Rationale and Trial Design of Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes: The Occurrence of Renal Events (BEACON)

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Abstract
Background: Chronic kidney disease (CKD) associated with
type 2 diabetes mellitus constitutes a global epidemic com-
plicated by considerable renal and cardiovascular morbidity
and mortality, despite the provision of inhibitors of the re-
nin-angiotensin-aldosterone system (RAAS). Bardoxolone
methyl, a synthetic triterpenoid that reduces oxidative stress
and inflammation through Nrf2 activation and inhibition of
NF-κB was previously shown to increase estimated glomeru-
lar filtration rate (eGFR) in patients with CKD associated with
type 2 diabetes mellitus. To date, no antioxidant or anti-in-
flammatory therapy has proved successful at slowing the
progression of CKD. **Methods:** Herein, we describe the de-
sign of Bardoxolone Methyl Evaluation in Patients with
Chronic Kidney Disease and Type 2 Diabetes: the Occurrence

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of Renal Events (BEACON) trial, a multinational, multicenter, double-blind, randomized, placebo-controlled Phase 3 trial designed to determine whether long-term administration of bardoxolone methyl (on a background of standard therapy, including RAAS inhibitors) safely reduces renal and cardiac morbidity and mortality. ***Results:*** The primary composite endpoint is time-to-first occurrence of either end-stage renal disease or cardiovascular death. Secondary endpoints include the change in eGFR and time to occurrence of cardiovascular events. ***Conclusion:*** BEACON will be the first event-driven trial to evaluate the effect of an oral antioxidant and anti-inflammatory drug in advanced CKD.

Introduction

Type 2 diabetes mellitus prevalence is increasing worldwide. Sequelae vary among affected persons but, in general, multiple treatment strategies are required to prevent or halt progressive multiorgan disease. Diabetes is the most common cause of end-stage renal disease (ESRD), which occurs in ~30% of all patients globally [1]. Loss of kidney function is progressive and associated with high cardiovascular (CV) and renal morbidity and mortality, equaling or exceeding mortality of many treated cancers [2].

Several treatments, such as drugs that block the renin-angiotensin-aldosterone system (RAAS), can reduce or postpone renal and CV events in patients with chronic kidney disease (CKD) and type 2 diabetes [3–7]. However, despite relative risk reductions of 15–30% for composite renal outcomes (i.e. doubling of serum creatinine, dialysis or renal transplantation, and death) and 20–30% for slowing progression to ESRD, residual risk remains extremely high and mean time to dialysis is delayed by <6 months. Additional therapeutic strategies or interventions to attenuate, arrest, or reverse disease progression are needed.

In recent years, several approaches, including endothelin receptor antagonists (e.g. avosentan), glucosaminoglycans (e.g. sulodexide), advanced glycation end-product (AGE) inhibitors (e.g. pyridorin), erythropoiesis-stimulating agents (e.g. darbepoetin alpha), HMG-CoA reductase inhibitors alone or in combination with other cholesterol-lowering agents (e.g. simvastatin + ezetimibe) and RAAS inhibitor combination strategies (e.g. angiotensin-converting enzyme inhibition (ACEi), plus angiotensin receptor blockade (ARB) or ACEi or ARB plus a direct renin inhibitor (DRI)) have produced generally disappointing results [8–14].

More recently, progressive kidney function loss in diabetes mellitus has been recognized, at least in part, to be inflammatory in origin [15–19]. The association between inflammation and progressive kidney disease has directed attention toward new pathways of intervention. Compelling experimental and early-phase clinical data showed bardoxolone methyl, a synthetic triterpenoid that reduces oxidative stress through Nrf2 activation and supports resolution of inflammation through NF-κB inhibition, increases estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes mellitus and stage 3b/4 CKD [20, 21]. These findings raise the possibility that bardoxolone methyl could delay the need for dialysis or transplantation and/or reduce CV complications in patients with type 2 diabetes mellitus and progressive CKD. However, the eGFR increase could also reflect an increase in intraglomerular pressure and thus a potential risk of hyperfiltration-related kidney injury.

