PRESS RELEASE

ASN Contact:
Christine Feheley (202) 640-4638 | cfeheley@asn-online.org

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HIGH-IMPACT CLINICAL TRIALS YIELD RESULTS THAT COULD IMPROVE KIDNEY CARE

Philadelphia, PA (November 3, 2023) — The results of numerous high-impact clinical trials that could affect kidney-related medical care will be presented in-person at ASN Kidney Week 2023 November 1–November 5.

- In patients with IgA nephropathy, the IgA protein accumulates and damages the filtering part of the kidney, or glomerulus. Endothelin and angiotensin II contribute to the pathogenesis of this condition through different pathways. The phase 3 PROTECT trial compared sparsentan, a dual endothelin and angiotensin II receptor blocker, with irbesartan, an angiotensin II receptor blocker, in patients with IgA nephropathy. During the first 9 months of the PROTECT trial, patients in the sparsentan group achieved a significantly greater reduction of proteinuria (elevated protein in the urine, which is a sign of kidney dysfunction) than those treated with irbesartan. The trial continued for 15 more months, and patients treated with sparsentan were found to have a clinically important reduction in loss of kidney function along with persistently lower proteinuria than patients in the irbesartan group. “The PROTECT results demonstrate that sparsentan is superior to irbesartan alone for patients with IgA nephropathy and may be a preferred initial treatment for IgA nephropathy,” said corresponding author Brad Rovin, MD, of Ohio State University. Earlier this year, the US Food and Drug Administration approved sparsentan for the treatment of IgA nephropathy.
Pivotal Results of the Phase 3 PROTECT Trial of Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Immunoglobulin A Nephropathy (IgAN)

- A phase 3 clinical trial tested the potential of sparsentan (a dual endothelin and angiotensin II receptor blocker) versus irbesartan (an angiotensin II receptor blocker) for the treatment of focal segmental glomerulosclerosis (FSGS) in children and adults, a type of kidney disease that causes scarring in the glomerulus. Sparsentan led to a greater reduction in proteinuria compared with irbesartan, with more than twice as many patients achieving complete remission of proteinuria. “These data from the largest clinical trial of pediatric and adult patients with FSGS and the only study testing against a maximally dosed active comparator suggest sparsentan may provide kidney protection by significantly reducing proteinuria levels through 2-years

of treatment," said corresponding author Michelle Rheault, MD, of the University of Minnesota Medical School. "Although the glomerular filtration rate endpoint after 2 years of treatment was not achieved, the significant proteinuria reduction, including higher rates of partial or complete remission, and lower rates of reaching end-stage kidney disease demonstrated in the sparsentan arm of the study suggest sparsentan could be a potential new treatment option for FSGS. Clinically, reduction of proteinuria, a proven indicator of kidney damage, and delaying time to kidney failure are critically important for patients."
Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Focal Segmental Glomerulosclerosis (FSGS): Results from the Phase 3 DUPLEX Trial

- Bardoxolone methyl (BARD) is an activator of the Keap1-Nrf2 pathway, which helps protect cells from stresses caused by reactive oxygen species and electrophiles. A previous phase 3 trial demonstrated that BARD improves kidney function, but the trial was terminated prematurely because of an imbalance in heart failure between BARD and placebo groups. A subsequent phase 2 trial demonstrated no incidence of heart failure, with improved kidney function (inulin clearance), in diabetic kidney disease patients without heart failure risk factors. Now investigators have conducted the phase 3 AYAME clinical trial to evaluate the efficacy and safety of BARD compared with placebo in 1,013 patients with diabetic kidney disease without heart failure risk factors, with a treatment period of 3–4 years and a post-treatment observation period of 16 weeks. BARD was superior to placebo in slowing kidney function decline, and a similar number of cardiac events occurred in the two groups. The primary and the key secondary endpoints were the time to onset of a ≥30% and ≥40% decrease in estimated glomerular filtration rate (eGFR, a measure of kidney function) or kidney failure, respectively. Other secondary endpoints were the time to onset of a ≥53% decrease in eGFR or kidney failure and the time to onset of kidney failure. Safety endpoints were adverse events and the time to onset of cardiac events, including heart failure. "BARD successfully achieved the primary and key secondary endpoints based on eGFR without new safety concerns in our study; however, there were no significant differences in kidney failure rates in the BARD and placebo groups," said corresponding author Tadao Akizawa, MD, PhD, of the Showa University School of Medicine, in Tokyo
AYAME Study: Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Bardoxolone Methyl in Diabetic Kidney Disease (DKD) Patients

- Aldosterone—a hormone involved in blood pressure and potassium regulation among other effects—accelerates chronic kidney disease (CKD) progression. In a phase 2 trial, a novel selective aldosterone synthase inhibitor called BI 690517 demonstrated dose-dependent reductions in albuminuria (albumin in the urine, a sign of kidney damage) by up to 40% versus placebo in patients with CKD. Albuminuria reduction >30%, indicating treatment response, occurred in 70% of patients who

were also randomized to receive the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin, another kidney protective drug, along with BI 690517. In contrast, the response rate with BI 690517 alone was 50%. These data suggest that kidney-protective effects of BI 690517 and empagliflozin may be additive. "Aldosterone synthase inhibition is a promising new therapy for CKD, with or without type 2 diabetes, that will be tested in a large phase 3 kidney disease outcome trial," said corresponding author Katherine R. Tuttle, MD, of the University of Washington, Seattle
Aldosterone Synthase Inhibition with or Without Background Sodium Glucose Cotransporter 2 Inhibition in CKD: A Phase II Clinical Trial

