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Developing Treatments for Chronic Kidney Disease in the 21st Century

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Summary

Chronic kidney disease (CKD) is a lethal and rapidly increasing burden on society. Despite this, there are relatively few therapies in development for the treatment of CKD. Several recent costly phase 3 trials have failed to provide improved renal outcomes, diminishing interest in pharmaceutical investment. Furthermore, poor patient, physician, and payer awareness of CKD as a diagnosis has contributed to slow trial enrollment and successful implementation of these trials. Nevertheless, several therapeutics remain in development for the treatment of CKD, including mineralocorticoid-receptor antagonists, sodium/glucose cotransporter 2 inhibitors, anti-inflammatory drugs, and drugs that mitigate oxidative injury. Success of future CKD therapeutic trials will depend not only on improved understanding of disease pathogenesis, but also on improved trial enrollment rates, through increasing awareness of this disease by the public, policy makers, and the greater medical community.

Keywords

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Kidney failure is among the most deadly and economically costly diseases faced by patients and modern society. More than 100,000 new patients in the United States start on dialysis each year while approximately the same number die each year.¹ More than 20% of patients starting dialysis are dead within the first year² and more than 70% of diabetic patients starting dialysis are dead within 5 years,³ making the prognosis of end-stage renal disease (ESRD) worse than most cancers. However, fewer than 1 in 10 patients are even aware of carrying the diagnosis of early chronic kidney disease (CKD) and a similar number of physicians fail to make the diagnosis when CKD is present.⁴ Societal awareness of the emergence of renal failure as a major health and economic burden remains similarly

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complacent despite the fact that care of patients in the United States with kidney disease consumed more than \$50 billion in 2013, representing 20% of all Medicare spending in patients older than 65 years old. Care of patients on dialysis comprised an additional \$31 billion in 2013.¹ It is estimated that globally there are nearly 500 million adults with chronic kidney disease.⁵ Despite these sobering facts there are fewer interventional trials to develop therapeutics to stop the progression of kidney disease than almost any other medical subspecialty.^{6,7} Slow patient enrollment (in part because of a lack of disease awareness), regulatory requirements for hard patient outcomes for drug registration, and lack of payer engagement are among the major obstacles impeding drug development for CKD.^{6,8–10} Only consideration of the unmet medical need has continued to attract some pharmaceutical companies to the development of drugs for this indication.

Diabetic nephropathy (DN) is the major cause of renal failure in the developed world and the burden of ESRD from type 2 diabetes mellitus (T2DM) is expected to burgeon by four-fold in the coming decades,^{11,12} in part owing to increased prevalence of T2DM in younger populations.¹³ Although only a minority of diabetic patients develop nephropathy, even the 10% to 30% who do develop ESRD represent an untenable burden on society.^{14,15} Precisely why some diabetic patients develop nephropathy whereas others do not remains unclear because genetic studies have not been convincingly informative.^{16–19} Nevertheless, because of its prevalence relative to other causes of ESRD, and the high unmet need for the therapies to halt or slow the development of kidney failure, many therapeutic development programs have focused on DN as an indication.

In diabetic patients who go on to develop nephropathy, its pathogenesis remains obscure. Roles for impaired mesangial,²⁰ podocyte,^{21,22} and endothelial glycocalyx^{23,24} function all have been suggested, but precisely which cellular and molecular disturbances drive the disease remain unknown. In the case of type 2 diabetes mellitus, the understanding of nephropathy pathogenesis is complicated further by heterogeneity of biopsy findings, whereby only roughly 40% of patients have evidence of classic DN lesions.^{25–27} In patients with classic histopathologic features of DN, accumulating literature supports roles not only for controlling glomerular hyperfiltration²⁸ and albuminuria,^{29–31} but also points to involvement of inflammation.^{32–34} It is notable that tubulointerstitial inflammation correlates more strongly with poor renal outcomes than the severity of the glomerular lesions³⁵ and potential roles for anti-inflammatory drugs have been proposed.³⁶ Nevertheless, many T2DM patients who have undergone a biopsy also show histopathologic features of acute tubular necrosis, focal segmental glomerulosclerosis, or hypertensive nephropathy,³⁷ complicating the identification for appropriate therapies to slow progression of disease in a specific patient.