Validating the effect of bardoxolone methyl on eGFR requires study of the drug's effects on clinically meaningful endpoints. Primary outcomes of most CKD progression trials typically include the classic composite endpoint consisting of time-to-first occurrence of doubling of serum creatinine, ESRD, or death. However, since bardoxolone methyl reduces serum creatinine levels, a renal endpoint that includes serum creatinine change could be considered inappropriate, leaving initiation of dialysis or death as the most clinically relevant endpoints. For feasibility and practicality the study population of such a trial should include patients with advanced (stage 4) CKD (eGFR 15 to <30 ml/min/1.73 m^2). No other trial has tested an agent with the aim of delaying progression to ESRD in patients with such advanced CKD.

This communication describes the design of the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) trial, which will test the effects of bardoxolone methyl against placebo on the risk of ESRD and CV death in patients with type 2 diabetes mellitus and stage 4 CKD receiving standard of care. We describe specific challenges faced in designing such a trial, in which the intervention appears to alter an intermediate functional measurement (in this case, serum creatinine or eGFR) that may influence the 'hard' outcome (dialysis or transplantation), and how we incorporated data from previously conducted clinical trials in earlier CKD stages to inform our sample size and estimated event rate.

Table 1. Inclusion and exclusion criteria of the study population

Inclusion criteria

Screening eGFR ≥15.0 and <30.0 ml/min/1.73 m^2

History of type 2 diabetes mellitus

≥18 years of age

Stable treatment with an ACE inhibitor and/or ARB for at least 6 weeks prior to and during screening, unless medically contraindicated with documentation

SBP ≤160 mm Hg and ≥105 mm Hg; DBP ≤90 mm Hg

Use of birth control methods during screening, on study, and for at least 30 days after the last dose of study drug

Serum magnesium ≥1.3 mEq/l (0.65 mmol/l) at screening

Exclusion criteria

Type 1 diabetes mellitus

Known non-diabetic renal disease

Ongoing clinical investigation with evidence suggesting non-diabetic renal disease other than nephrosclerosis

History of a renal transplant or a planned transplant from a living donor

Albumin/creatinine ratio (UACR) >3,500 mg/g (395.5 mg/mmol) at screening

Hemoglobin A$_{1c}$ level >11.0% (97 mmol/mol) at screening

Acute dialysis or acute kidney injury within 12 weeks prior to or during screening

Clinical signs and/or symptoms of uremia and expected need for renal replacement therapy within 12 weeks following randomization, as assessed by the investigator

Recently active cardiovascular disease defined as:
Unstable angina pectoris within 12 weeks before study randomization
Myocardial infarction, coronary artery bypass graft surgery, or percutaneous transluminal coronary angioplasty/stent within 12 weeks before study randomization
Cerebrovascular accident, including transient ischemic attack within 12 weeks before study randomization
Current diagnosis of Class III or IV NYHA congestive heart failure
Clinical diagnosis of severe obstructive valvular heart disease or severe obstructive hypertrophic cardiomyopathy

Atrioventricular block, 2° or 3°, not successfully treated with a pacemaker

Administration of a contrast agent that may induce nephropathy within 30 days prior to study randomization or planned during the study

Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to randomization or anticipated need for immunosuppression during the study

Total bilirubin, aspartate transaminase (AST), or alanine transaminase (ALT) level greater than the upper limit of normal (ULN) or alkaline phosphatase level greater than two times the ULN on ANY screening laboratory test result

Female patients who are pregnant, intend to become pregnant during the study, or are nursing

BMI <18.5

Known hypersensitivity to any component of the study drug

Current history of drug or alcohol abuse, as assessed by the investigator

Clinically significant infection requiring intravenous administration of antibiotics or hospitalization within 6 weeks prior to screening

Diagnosis or treatment of a malignancy in the past 5 years, excluding non-melanoma skin cancer and carcinoma in situ of the cervix or a condition highly likely to transform into a malignancy during the course of the study

A clinical condition that, in the judgment of the investigator, could potentially pose a health risk to the subject while involved in the study

Participation in a clinical study involving any intervention within 30 days prior to randomization, concurrent participation in such a study, or participation in a prior clinical study involving bardoxolone methyl in any form

BEACON Design

Study Population

The study population includes approximately 2,000 patients with type 2 diabetes mellitus defined as onset at ≥30 years of age; if diagnosed at a younger age, fasting C-peptide level was used to confirm type 2 diabetes mellitus. Patients should have stage 4 CKD, defined as eGFR of 15 to <30 ml/min/1.73 m^2. See table 1 for additional inclusion and exclusion criteria.

