, amputation, revascularization). All composite cardiovascular end points and key secondary end points, including stroke, bone fracture, and parathyroidectomy, will be adjudicated by the Clinical Events Classification group at Duke Clinical Research Institute in an unbiased and consistent manner according to prespecified end point criteria.

Procedures and Assessments

This section describes key procedures and assessments during the screening, titration, and follow-up phases of the study, according to the frequency of visits and duration of study phases shown in Figure 3. Screening procedures include medical history; physical examination; electrocardiogram (ECG); serum pregnancy test for all women; and blood samples for PTH, calcium, phosphorus, and calcium-phosphorus product. Assessment of dialysis dosage (single-pool Kt/V or urea reduction ratio) and patient-reported outcomes (PRO) will also be collected during this period. At day 1 (the day of the first dose of study drug), the following will be assessed: Vital signs and blood samples for PTH, calcium, phosphorus, calcium-phosphorus product, bone-specific alkaline phosphatase (BALP), serum N-telopeptide (NTx), 25(OH)D, 1,25(OH)2D, hematology, lipid profile, and serum chemistry. During the titration phase, serum calcium, phosphorus, and PTH will be measured at all study visits. In addition, at the 20-wk study visit, vital signs will be recorded; PRO assessment and health resource utilization questionnaires will be completed; and additional blood samples will be collected for hematology, lipid profile, biochemistry, BALP, and NTx. Dialysis dosage will also be assessed during this visit. During the course of the follow-up phase, PTH, calcium, phosphorus, and calcium-phosphorus product will be assessed at all study visits and approximately 1 to 2 wk after a dosage change in study drug; BALP, NTx, hematology, lipid profile, and biochemistry will be assessed at week 52 and approximately yearly thereafter; and PRO, physical examination with vital signs, and ECG will be performed at week 52 and approximately yearly thereafter (except for BP and weight, which will be collected every 6 mo). Patients who experience a suspected end point will have a PRO assessment at the next scheduled study visit. Assessment of dialysis dosage will be completed at week 52 and approximately every 6 mo thereafter. Finally, at end of study, physical examination with vital signs, ECG, PRO assessment, dialysis dosage, PTH, calcium, phosphorus, calcium-phosphorus product, BALP, NTx, hematology, lipid profile, biochemistry, and serum pregnancy test (women) will be performed and assessed, as appropriate.

End of Treatment and End of Study

Patients who have study drug discontinued for any reason will continue to be followed until the completion of the trial. Patients who do not wish to continue participation in study activities will be monitored for the purposes of collection of study end point data. These patients will remain in the study and will have this information collected, typically through a review of medical records and/or telephone contact. Patients who have study drug discontinued for any reason during the course of the study and do not wish to be followed for the collection of study end point data (effectively withdrawing consent) will be permanently discontinued from study on the date of this request.

End of the study for any given patient will be defined as the date of study completion/termination communicated to sites (when 1882 patients have experienced a primary event), the date of the last study-related assessment for patients who prematurely and permanently withdraw from the study, or the date of death. End of treatment is defined as the date of the last dose of the study drug for patients who discontinue its administration.

Patients who interrupt or discontinue study drug for any reason, except for parathyroidectomy, but remain in the study may restart the blinded study drug at any time during the study. They are to reinitiate therapy at the 30-mg dosage level if discontinued for >4 wk.

Statistical Considerations

EVOLVE is event driven and will continue until approximately 1882 patients have experienced a primary event. Enrolled patients will be randomly assigned at a 1:1 ratio to cinacalcet or control group. Randomization will be stratified according to history of diabetes and by country. On the basis of a two-sided log-rank test for equality of survivor functions using a two-sided 0.049 significance level (allowing for one formal interim analysis with a significance level of 0.001), it is anticipated that a sample size of 3800 will yield the required 1882 primary events with 90% power to detect a hazard ratio of 0.80 (*i.e.*, treatment effect of 20%) over a maximum follow up of 4 yr (median follow up expected to be approximately 3 yr). The sample size estimate includes consideration of treatment effect attenuation as a result of a 10-wk delay in separation of the Kaplan-Meier curves at trial start, a lost to follow-up rate of 1% per year, a withdrawal from treatment (dropout) rate of 10% per year in the cinacalcet group, and a drop-in rate in the placebo group of 10% per year. All patients will be followed from randomization through to the date of study termination, except for patients who permanently withdraw consent. Efficacy analyses will be performed in accordance with the intention-to-treat principle.

Conclusions

The need for investigation of novel therapeutic interventions that target mortality and cardiovascular morbidity is high-

lighted by the 10- to 30-fold enhanced risk for cardiovascular events, including death, among hemodialysis patients compared with the general population (27). Prospective clinical trials in dialysis populations have failed to demonstrate a beneficial effect of some interventions to ameliorate cardiovascular risk (3–5), suggesting a need to investigate therapeutic interventions that are targeted toward nontraditional risk factors in this patient population. sHPT and the associated changes in calcium and phosphorus constitute nontraditional yet modifiable risk factors for the high mortality and cardiovascular morbidity observed in this population, yet no adequately powered clinical trials have addressed this issue. Although the complex nature of sHPT and the effects of cinacalcet on PTH, calcium, and phosphorus may not allow exact determination of the mechanism(s) of effect, EVOLVE should answer the critical question of whether an approach that targets multiple laboratory parameters of CKD-MBD results in an improvement in outcomes of importance to hemodialysis patients.

Disclosures

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