

deceased donor kidney transplantation. Although there is geographic heterogeneity in organ recovery and utilization rates, geographic disparities in access to organs for transplantation would persist because of the current allocation system borders even if practice variation was reduced. Allocation proposals eliminating the current arbitrary DSA and regional boundaries (i.e., a “borderless allocation system”) are being considered,⁹ and our findings suggest that updating or eliminating allocation boundaries may improve equity in access to deceased donor kidney transplantation among wait-listed candidates in the United States.

DISCLOSURE

All the authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

Study design: KLK, SAH, SM; data analysis: KLK; data interpretation: KLK, SAH, SM; supervision and mentorship: SM. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Implementing the Kidney Health Initiative Surrogate Efficacy Endpoint in Patients With IgA Nephropathy (the PROTECT Trial)



Jonathan Barratt¹, Brad Rovin², Ulysses Diva³, Alex Mercer⁴ and Radko Komers⁵; on behalf of the PROTECT Study Design Group

¹Department of Cardiovascular Sciences, University of Leicester and Leicester General Hospital, Leicester, UK; ²Department of Medicine, Ohio State University Wexner Medical Center, Columbus, Ohio, USA; ³Biometrics, Retrophin, Inc., San Diego, California, USA; ⁴Clinical Drug Development, JAMCO Pharma Consulting AB, Stockholm, Sweden; and ⁵Nephrology, Retrophin, Inc., San Diego, California, USA

Correspondence: Jonathan Barratt, Department of Cardiovascular Sciences, University of Leicester and Leicester General Hospital, Gwendolen Road, Leicester LE5 4PW, UK. E-mail: jb81@leicester.ac.uk

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There has been little progress in the development and regulatory approval of novel therapies for glomerular diseases. There are several reasons for this dilemma, including safety and efficacy of tested therapies, the slowly progressive nature of glomerular diseases, challenges with clinical trial design, and the traditional endpoints required by regulatory agencies for drug labeling. This is compounded by the fact that most primary glomerular diseases are recognized internationally as rare diseases. The time required and feasibility to conduct large-scale phase 3 clinical trials to evaluate whether a new therapy improves kidney survival and decreases the development of end-stage kidney disease (ESKD) is prohibitive, particularly when that disease is rare. Even using doubling of serum creatinine concentration, an accepted surrogate endpoint of ESKD, requires expensive trials with lengthy follow-up.

To address clinical trial endpoints, a scientific workshop was co-sponsored by the National Kidney Foundation (NKF), US Food and Drug Administration, and European Medicines Agency to evaluate change in albuminuria and rate of change/slope in glomerular filtration rate (GFR) as surrogate endpoints for clinical trials evaluating treatments for early-stage chronic kidney disease.¹ A meta-analysis of randomized controlled trials supported the use of these surrogate endpoints to evaluate the potential effect of a therapeutic on progression of chronic kidney disease.² In addition, to facilitate clinical development of new drugs for kidney diseases, the American Society of Nephrology partnered with the Food and Drug Administration under the auspices of the Kidney Health Initiative (KHI). The KHI recently published the recommendations of a workgroup that examined clinical trial endpoints for drug approval in the rare glomerular disease IgA nephropathy (IgAN).³ The IgAN workgroup concluded that proteinuria reduction was a reasonably likely surrogate for a drug's effect on progression to ESKD and that it could be used as a basis for accelerated approval of new IgAN therapies.³

We have designed a novel phase 3 trial (PROTECT Trial; see [Supplementary Tables S1 and S2](#)) implementing these surrogate endpoints for the treatment of IgAN, using the KHI and NKF recommendations of proteinuria reduction and the slope of estimated GFR (eGFR) decline