Study Outcomes

The primary efficacy aim of BEACON is to assess efficacy of bardoxolone methyl relative to placebo in delaying progression to ESRD (maintenance dialysis, kidney transplantation or kidney death (i.e. loss of kidney function with refusal of dialysis or transplantation)) or CV death. The composite primary outcome includes CV death because it is an important competing risk in these patients. Non-CV and non-renal mortality were not included in the primary endpoint as they are not assumed to be related to kidney disease progression.

Secondary efficacy endpoints of BEACON are (1) change in eGFR over the study duration, (2) time-to-first hospitalization for heart failure or death due to heart failure, and (3) time-to-first event in a composite CV endpoint consisting of CV death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for heart failure.
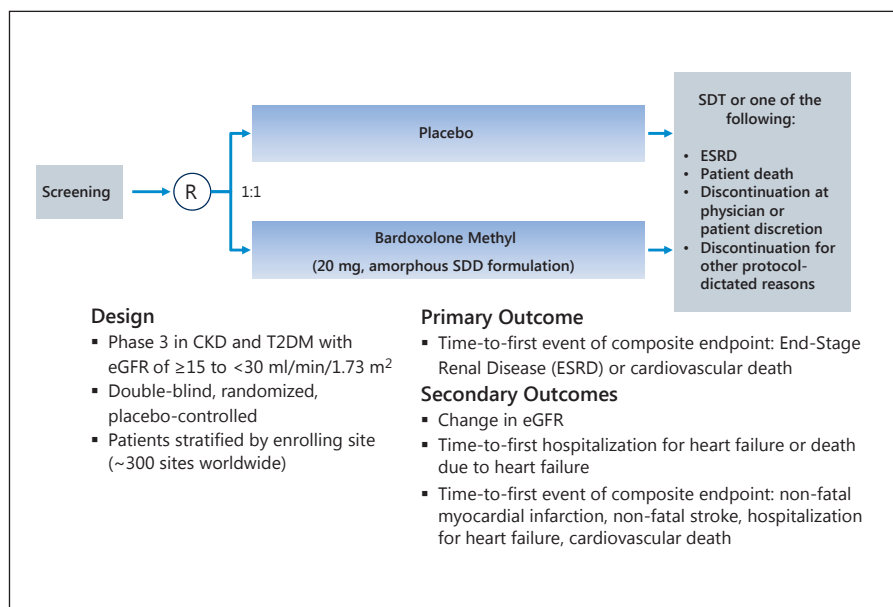
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Fig. 1. BEACON design overview and study objectives. R = Randomization; SDT = study drug termination; SDD = spray-dried dispersion. * During week 4, patients will begin in-person visits every 4 weeks until week 20. Beginning week 20, telephone contact will alternate with in-person site visits every 4 weeks for the duration of the study. Patients will undergo more extensive evaluations during semi-annual visits at week 24 and every 24 weeks thereafter.

Study Design

BEACON is a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase 3 study comparing the efficacy and safety of bardoxolone methyl relative to placebo in patients with type 2 diabetes mellitus and stage 4 CKD receiving standard of care. Study patients who met all inclusion criteria and no exclusion criterion and satisfied screening evaluations were randomized 1:1 to receive placebo or 20 mg bardoxolone methyl (amorphous spray-dried dispersion (SDD) formulation; fig. 1). Patients are to take one study drug capsule orally each morning on an empty stomach (1 h before or 2 h after eating). Randomization was stratified by enrollment site. To ensure a balanced study population at risk for ESRD, a maximum of 25% of all enrolled patients may demonstrate a urine albumin-to-creatinine ratio (UACR) <30 μg/mg (3.39 mg/mmol). To ensure the study population reflects patients currently following clinical practice guidelines treatment, a maximum of 1 in 8 (12.5%) of patients are permitted to be off ACEi or ARB treatment (or not on a K/DOQI goal dose of ACEi or ARB) at the start of study for a medical contraindication (e.g. hyperkalemia, hypotension, angioedema).

Follow-Up, Study Visits and Management

Patients are assessed every 4 weeks throughout the trial. After randomization, patients are seen every 4 weeks through to Week 16 (fig. 1), after which in-person visits alternate with telephone contact visits every 4 weeks. At

Week 24 and every 24 weeks thereafter, each subject undergoes a more extensive evaluation (fig. 1).