CURRENT THERAPY OF CHRONIC KIDNEY DISEASE

Today, angiotensin-converting enzyme inhibitors (ACEis) or angiotensin-receptor blockers (ARBs) comprise the standard of care for treatment of diabetic nephropathy as well as many other forms of CKD.^{38,39} ACEi/ARB therapy not only reduces proteinuria (and albuminuria), but decreases the yearly number of diabetic patients going on to require dialysis.^{40–42} This renoprotective effect has been attributed to the capacity of this class of

drugs to normalize glomerular hyperfiltration in the diabetic kidney.^{43,44} Reduced hyperfiltration is consistent with the clinical observation that introduction of ACEi/ARB therapy is associated with an acute decrease in estimated glomerular filtration rate (eGFR) and the fact that greater eGFR reductions were associated with less long-term loss of renal function.⁴⁵ Although ACEi/ARB therapy slows renal functional loss in DN, it by no means induces remission or even halts progression to ESRD. Attempts to achieve improved renal protection recently have focused on further inhibition of the renin angiotensin system, however, using combinations of ACEi plus ARB or renin blockade plus ACEi or ARB have been disappointing.^{46,47} Both approaches were associated with increased hyperkalemia and hypotension and acute kidney injury in the combination treatments, causing premature termination of the trials. Both hyperkalemia and hypotension likely are mechanisms associated with adverse effects, making combination approaches problematic.

Mineralocorticoid-receptor antagonists including spironolactone and eplerenone also reduce blood pressure, eGFR, and albuminuria in diabetic nephropathy, but are associated with hyperkalemia.^{48–50} Trials combining ACEi and ARB with novel mineralocorticoid-receptor antagonists, designed to reduce the risk of hyperkalemia in diabetic nephropathy, are currently in development by several companies including Finerenone (Bayer),⁵¹ CS-3150 (Diachii Sankyo), and MT-3995 (Mitsubishi).⁵¹ Results from a phase 2 trial of Finerenone in T2DM patients with nephropathy were encouraging, showing a dose-dependent reduction in the placebo-corrected urinary albumin to creatinine ratio of 21% to 38%.⁵¹ Whether the risk of hyperkalemia of these newer mineralocorticoid receptors will distinguish themselves sufficiently from spironolactone or eplerenone to encourage their wider use in patients with kidney disease remains to be determined.

With the lack of clinically validated targets beyond the renin-angiotensin system, identification of new targets for CKD and diabetic nephropathy is critical for the development of novel therapeutics. Inhibition of the sodium/glucose cotransporter 2 (SGLT2) for the treatment of T2DM has recently been studied in patients with diabetic nephropathy. When superimposed on ACEi or ARB in DN, SGLT2 inhibition by either empagliflozin or canagliflozin is associated with further acute albuminuria reduction and a modest acute decrease in eGFR.^{52,53} Because albuminuria reduction is associated closely with improved renal outcomes,⁵⁴ it is anticipated that this class will reduce ESRD events. Notably, empagliflozin treatment recently has been shown to improve cardiovascular outcomes dramatically in a high-risk diabetic population,⁵⁵ offering additional substantiation of a likely benefit of SGLT2 inhibition on renal outcomes in proteinuric patients with T2DM and nephropathy. It is attractive that unlike ACEi/ARB, empagliflozin treatment does not seem to be associated with hyperkalemia, therefore its addition to ACEi or ARB may not be burdened by this safety liability.⁵⁶ Similar to ACEi/ARB, the mechanism underlying the potential benefit of this class of drugs in diabetic nephropathy has been proposed to involve reduced glomerular hyperfiltration.²⁸ SGLT2 inhibitors not only reduce hyperglycemia in type 2 DN but they markedly reduce glomerular hyperfiltration in glucose-clamped euglycemic patients with type 1 DM.²⁸ These findings are consistent with the class of drugs increasing NaCl delivery to the macula densa, thereby activating tubuloglomerular feedback and afferent arteriolar constriction.^{57,58} The CREDENCE trial will formally test the benefit of canagliflozin in patients with diabetic nephropathy and is enrolling 4200 subjects at 675