as primary and confirmatory efficacy endpoints ([Supplementary Table S3](#)). The PROTECT Trial (<https://clinicaltrials.gov/ct2/show/NCT03762850>) is a global, randomized, double-blind, active-controlled trial that compares sparsentan, a first-in-class investigational compound combining an angiotensin II type 1 receptor blocker and endothelin type A inhibitor, to an angiotensin receptor blocker (irbesartan) for the treatment of IgAN ([Supplementary Figures S1 and S2](#)). The trial, which is currently ongoing, is designed to enroll 280 patients, 18 years or older, with eGFR ≥ 30 ml/min per 1.73 m^2 , who remain at a high risk of progressive kidney disease (defined as continued proteinuria above $1.0\text{ g}/24\text{ h}$) despite receiving maximal supportive care, including maximally tolerated inhibition of the renin-angiotensin system. At screening, the patients cannot receive or have a recent history of treatment with immunosuppressive agents. Patients will be randomized 1:1 to receive either sparsentan or irbesartan.

The primary efficacy endpoint in PROTECT is the change from baseline (i.e., the last pretreatment value available before the first dose of study medication) in the urine protein/creatinine ratio, based on a 24-hour urine collection, at week 36. This endpoint uses the KHI recommendation that in IgAN, reduction in proteinuria is a reasonably likely surrogate for a drug's effect on progression to ESKD.³ Subsequently, all patients will be followed on an intent-to-treat basis up to week 110 while remaining on the allocated drug regimen, and for an additional 4 weeks after cessation of study drug and transition to standard of care. Consistent with the NKF recommendations, the rate of change of eGFR (eGFR slope) at week 110 and change in eGFR from baseline at week 114 ([Figure 1](#)) will be assessed as confirmatory endpoints of treatment effect for full drug approval. Rate of eGFR change endpoints are statistically more efficient (i.e., a smaller patient sample is required to demonstrate benefit) than event-based endpoints for a slowly progressive disease, and when applied as the confirmatory endpoint, they allow for shorter, smaller, and more feasible trials to be conducted. In addition, unlike the ultimate endpoint of ESKD or the traditional surrogate endpoint of doubling of serum creatinine for ESKD, they are less affected by baseline eGFR, thus facilitating broadening of the