Blood pressure is measured 3 times at each visit with an oscillometric automated device (SunTech 247) provided by the sponsor. Consistent with current clinical practice guidelines for management of hypertension in patients with type 2 diabetes mellitus, investigators are instructed to target blood pressure to a level of ≤130/80 mm Hg for patients with an UACR ≥300 mg/g (33.9 mg/mmol) and ≤140/90 mm Hg for patients with an UACR ≤300 mg/g (33.9 mg/mmol). The protocol discourages change or discontinuation of either ACEi or ARB treatment, unless required secondary to development of a medical contraindication. For management of all other comorbidities, investigators are instructed to follow standard of care.

At each in-person visit, symptoms considered related to uremia are systematically captured, and for each subject requiring maintenance dialysis, primary and secondary reasons for initiating dialysis are obtained (table 2). Patients are to receive study drug until they reach ESRD, they die, they or the investigator decides to discontinue study drug, they withdraw consent to participate in the study, or they meet additional protocol-dictated reasons that warrant discontinuing study drug. Otherwise, patients are to continue receiving study drug until the study drug termination (SDT) date, as defined below. Even after study drug discontinuation, patients are to return for in-person and/or participate in telephone visits to capture potential primary or secondary endpoints.

Table 2. Indications for initiation of dialysis (indications for dialysis initiation will be captured at each visit on a standardized case report form, marked as primary or secondary, and classified according to the listed classification terms)

Primary or secondary indications for initiation of dialysis
Nausea/vomiting
Fatigue
Deterioration in nutritional status/recent significant
    weight loss
Neurologic dysfunction (neuropathy, encephalopathy,
    psychiatric disturbances, seizures)
Volume overload
Hyperkalemia
Metabolic acidosis
Hyperphosphatemia
Hypercalcemia/hypocalcemia
Anemia
Azotemia
Bleeding diathesis
Pleuritis/pericarditis of uremic origin
Malignant hypertension/uncontrolled hypertension
Intractable sleep disturbances
Intractable anhedonia

Classification
New, urgent
Refractory to treatment
Worsening
Severe

The study protocol was designed and implemented in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (as adapted by local health authorities), with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21) and with the ethical principles laid down in the Declaration of Helsinki. The study is registered at http://www.clinicaltrials.gov (NCT01351675).

Laboratory Measurements

Key laboratory assessments were done during screening and at all in-person visits starting at Day 1 (day of the first dose of study drug). These assessments include serum pregnancy tests in women of childbearing potential; clinical chemistries including albumin (determined photometrically), transaminases, blood urea nitrogen, calcium, creatinine (enzymatic), eGFR (4-variable MDRD calculation using enzymatic creatinine determination [22]), total and direct bilirubin, γ-glutamyl transferase, lactate dehydrogenase, magnesium, phosphorus, uric acid, and HbA$_{1c}$; urine for urinalysis and microscopy (only during

screening), first morning void for ACR (3 during screening; 2 prior to each in-person study visit); hematology with differential; hepatitis B surface antigen (only performed at screening if lacking evidence of a negative assay in the past year); troponin-T and BNP (Day 1 only). At semi-annual visits only (every 24 weeks starting at Day 1), the following will be measured in addition to the laboratory variables described above: lipid panel and plasma and urine samples for biomarkers (if consent given). Blood draws for plasma concentration (pharmacokinetic (PK) samples) of study drug will occur at weeks 4 and 12, and at semi-annual visits thereafter (starting at Week 24).

All blood and urine specimens are shipped at ambient temperature (except for PK and biomarker samples, which are shipped frozen) to central laboratories around the world using an overnight commercial carrier. Validations for laboratory measurements took place at the US site and global correlations occurred for all other locations. Biomarker samples are stored at –80°C.

Definition of ESRD and other Endpoints

For purposes of endpoint adjudication (to be performed by a blinded and independent events adjudication committee (EAC)), ESRD is defined as the need for maintenance dialysis (peritoneal or hemodialysis) for ≥12 weeks or kidney transplantation, or death due to kidney failure. The 12-week duration criterion was incorporated to avoid misclassification of ESRD events requiring acute dialysis resulting from either or both acute kidney injury or acute fluid overload. If ESRD is reached <12 weeks before the study termination date, or if a subject dies <12 weeks after dialysis initiation, the EAC will adjudicate whether the event represented ESRD or not. An EAC charter documents instructions for adjudication and presents detailed definitions for all renal and CV endpoints.