sites globally.⁵⁹ At present, the use of SGLT2 inhibitors is not recommended with low eGFR and is contraindicated in severe renal impairment. Consistent with this, the CREDENCE trial requires patients who are included to have an eGFR of greater than 30 mL/min/1.73 m², raising uncertainty regarding the utility of this class of agents in stages 4 or 5 CKD.

EMERGING THERAPIES FOR CHRONIC KIDNEY DISEASE

The endothelin receptor type A antagonist (ETR_A), atrasentan, also is being tested in a phase 3 renal outcomes trial in patients with diabetic nephropathy.⁶⁰ Similar to SGLT2 inhibitors, treatment with ETR_A-receptor antagonists has been shown to produce a prompt reduction in albuminuria in patients with diabetic nephropathy on ACEi/ARB, although halting therapy produces a similarly prompt return to the previous higher baseline values.^{61,62} These changes are consistent with the observed decrease in systemic arterial blood pressure during ETR_A blockade contributing to the decrease in albuminuria.^{61,62} Although not associated with hyperkalemia, this class of drugs is associated with edema and possible congestive heart failure.⁶³ For this reason, Study Of Diabetic Nephropathy With Atrasentan, a phase 3 trial of atrasentan in patients with diabetic nephropathy,⁶⁰ excludes patients with increased brain natriuretic peptide greater than 200 pg/mL, prior history of heart failure, or severe peripheral edema or facial edema requiring diuretics. Although these exclusion criteria should minimize safety concerns, they will slow recruitment significantly, and, given the high prevalence of heart failure in patients with CKD, limit more broad use of this class of therapy in patients with diabetic nephropathy. It also is notable that similar to ACEi/ARB and SGLT2 inhibitors, atrasentan is associated with an acute decrease in eGFR.⁶² The common effect of atrasentan, SGLT2 inhibitors, and ACEi/ARB to acutely decrease eGFR raises the question as to whether future studies examining combinations of these drugs might observe increased acute renal failure possibly owing to reduced renal blood flow, as was seen in ACEi plus ARB trials.

It is unclear whether beneficial renal outcomes from a therapeutic can be separated from the earlier-noted triad of blood pressure reduction, and acute reduction in eGFR and albuminuria. The preceding effects routinely are accompanied by a reduction in proteinuria (or albuminuria). Several therapeutics that do not acutely reduce eGFR or proteinuria have been tested clinically, but none of these have translated successfully into improved renal outcomes. These include the proposed Nrf2 activator bardoxolone, which was associated with increased cardiovascular events and actually increased eGFR and albuminuria⁶⁴; sulodexide, which did not affect blood pressure or serum creatinine level⁶⁵; and a monoclonal antibody to transforming growth factor β 1,⁶⁶ which had no detectable effect on any of these parameters. It remains controversial as to whether a drug that reduces proteinuria via any mechanism would provide renal benefit,^{67,68} or if a reduction in proteinuria also must be accompanied by acute eGFR and blood pressure reduction to achieve renal benefit. For instance, nonsteroidal anti-inflammatory drugs can acutely reduce proteinuria and glomerular hyperfiltration,⁶⁹ but increase blood pressure and are associated with increased cardiovascular mortality and renal events,^{70–73} making their utility in treating CKD questionable. Two recent phase 2 diabetic nephropathy trials of a NOX1/4 inhibitor, GKT137831, and a phosphodiesterase inhibitor, CTP-499, failed to observe any detectable

effect on any of these parameters (Table 1). These costly failures have discouraged pharmaceutical investment in chronic kidney disease.