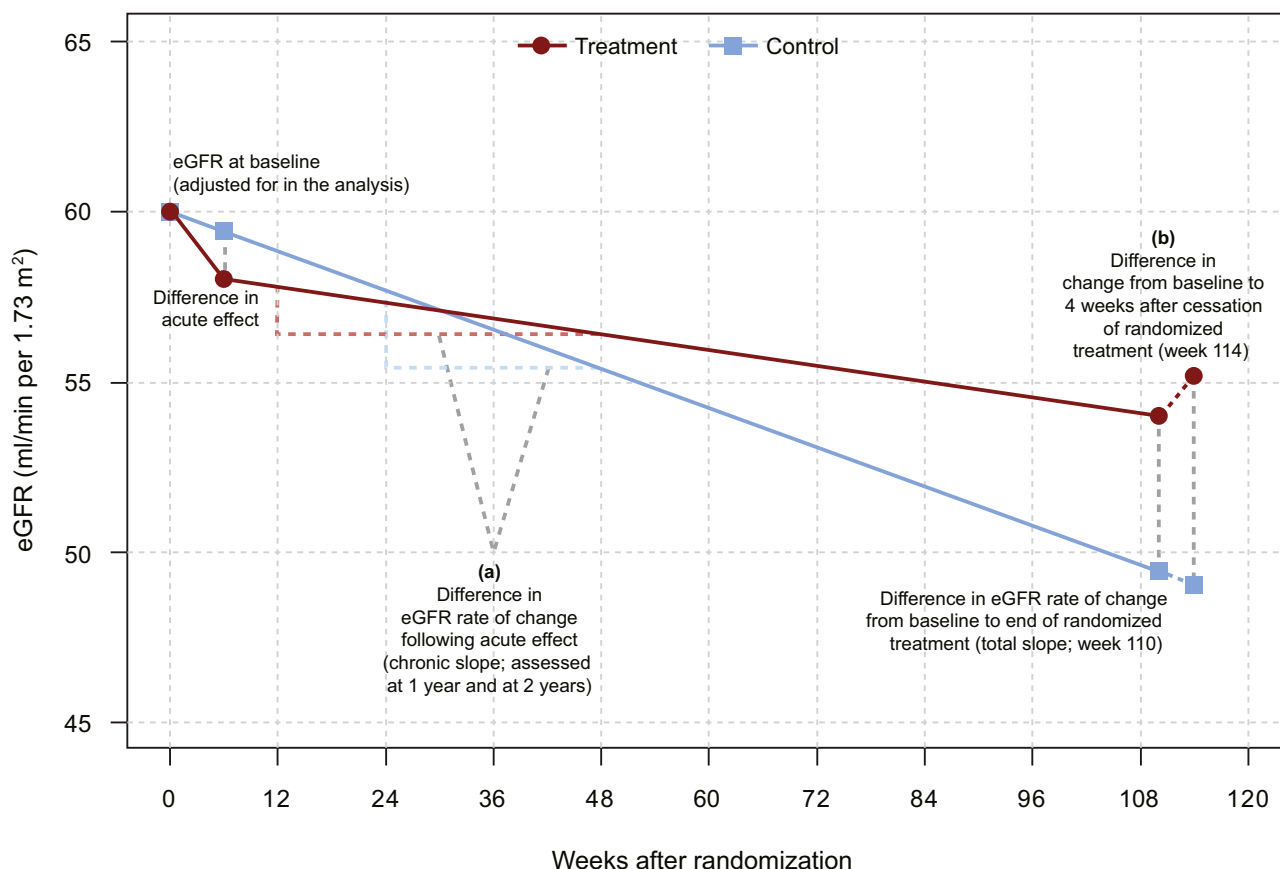


Figure 1. Hypothetical conceptualization of estimated glomerular filtration rate (eGFR) rate of change efficacy endpoints.

patient population to include those with early-stage chronic kidney disease.

PROTECT has been powered to detect a 30% difference in proteinuria between sparsentan and placebo, based on an analysis of 2 large IgAN patient registries from Leicester and Glasgow. The Leicester analysis showed that patients with IgAN with proteinuria ≥ 1.0 g/d who achieved a 30% reduction in proteinuria at 9 months with renin-angiotensin-aldosterone system blockade had a decrease in long-term eGFR decline that translated into an eGFR that was higher by 6.64 ml/min per 1.73 m², with a 95% confidence interval of 0.83–12.44 at 2 years, compared with patients who did not achieve this level of proteinuria reduction (Figure 2). Consistent with findings from the NKF workshop,² and based on the KHI white paper,³ a 30% reduction in proteinuria at 9 months is also predicted to reflect a treatment effect on clinical outcomes (doubling of serum creatinine, ESKD, or death).

We have incorporated multiple ways of assessing the rate of change in eGFR into the PROTECT design (Figure 1), including rate of change following the initial acute effect of therapy over approximately 1 year and at 2 years (explanation [a] in Figure 1), and the change from baseline to 4 weeks post-cessation of randomized treatment (week 114; explanation [b] in Figure 1).

Different approaches to analysis of changes in eGFR over time have been explored in some recent trials with drugs that possess glomerular hemodynamic actions. For example, in the EMPA-REG OUTCOME trial, “chronic slope” of eGFR (i.e., rate of decline of kidney function measured after excluding an initial period to account for the acute hemodynamic effect of the drug to the end of the treatment period) reflected well the beneficial therapeutic effect of empagliflozin as compared with placebo.⁴ Moreover, after drug withdrawal, eGFR increased significantly in the empagliflozin group but remained the same in placebo-treated patients. Similar observations were reported by Torres *et al.*⁵ in a study with tolvaptan in patients with autosomal-dominant polycystic kidney disease. Another endpoint of clinical interest that will be evaluated in this study is the “total slope” of eGFR (i.e., rate of decline of kidney function measured from baseline to the end of the treatment period). It will be interesting to observe how these different approaches to measurements of changes in kidney function perform in PROTECT where both arms are, in contrast to the previously mentioned placebo-controlled studies, treated with drugs that possess renal hemodynamic actions.