End of Study

The end of study is defined as the last post-treatment visit occurring after the SDT date. SDT is determined as the date when approximately 300 patients have experienced a primary endpoint as evaluated by the EAC. The primary efficacy analysis includes all events up to the SDT date. All primary endpoints, including those occurring after the SDT, will be assessed in a sensitivity analysis. While the BEACON Steering Committees remain blinded to the actual results, the trial was terminated prematurely following a recommendation from the independent data monitoring committee.

Statistical Considerations

Estimation of Placebo Event Rate

We built a model that calculated the proportion of patients, based upon baseline eGFR, who would reach dialysis, assuming a mean ± SD dialysis initiation threshold of 11.1 ± 4.8 ml/min/1.73 m² [23] and the eGFR decline rate reported in the placebo group of a previous trial of bardoxolone methyl. Assuming equal distribution of study subject enrollment across a baseline eGFR of 15 to <30 ml/min/1.73 m², 23% of patients are expected to initiate maintenance dialysis over 24 months of follow-up. In addition, trials with roughly similar inclusion criteria indicate that on average 21% of patients are expected to experience ESRD and 5% CV death over 24 months [3, 4, 8, 13, 24–30]. Thus, the 5% CV death rate and 21 or 23% ESRD rate from literature sources and deterministic modeling led to a range of 24-month event rates for the composite endpoint (ESRD + CV death) of 26–28%. Although this estimate reflects the best available data, we recognize some limitations to the literature sources. First, several studies were conducted more than 10 years ago and some improvements may have occurred in standard of care over time. Secondly, there are only limited data about the specific subject population studied in BEACON (i.e. stage 4 CKD with varying levels of albuminuria). Thus, on the basis of the literature described above and output of the deterministic model described below, we predict a slightly lower placebo event rate of 24% over 24 months for BEACON. We anticipate approximately 75% of the composite endpoint events will be attributed to ESRD, and 25% to CV death.

Deterministic Model to Predict Composite Outcome

We developed a deterministic model to predict likelihood of dialysis or death in placebo- and bardoxolone methyl-treated patients. The model is based on the premise that rate of dialysis events is driven by the proportion of patients with appreciable eGFR loss, which we defined as ≥3 ml/min/1.73 m² per year from baseline.

Three inputs were used for the model: (1) anticipated distribution of patients with macroalbuminuria at baseline, (2) proportion of patients with appreciable eGFR loss within those subgroups, and (3) their respective rates of eGFR decline. We used likelihood of eGFR decline among patients with macroalbuminuria, microalbuminuria or without measurable albuminuria from a Phase 2b trial of bardoxolone methyl in patients with stage 3b/4 CKD and type 2 diabetes mellitus [21]. We included pro-jections for duration of enrollment (14 months), study drug discontinuation (13.5% per year on study), and loss to follow-up (2.5% per year). We took into account the possibility that discontinuation from study drug would be more common in bardoxolone methyl-treated patients. To be conservative, we assumed no effect of bardoxolone methyl on CV death.

Model output: Using specified rates of eGFR decline in patients with type 2 diabetes mellitus and stage 4 CKD with and without macroalbuminuria, the model predicted eGFR over time for declining placebo- and bardoxolone methyl-treated patients whose baseline eGFR values are assumed to be uniformly distributed throughout the 15 to <30 ml/min/1.73 m² range. Taking into account time on study, the model predicted if and when a dialysis event occurred by noting when eGFR would be expected to fall below the specified dialysis initiation threshold (see above). The model estimated the number of dialysis events occurring each month in the placebo and bardoxolone methyl treatment arm to obtain the estimated drug-attributable risk reduction.

Simulations: We previously showed a large discrepancy between time to reach a fixed eGFR value and time to initiation of dialysis [31]. To account for this discrepancy and inherent variability, Monte Carlo simulations were used to stochastically vary eGFR thresholds for initiating dialysis. Several scenarios were modeled including different thresholds for initiating dialysis in placebo and bardoxolone methyl-treated patients, since several previously reported side effects of bardoxolone methyl might be confused with signs of uremia (e.g. muscle cramps, dysgeusia, and weight loss). For each scenario, the frequency distribution from 1,000 trials was used to estimate drug risk reduction for the primary outcome.

Results of the model building and simulations showed an estimated risk reduction for dialysis or CV death with bardoxolone methyl of 44% (base case scenario) (table 3; fig. 2). Additional sensitivity analyses of model parameters to simulate multiple worst-case and best-case scenarios showed the minimum expected relative risk reduction with bardoxolone methyl was 33% (table 3; fig. 2).

