EFfect of FinErenone in Kidney TransplantiOn Recipients (EFFEKTOR): A Pilot Study

A. Mottl MD[1], S. Kelley MPH[1], A. Srivastava MD[2], A. Garg MD[3], D. Sawinski MD[4], P. Prasad PhD[5], K. Shuping MPHTM[1], C. Poulton MSW[1], P. Roy-Chaudhury MD PhD[1]

1-University of North Carolina Kidney Center; 2- University of Illinois at Chicago; 3-University of Cincinnatti; 4-Cornell University; 5-North Shore University Health System

BACKGROUND AND RATIONALE

Despite excellent 1-year graft survival for kidney transplant recipients (KTRs), there is an important unmet clinical need for new therapies that can reduce long term graft loss and cardiovascular morbidity and mortality.

Finerenone is an oral nonsteroidal mineralocorticoid receptor antagonist (ns-MRA) currently approved by the FDA for patients with CKD and T2D to reduce the risk for worsening kidney function and end-stage kidney disease, reduce the risk for heart failure hospitalization and cardiovascular mortality.

There is preliminary data to suggest MRAs may ameliorate calcineurin inhibitor toxicity, a contributor to long-term graft loss.

We report on the clinical trial design of the EFFEKTOR trial which will evaluate the feasibility, safety and efficacy of using finerenone in KTRs.

POPULATION

Study sites: University of North Carolina, University of Cincinatti, Cornell University

Inclusion criteria: age ≥18yrs, ≥6m post kidney transplant,, eGFR ≥25ml/min per 1.7m2, stable allograft function (within 20% baseline eGFR), UACR ≥ 30mg/g on two first void morning urine samples.

Exclusion criteria: non-renal solid organ transplant, potassium >5.0mg/dl at screening, UACR>3500mg/g at screening, indication for steroidal MRA, cardiovascular event within 3 months, AKI requiring dialysis within 6 months, recurrent lupus nephritis, ANCA vasculitis or membranoproliferative glomerulonephritis, Addison's disease, Child-Pugh C hepatic insufficiency, use of potent CYP3A4 inhibitor/inducer

STUDY DESIGN

Phase 2, multicenter, randomized, double-blinded, placebo-controlled trial of finerenone over 12 months with an off-treatment study visit one month after stopping treatment.

Intervention: finerenone 10 or 20mg taken orally once daily dosed according to screening eGFR and titrated according to serum potassium levels

Randomization is 2:1, finerenone: placebo with stratification by recruitment site, enrollment in kidney biopsy substudy and screening eGFR≥ 45ml/min per 1.73m^2.

ENDPOINTS

The primary endpoint is feasibility as a single center study, defined as enrollment 20% of the cohort within 3 months. This endpoint was not met; however, the Data Safety and Monitoring Board allowed for the continuation of EFFEKTOR as a multicenter trial.

Secondary endpoints include tolerability, safety and efficacy:

- Tolerability: relative percent time on investigational product with a target of 75%.
- Safety: Difference in rate of hyperkalemia, acute kidney injury and serious adverse events.
- Efficacy: (i) relative mean change in UACR from randomization to 12-month visit; (ii) relative risk for heart failure requiring acute care).

Exploratory: (i) *Clinical:* differences in chronic and total eGFR slope, major adverse cardiovascular events (ii) *Radiologic:* Absolute change in kidney cortical perfusion, oxygen availability and cortical fibrosis; (iii) *Pathologic:* relative change in percent interstitial fibrosis from baseline to 12-month visit; (iv) *Molecular:* Relative change in urine, blood or kidney tissue of TGF-β, TNFr-1/2, IL-6, Il-1, TNF-α.

PROCEDURES

The study visit schedule is illustrated in Figure 1. Safety labs include potassium and creatinine drawn locally.