Despite the preceding observations, several companies are in phase 2 stages of drug development for the treatment of chronic kidney disease that do not show all (or any) of the earlier-described functional characteristics. Many of these drugs target anti-inflammatory or antifibrotic mechanisms (Fig. 1). The utility of anti-inflammatory steroids and immunosuppressive drugs in the treatment of acute glomerulonephritides is well established, however, their effectiveness in chronic kidney disease is less clear.^{74–76} Strong associations between inflammation and progressive CKD including diabetic renal failure have been long recognized. Bohle et al^{35,77} described the association of increased tubulointerstitial inflammatory cell infiltrates in CKD and diabetic nephropathy human kidney biopsy specimens, with higher serum creatinine levels and longer duration of disease. More recent messenger RNA profiling of renal biopsy specimens from patients with diabetic nephropathy confirm that inflammatory pathways are increased significantly in glomeruli and tubules^{32,33,78} and have provided evidence for stimulation of macrophage and dendritic cell maturation pathways and cytotoxic T-lymphocyte–mediated apoptosis, in glomeruli as well as in tubulointerstitial compartments. In later stages of diabetic nephropathy, leukocyte migration and complement system activation signatures were identified in glomeruli.³³ However, even biopsy specimens from early stages of DN had evidence of activation of inflammatory pathways including activation of the Janus kinase (JAK)/signal transducer and activators of transcription (STAT) pathway and nuclear factor- κ B signaling.^{32,79}

Complement Inhibition

Complement activation plays a well-established role in the pathogenesis of diverse renal diseases, including membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, hemolytic uremic syndrome, and IgA nephropathy.^{80,81} Eculizumab (Alexion Pharmaceuticals) is a monoclonal antibody targeting C5, which blocks the cleavage of the C5 complement protein to C5a and C5b, thereby preventing the generation of the proinflammatory peptide C5a and the membrane-attack complex C5b-9.⁸² Eculizumab treatment improved eGFR in patients with atypical hemolytic uremic syndrome and the associated thrombotic microangiopathy.^{82,83} Although these were small phase 2 trials, the effects were sufficiently profound to support the registration of eculizumab, for which it now is approved.

In addition to immune glomerulonephritides, complement activation has been proposed to contribute to the pathogenesis of diabetic nephropathy, possibly through glucose-associated production of neoepitopes activating the lectin complement pathway.^{84,85} This hypothesis has received additional support from molecular profiling studies of human diabetic nephropathy kidney biopsy specimens and plasma, which show complement to be among the most activated pathways.^{33,86} C3 is expressed robustly in kidney biopsy specimens of human diabetic nephropathy.³³ Although complement inhibition has not been tested clinically in diabetic nephropathy, inhibition of complement in animal models of the disease support potential therapeutic benefit.⁸⁷ The high cost of eculizumab is a significant barrier for testing this specific agent in diseases more common than atypical hemolytic uremic

syndrome. Potential risks of increased infections using this approach must be balanced with efficacy.

JAK/STAT Inhibition

Inhibitors of JAK, including tofacitinib and baricitinib, currently are approved or in regulatory review, respectively, for the treatment of autoimmune inflammatory diseases including rheumatoid arthritis and ulcerative colitis.^{88–90} These drugs inhibit JAK and STAT, which are important intracellular mediators of inflammatory signaling by interferon (IL) alfa, IL-6, IL-12, and IL-23, as well as other growth factors including erythropoietin, growth hormone, and epidermal growth factor.^{91,92} Ligand binding to their receptors leads to multimer or receptor homodimer assembly, activating the autophosphorylation activity of JAK and subsequent STAT phosphorylation and translocation to the nucleus,⁹³ leading to transcription of additional proinflammatory target genes including MCP1, as well as *GATA3*, *IL24*, *LTB*, and *SOC3*.^{94–96} Increased expression of these genes comprises a major genetic signature not only for diabetic nephropathy but also for lupus nephritis.^{32,79,97,98} Evidence of JAK/STAT activation in experimental models of kidney disease, including diabetic mice and rats, also has been reported,^{32,79} and the use of a nonselective JAK inhibitor (AG-490) significantly reduced urinary protein excretion in diabetic rats.⁹⁹