- The phase 2b ZENITH-CKD trial assessed the effects of zibotentan, a selective endothelin receptor antagonist, when administered concomitantly with an SGLT2 inhibitor in patients with CKD. A low dose of zibotentan (0.25 mg once daily) combined with the SGLT2 inhibitor dapagliflozin resulted in a clinically relevant 27% reduction in albuminuria compared with dapagliflozin alone, with an acceptable tolerability profile. "These results indicate that zibotentan is an attractive option to reduce CKD progression in patients already optimally managed with therapy including SGLT2 inhibitors," said corresponding author Hiddo Lambers Heerspink, PhD, PharmD, of University Medical Center Groningen, in The Netherlands. "A phase 3 trial will investigate long-term efficacy and safety."
ZENITH-CKD: A Phase 2B Study of Zibotentan in Combination with Dapagliflozin and Dapagliflozin Alone in Patients with CKD

- Individuals on long-term dialysis have poor cardiovascular prognoses. Investigators recently conducted a clinical trial to investigate the effects of the steroidal mineralocorticoid receptor antagonist spironolactone—a medication commonly used to treat heart failure, high blood pressure, or low blood potassium levels in patients without advanced kidney disease—on cardiovascular outcomes in these dialysis patients. The ALdosterone antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST) was an international, multicenter, double-blind, randomized, placebo-controlled event-driven trial including patients on chronic hemodialysis with at least one cardiovascular comorbidity, abnormality, or risk factor. In the trial, 644 patients were randomized and were followed for a median of 32.6 months. "Treatment with spironolactone did not significantly reduce the incidence of the primary composite outcome of non-fatal heart attack, acute coronary syndrome, hospitalization for heart failure, non-fatal stroke, or cardiovascular death. The treatment was well tolerated. Of the components of the primary outcome, only hospitalization for heart failure had a significantly lower incidence in the spironolactone group," said principal investigator Patrick Rossignol, MD, PhD, of the University of Lorraine, in France, and the Princess Grace Hospital, in Monaco. "Secondary analyses will help us understanding this finding."

ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST): Primary Results

- Individuals with advanced CKD have the best chance for a longer and healthier life if they receive a kidney transplant, but barriers to transplantation exist. A team in Ontario, Canada conducted a clinical trial to test whether a multi-component intervention that targets many of these barriers can help potentially transplant-eligible patients with advanced CKD complete key steps toward receiving a kidney transplant. In the randomized clinical trial that included 20,375 patients from 26 CKD programs, the intervention, compared with usual care, did not significantly increase the rate of steps completed toward receiving a kidney transplant. “Improving access to kidney transplantation remains a global priority that requires substantial effort,” said corresponding author Amit Garg, MD, PhD, of Western University, the London Health Sciences Centre Research Institute, and ICES in Ontario. “Lessons learned from this trial can help guide future efforts.”
  Effect of a Multi-Component Intervention to Improve Patient Access to Kidney Transplantation and Living Kidney Donation

- Investigators reported promising updated results from a phase 3 randomized controlled trial of MDR-101, a novel cellular immunotherapy, for kidney transplant recipients. The study examined whether kidney transplant recipients who received a living donor kidney from an HLA-matched relative with the same transplant genes could be taken off all immunosuppression and remain off immunosuppression for 2 years after withdrawal without organ loss, death, acute kidney rejection, or graft versus host disease. To date, treatment success (at least 2 years immunosuppression-free) was observed in 63% of patients treated with MDR-101. “This study shows that some kidney transplant recipients can achieve ‘functional tolerance’ and be free of immunosuppressive drugs normally required to prevent rejection and failure of the kidney transplant,” said Medeor Therapeutics consulting Chief Medical Officer Dan Brennan, MD. “This is done by establishing mixed chimerism, from allowing a low level of donor blood cells remain in the blood of the kidney recipient after infusion of stem cells from the donor of the kidney transplant, in HLA-matched living related donor kidney transplants at the time of kidney transplant.”
  MDR-101-MLK Update: Operational Immune Tolerance Achieved in Living Related HLA-Matched Kidney Transplant Recipients

The world's premier nephrology meeting, ASN Kidney Week, brings together approximately 12,000 kidney professionals from across the world. The largest nephrology meeting provides participants with exciting and challenging opportunities to exchange knowledge, learn the latest scientific and medical advances, and listen to engaging and provocative discussions with leading experts in the field.

About ASN

Since 1966, ASN has been leading the fight to prevent, treat, and cure kidney diseases throughout the world by educating health professionals and scientists, advancing research and innovation, communicating new knowledge and advocating for the highest quality care for patients. ASN has nearly 21,000 members corresponding 140 countries. For more information, visit www.asn-online.org and follow us on Facebook, X, LinkedIn, and Instagram.

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