Finerenone (or placebo) are initially dosed at 20mg daily if eGFR ≥60ml/min/1.73m2; otherwise initial dose is 10mg daily. Doses are titrated according to quarterly safety labs:

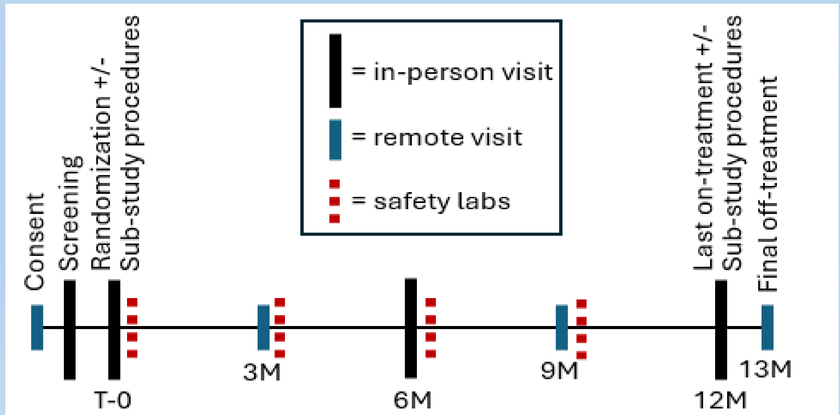


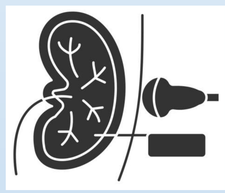
Figure. EFFEKTOR Study protocol visit scheme. UACR collected at screening, randomization, 6M, 12M and 13M. Potassium and creatinine collected at every visit after consent.

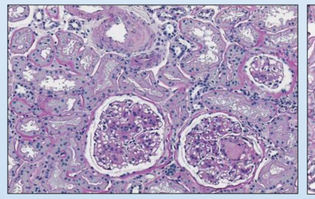
OPTIONAL SUBSTUDIES

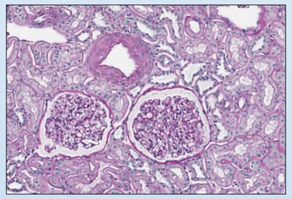
Procedures are performed at baseline (T-0) and 12-month visits.

Biopsy Substudy: Target enrollment N=20. Safety inclusion criteria and tissue processing follow the protocol for the Kidney Precision Medicine Project (www.kpmp.org).

Pathology is interpreted by a single nephropathologist. Parameters of interest include percent global glomerulosclerosis, percent segmental sclerosis, percent interstitial fibrosis, macrophage M1:M2 ratio, percent tubules with ≥ moderate atrophy, percent interstitial inflammation, arteriolar hyalinosis.

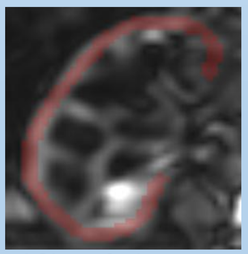


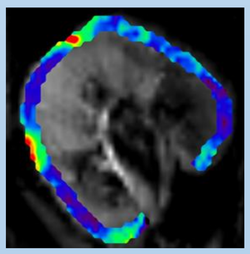


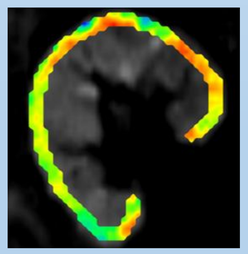


Functional MRI Substudy: Target enrollment N=20. All images are interpreted at the University of Illinois Chicago and North Shore Health System. Parameters of interest include:

- Cortical perfusion (ml/min/100g), estimated using arterial spin labeling (ASL) MRI;
- Cortical oxygen availability, estimated by R2* (s^{-1}) using blood oxygenation level dependent (BOLD) MRI; and
- Cortical fibrosis, estimated by apparent diffusion coefficient (ADC), (x10^{-3}/s) using diffusion-weighted MRI.


ASL perfusion map


BOLD image


Diffusion weighted map

CONCLUSIONS

EFFEKTOR is a pioneering study that aims to assess the potential risks and benefits of finerenone in KTRs. This study will inform the feasibility and design of larger trial powered to address clinical endpoints and long-term kidney survival.

This study is supported by an investigator grant by Bayer US LLC