The clinically documented anti-inflammatory efficacy of JAK inhibitors, together with the gene pathway signature in diabetic nephropathy, have prompted a phase 2 exploration to test the clinical efficacy of these JAK inhibitors in kidney disease.^{100,101} The effects of 24 weeks of treatment of the JAK1 and JAK2 inhibitor Baricitinib (Eli Lilly/Incyte) on albuminuria was investigated in 129 subjects with proteinuric diabetic nephropathy already taking ACEis or ARBs for a reduction in albuminuria.¹⁰⁰ Baricitinib treatment was associated with a 30% to 40% dose-dependent reduction in albuminuria. However, a side effect of this class of drugs is that they reduce hemoglobin levels and a 1.0 ± 0.35 g/dL reduction in hemoglobin was observed with baricitinib, however, no reduction in blood pressure was observed.¹⁰⁰ It remains to be determined whether or not these effects on albuminuria reduction translate into long-term benefit on kidney function and mortality.

Monocyte Chemoattractant Protein-1/Chemokine Receptor 2 Inhibition

The specific cytokines that activate JAK-STAT signaling in specific kidney diseases remain unknown, however, monocyte chemoattractant protein-1 (MCP-1), also known as chemokine (C-C motif) ligand 2, not only is increased by JAK/STAT signaling, it may activate it. MCP-1 is a 99 amino acid residue secreted protein that interacts with the chemokine receptor 2 (CCR2) receptor on T cells and macrophages, recruiting these cells to sites of tissue injury^{101,102} by activating JAK2.¹⁰³ Renal expression of MCP-1 is increased in patients with proteinuric nephropathy, being expressed predominantly in the tubulointerstitium rather than the glomerulus.^{104–106} Urinary excretion of MCP-1 also is increased in patients with diabetic nephropathy, and higher urine MCP-1 appears to be predictive of worse renal outcomes.¹⁰⁷ Finally, in animal models, blockade of CCR2, the receptor for MCP-1, ameliorated progression of diabetic nephropathy in db/db mice as well as diabetic Ins2^{C96Y} Akita mice.^{108,109}

Several companies have established clinical programs to test the efficacy of CCR2 inhibitors in human diabetic nephropathy. Chemocentryx and Pfizer have ongoing clinical development programs of oral receptor antagonists for MCP-1/CCR2 (CCX140) and CCR2/CCR5 (PF489791), respectively, and are testing them for their ability to reduce proteinuria in patients with diabetic nephropathy.¹¹⁰

A 52-week, phase II clinical trial of CCX140 in 332 patients with diabetic nephropathy^{80,111} met its primary end point, showing that treatment with CCX140 added to an ACEi or ARB statistically significantly reduced the urinary albumin creatinine ratio, beyond that achieved with standard of care. The maximum treatment effect, an 18% reduction in urinary albumin creatinine ratio, was seen in the 5-mg dose group at 12 weeks, and sustained reduction in albuminuria induced by CCX140 relative to SOC alone was observed over the full year.¹¹¹ Whether the reported reduction in albuminuria will translate into long-term improvements in patient outcomes and reduce the rate of renal function deterioration remains to be tested.