The impact that the outputs from the KHI IgAN workgroup and NKF/Food and Drug Administration/

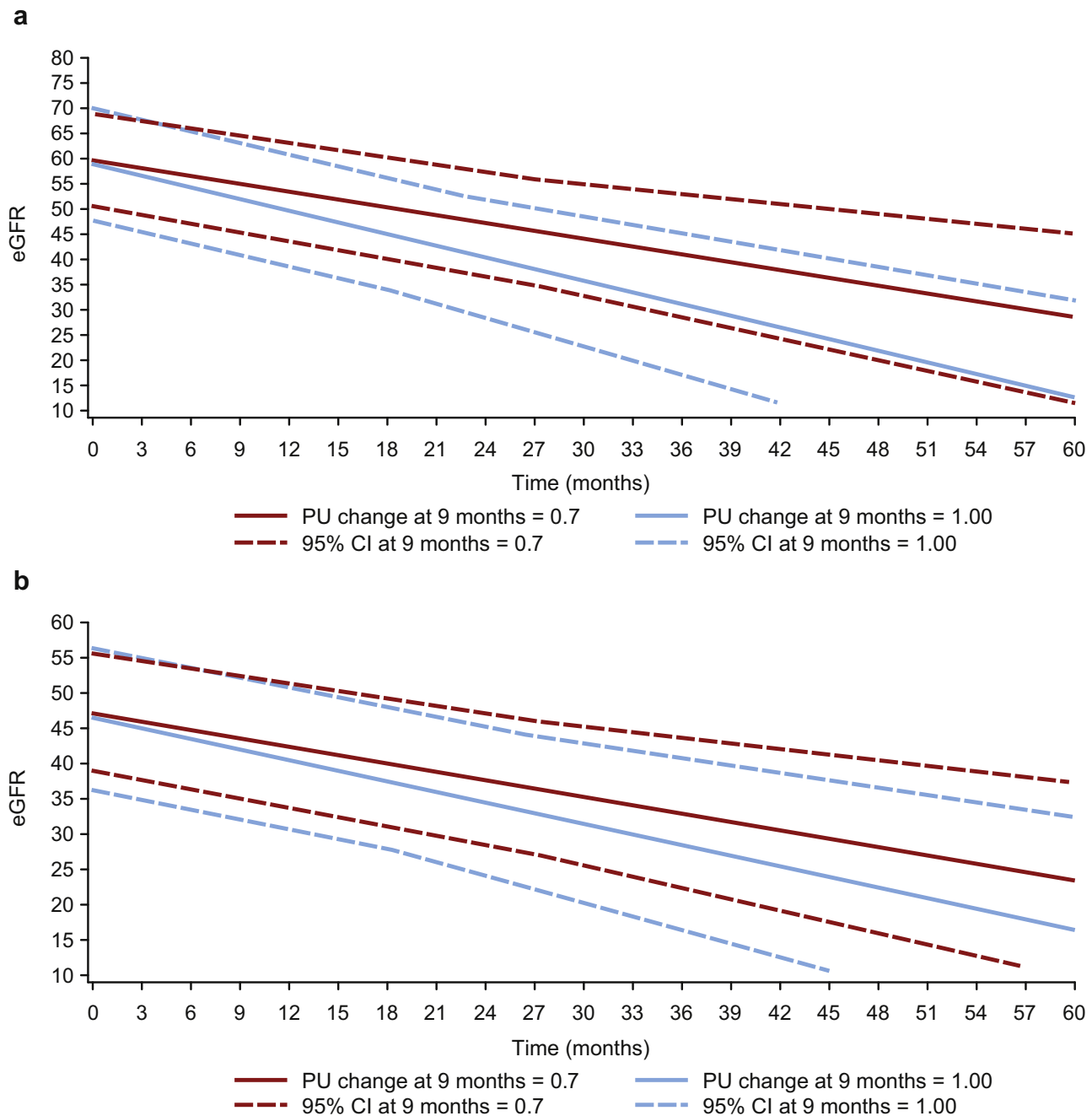


Figure 2. Estimated glomerular filtration rate (eGFR) rate of change from 0 to 24 months in the Leicester (a) and Glasgow (b) IgA nephropathy patient registries. The slope was extrapolated using a mixed-model random coefficients analysis incorporating eGFR values measured over the period from baseline to 24 months. Proteinuria (PU) change equal to 0.7 indicates a 30% reduction in PU. CI, confidence interval.