Power Calculation

The power calculation is based on a two-sided log-rank statistic tested at a two-sided type I error rate of 0.05. We will enroll approximately 2,000 patients, anticipating approximately 300 composite primary endpoints during 24 months of follow-up. Under these assumptions, if a log-rank test were used to compare groups, BEACON would have 85% power to detect a 32% relative risk reduc-
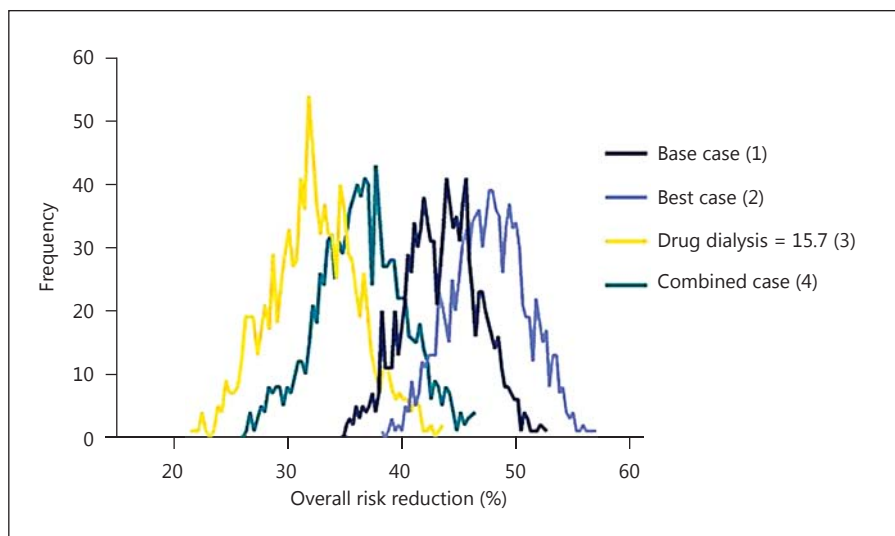
Fig. 2. Frequency distribution of simulated overall drug risk reduction for the primary outcome. Each curve represents the predicted drug risk reduction from 1,000 trial simulations of four scenarios described in table 3.

Table 3. Modeling of overall relative risk

Scenario	Modified parameter	Timing of 300 events	Overall RR, % (95% CI)
Base case	eGFR decline rate = M: –8.0, NM: –5.5; dialysis threshold (PBO and drug) = 11.1	24 months	44±3 (38, 49)
Best case (removing conservative assumptions)	CV death RR = 10%; PBO eGFR decline rate: M: –10.8, NM: –8.7; drug eGFR decline rate: M: –7.4, NM: –6.5	+1 week	48±3 (42, 53)
Patients on drug start dialysis earlier than patients on placebo (with base case)	dialysis threshold: PBO = 12.7; drug = 15.7	–4 weeks	33±4 (26, 39)
Patients on drug start dialysis earlier than patients on placebo (combined with best case)	CV death RR = 10%; PBO decline rate: M: –10.8, NM: –8.7; drug decline rate: M: –7.4, NM: –6.5; dialysis threshold: PBO = 12.7; drug = 15.7	–3 weeks	37±4 (30, 43)
More variability in eGFR at dialysis initiation for patients on drug	dialysis variability: PBO = 8.0; drug = 9.5	+1 week	45±3 (40, 51)
Decreased ESRD event rate prolongs study	eGFR decline rate (PBO and drug) = M: –5.0, NM: –3.0	+23 weeks	36±4 (29, 43)

RR = Relative risk; CI = confidence interval; CV = cardiovascular; PBO = placebo; M = macroalbuminuric; NM = non-macroalbuminuric; eGFR = estimated glomerular filtration rate; ESRD = end-stage renal disease. Units of measure: eGFR decline rate in ml/min/1.73 m². Dialysis threshold given in ml/min/1.73 m².

tion (bardoxolone methyl vs. placebo) in incidence of ESRD or CV death. Actual power is likely to be slightly >85% because, as described below, the analysis will use a Cox model. If the observed relative risk reduction is roughly 23%, approximately half of the modeled effect, the p value would be 0.05.

We pre-specified two pooled, blinded sample size recalculations during BEACON. The first sample size recalculation, conducted after 1,600 patients are randomized, will be used to update sample size model parameters, including enrollment rate, rate of loss to follow-up, discontinuation of study drug rate, eGFR at baseline, and proportion of macroalbuminuric patients. The second sam-

ple size recalculation, which will assess the event rate for the primary composite outcome event rate and relative proportion of ESRD and CV death events, will be conducted when approximately 200 primary events are adjudicated. The estimated hazard ratio and number of primary events may be updated after one or both sample size recalculations to maintain statistical power.

Efficacy Assessment

The primary efficacy analysis will be based on a modified intention-to-treat population, defined as all randomized patients who received at least one dose of study drug. The duration of follow-up within BEACON for any given subject depends on the time when the subject enters the study and when the study ends. The primary analysis will employ Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals comparing time-to-event outcomes. Because of the importance of UACR and eGFR as predictors of ESRD and CV death, and because of the skewed distribution of UACR, models will be adjusted for log-transformed baseline UACR and baseline eGFR. A log-rank test of unadjusted survival curves will be used as a sensitivity analysis. Kaplan-Meier curves will display the time-to-event.

Safety Assessment

Safety assessments, including physical examinations, vital sign measurements, centrally read 12-lead electrocardiograms (ECGs), and centrally analyzed clinical laboratory measurements are planned throughout BEACON. Serum creatinine, eGFR, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) values are masked to investigational sites and the sponsor to minimize the potential for unblinding. If ALT or AST values exceed 3 times the upper limit of normal, both the sponsor and site receive unmasked results. If eGFR exceeds 29 ml/min/1.73 m^2 for an individual subject, the site is informed to assess the dosage of renally-cleared medications. If required for subject safety, the investigator may request the eGFR, serum creatinine, ALT, or AST value at any time (the sponsor will not receive these values). Concomitant medications are recorded. Frequency, intensity, and relationship to study drug of adverse and serious adverse events, as well as abnormal clinical and laboratory test results, are also evaluated.

Patient-Reported Outcomes

Health-related quality of life assessments, using the EQ-5D-5L and Kidney Disease Quality of Life (KDQOL) surveys, are collected at baseline and every 24 weeks thereafter.

Discussion

Residual renal and CV risk remains high in patients with CKD and type 2 diabetes mellitus despite best practice. Recent trials with novel interventional strategies have failed to produce additional renal benefit. Targeting chronic inflammatory and oxidative pathways is a new approach not yet tested in a large-scale outcomes trial in this population. Neither anti-inflammatory drugs nor exogenous addition of antioxidants have proven successful, perhaps because mass endogenous production of reactive oxygen species (ROS) and/or inflammatory mediators was not altered. Bardoxolone methyl may differ as it acts on the endogenous production of ROS and inflammatory pathways simultaneously [32]. By binding KEAP1, it activates Nrf2, the master regulator of the antioxidant response, which induces numerous antioxidant enzymes. Bardoxolone methyl simultaneously downregulates pro-inflammatory signaling via NF-κB inhibition.

Clinical data on bardoxolone methyl come from two recently published studies in patients with stage 3b/4 CKD (eGFR range ≥15 to <45 ml/min/1.73 m^2) and type 2 diabetes mellitus: a Phase 2a study and the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) study [20, 21]. The BEAM study demonstrated bardoxolone methyl had several effects sustained over at least 1 year, including a mean eGFR increase of 8.1–9.4 ml/min/1.73 m^2 in the two higher-dose groups. Whether these effects translate into longer-term benefits is unknown. Complicating the picture is the observed increase in albuminuria. A combination of an early rise in eGFR and increase in albuminuria may not be renoprotective in the longterm, as an acute rise in eGFR has been associated with hyperfiltration, renal damage and subsequent rapid eGFR loss [33], whereas high urinary albumin levels have been associated with increased renal damage [34]. Still, BEAM showed the initial eGFR rise in bardoxolone methyl-treated patients was sustained, without a subsequent fall, during the year-long treatment [21], unlike effects observed with amlodipine in AASK [35]. Pharmacologic mechanisms for the albuminuria increase, such as increases in GFR and tubular reabsorption capacity of albumin, are under active investigation. A recent experimental study showed bardoxolone methyl interferes with megalin expression, which could indicate proximal tubular albumin reabsorption is attenuated [36]. Thus, the albuminuria rise may not be detrimental if albumin is not reabsorbed or bardoxolone methyl interrupts the inflammatory process of excess tubular albumin reabsorption. Results of BEACON will further clarify

whether the eGFR and albuminuria changes are beneficial or detrimental, or whether bardoxolone methyl added to standard of care will preserve or enhance kidney function to alter ESRD incidence versus standard of care alone.