European Medicines Agency scientific workshop have had on clinical trial design and clinical trial activity in IgAN over the past 2 years cannot be overstated. In particular, the KHI white paper supported the concept of a single study for approval of new therapies in IgAN that incorporates an early efficacy measure (proteinuria change) with a “post-marketing” phase 4 confirmatory study using a long-term kidney endpoint, such as slope of eGFR, doubling of serum creatinine, and progression to ESKD. PROTECT has embraced this concept and has been designed to gather data as efficiently as possible

from the 280 randomized/evaluable patients, to provide data on proteinuria and confirmatory endpoint (i.e., slope of eGFR decline) data over 2 years.

There is more clinical trial activity in IgAN now than at any point since the first description of the disease just more than 50 years ago. At the time of writing, there are 3 active phase 3 and multiple phase 2 studies testing novel drugs, each targeting different biochemical pathways believed to be important in IgAN. The change in endpoints, evolving consensus in guidelines, and consequent favorable regulatory landscape have allowed

investigators and sponsors to design more affordable trials, have facilitated an early measure of drug efficacy (allowing sponsors to stop development if there is no sign of early efficacy), and have shortened the duration of trials with the use of eGFR slope. Furthermore, in a slowly progressive disease like IgAN, this leads to positive advantages for clinical trial conduct and maintaining study integrity. There is a lower chance of off-protocol (rescue) treatments if the trial is shorter (2 years) compared with the predicted 5 years for traditional outcomes trials using a doubling of serum creatinine, ESKD, and/or death as the confirmatory endpoints. Patient discontinuations are also likely to be lower and investigator engagement greater, with a shorter study. In addition, a shorter-duration trial reduces time spent on inefficient treatment for patients randomized to placebo or less effective active control.

PROTECT also incorporates several other innovative components intended to promote recruitment and retention of patients. In a patient focus group, patients were asked about ideal patient-friendly study design features, and these discussions helped inform the PROTECT study design. A popular request from patients was to minimize the number of hospital visits as much as possible, particularly at the time of 24-hour urine collection. In response to this, processes have been put in place to deliver and collect 24-hour containers from the patient's home or place of work, negating the need for multiple hospital visits over the course of the trial. In addition, collaboration between site study teams is being encouraged by using social media via "WhatsApp" to support real-time communication and sharing of best practices in trial conduct among PROTECT study coordinators.

In summary, the recommendations of the KHI workgroup and NKF workshop have been implemented for the first time, to the best of our knowledge, to design a phase 3 trial for a novel therapy in patients with IgAN. This trial design represents a model for a more time-efficient way to study experimental therapeutics for rare kidney diseases and, if successful and leads to regulatory approval, it should spur the development of more innovative drugs for the nephrology community of patients and their caregivers.

DISCLOSURE

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an employee of Retrophin, Inc. and may have an equity or other financial interest in Retrophin, Inc. AM is a consultant for Omeros and Retrophin, Inc., and JAMCO Pharma Consulting (50% owner), and owns shares in Retrophin, Inc. RK is an employee of Retrophin, Inc. and may have an equity or other financial interest in Retrophin, Inc.

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AUTHOR CONTRIBUTIONS

All authors were involved in the writing, preparation, critical revision, and final approval of this research letter. All authors were involved in the decision to submit this research letter and will take public responsibility for all aspects of the publication.

SUPPLEMENTARY MATERIAL

[Supplementary File \(PDF\)](#)

Table S1. PROTECT key patient inclusion and exclusion criteria.

Table S2. PROTECT study visits.

Table S3. PROTECT efficacy endpoints.

Figure S1. PROTECT study design.

Figure S2. PROTECT blinded dose titration schedule.

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