Theoretically, the eGFR improvement observed in BEAM or other studies may not reflect an improvement in true GFR. However, clinical studies with bardoxolone methyl have shown the decline in serum creatinine is paralleled by a rise in creatinine clearance, with no change in 24-hour urine creatinine excretion, and therefore, no apparent change in creatinine production or breakdown [20]. In addition, eGFR changes inversely correlated with BUN, uric acid, and phosphorus changes [20, 21]. To confirm the effects, two parallel studies are underway testing the effect of bardoxolone methyl on GFR measured with exogenous filtration tracers, one in the US (NCT01500798) and one in Japan.

One dose arm of BEAM showed a small, but statistically significant, rise in blood pressure. Although not observed in other pre-clinical or clinical studies, it could be a safety signal. We are conducting a 24-hour blood pressure measurement substudy to more definitively assess blood pressure effects of bardoxolone methyl.

Using an ESRD endpoint in a trial with a drug that affects serum creatinine leads to other challenges. First, no recent trial data are available that allow us to estimate accurately ESRD incidence in a stage 4 CKD diabetic population. Second, to estimate the potential effect of bardoxolone methyl on need for dialysis or transplantation, we needed to consider how the drug might be expected to affect eGFR, and to what degree eGFR informs the decision to proceed with dialysis or transplantation. Although central laboratory serum creatinine and eGFR values obtained during BEACON are masked to investigators, site personnel may possibly gain knowledge of these data through other means. Even in the absence of previous trials and drugs that increase eGFR, one can estimate, extrapolate, and calculate the potential slowing of the time to ESRD. However, we needed to take into account the relation between eGFR and ESRD is not straightforward: ESRD is defined as initiation of maintenance dialysis or renal transplant, and decision to start renal replacement therapy is driven not only by eGFR but also other laboratory measures and clinical signs of uremia [37]. Since bardoxolone methyl may also affect parameters other than eGFR (e.g. muscle cramps, taste disturbances) that could mimic uremia, reasons for initiation of dialysis will be documented in each instance, which will help clarify the primary results of the trial.

In summary, administration of bardoxolone methyl has resulted in eGFR increases in several early phase trials. The adverse event profile associated with bardoxolone methyl in prior studies had not demonstrated evidence of any significant harm or resulted in adverse renal effects; however, per-subject exposure has been limited to 1 year. BEACON will test whether this possibly salutary effect on kidney function translates into a delay in progression to ESRD and/or a reduction in CV death or other CV events and will provide additional safety data relevant to bardoxolone methyl and potentially to related drugs.

Steering Committee Members of the BEACON Trial

Dick de Zeeuw, Glenn M. Chertow (co-chairs), Tadao Akizawa, Paul Audhya, George L. Bakris, Melissa Krauth, Colin J. Meyer, John J. McMurray, Giuseppe Remuzzi, Robert D. Toto, Nosratola D. Vaziri, Christoph Wanner, Hans-Henrik Parving, and Janet Wittes; Hiddo J. Lambers-Heerspink (external advisor).

Termination of the BEACON Trial

While the BEACON Steering Committee remains blinded to the actual results, the trial was terminated prematurely following a recommendation from the independent data monitoring committee.

Event Adjudication Committee Members of the BEACON Trial

Rajiv Agarwal (chair), Stefan Anker, Juan Francisco Arenillas, James Januzzi, Alan Jardine, Scott Kasner, Brett Kisslea, Daniel Kolansky, Johannes Mann, and Ravi Thadhani.

Independent Data Monitoring Committee Members of the BEACON Trial

Peter McCullough (chair), Peter Ivanovich, Markus Ketteler, John Lachin, and Janet McGill.

Contributors to This Communication

All authors were involved in the design of BEACON, as well as James Stolzenbach (JS). MC, HJLH, JW and Yili Pritchett (YP) provided statistical support. DdZ and GMC wrote the draft of the report, and all authors contributed to its revision. DdZ and GMC take responsibility for the report. Stacey Ruiz (SR) provided editorial assistance, and Ritu Rajan (RR), Angie Goldsberry (AG), Heidi M. Christ-Schmidt (HMCS), and Danielle M. Wrolstad (DMW) provided assistance on the statistical modeling and design.

Disclosure Statement

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