Antifibrotic/anti-inflammatory agents in early phases of testing—Vascular adhesion protein 1 is an endothelial sialoglycoprotein, whose cellular expression is induced under inflammatory conditions.^{112,113} Vascular adhesion protein 1, also known as amine oxidase, copper containing 3, possesses monoamine oxidase activity and interacts with leukocyte adhesion molecules including Siglec-9 and -10. Both of these functions are important in facilitating leukocyte egress into inflamed tissue.^{114,115} Based on these findings, Astellas has initiated a phase 2 study of ASP8232—a small-molecule inhibitor of amine oxidase, copper containing 3 activity, in 110 patients with diabetic nephropathy.¹¹⁶ The trial will explore urine ACR reduction after 12 weeks of treatment and is anticipated to read-out in June 2016.

Additional antifibrotic and anti-inflammatory approaches are in development but are not yet validated clinically. VPI-2690B (Vascular Pharmaceuticals) is a monoclonal antibody that binds to the C-loop domain sequence of integrin α V β 3.¹¹⁷ This antibody has been shown to reduce albuminuria in diabetic rats and atherosclerosis in diabetic pigs.^{107,108} It has been proposed that these effects are mediated by blocking the ability of integrin α V β 3 to stimulate insulin-like growth factor 1 signaling in vascular smooth muscle cells and mesangial cells.^{117,118} VPI-2690B is currently in phase 2 clinical testing for the treatment of diabetic nephropathy.¹¹⁹ This placebo-controlled trial will enroll 300 diabetic subjects and is projected to be completed in August 2017.

Apoptosis signal regulating kinase 1 (ASK1) is a mitogen-activated protein kinase kinase stress responsive kinase that can be activated by multiple stimuli including reactive oxygen species and tumor necrosis factor- α activation of tumor necrosis factor receptor 1.^{120,122} A recent report showed that ASK1 inhibition substantially improved glomerulosclerosis in a mouse model of diabetic nephropathy treatment, however, it did not reduce albuminuria.¹²³ Gilead Sciences has initiated a 300-patient, phase 2 program to test the efficacy of the selective ASK1 inhibitor GS-4997 in patients with diabetic nephropathy. The primary outcome will be the change in eGFR after 48 weeks of treatment. A secondary outcome will determine the proportion of participants achieving at least a 30% reduction in albuminuria at week 48 from baseline.^{124,125}

Challenges to drug development for chronic kidney disease—Although phase 2 trials for chronic kidney disease typically are performed with proteinuric patients in whom signs of efficacy are explored based on proteinuria reduction,⁵⁴ drug registration for treatment of CKD requires demonstration of a reduction in event numbers for patients developing renal failure, creatinine doubling, or death.⁹ Accruing a sufficient number of events in phase 3 trials may take years, whereas the development of drugs for indications such as rheumatoid arthritis or depression can be completed within weeks, putting CKD at a competitive disadvantage within pharmaceutical companies compared with these other disease indications. Although regulatory agencies have shown willingness to consider alternative end points that might shorten trials, such as a 40% decrease in eGFR for CKD drug registration,¹²⁶ the value to payers of drugs providing these intermediate benefits likely will be less compelling than showing a reduction of patients going on dialysis.

For reliable trial results, it is critical to enrich renal outcomes trials for patients who are likely to progress rapidly to the prespecified renal events. To date, high levels of proteinuria at enrollment remain the most reliable criterion for predicting progression of renal disease.^{127–130} Because all renal outcomes trials must be performed on the background of the current standard of care (ie, in patients optimally treated with ACEis or ARBs, which reduce proteinuria), it has become increasingly challenging to identify patients with high baseline proteinuria. Indeed, increasing numbers of diabetic patients show CKD without proteinuria, however, it remains unclear whether the disease pathogenesis in these patients is owing to ischemia or some other mechanism,¹³¹ complicating the interpretation of studies in which they are included.

Slow patient enrollment into renal trials has been another major hurdle to developing drugs for chronic kidney disease. Although many patients have some degree of CKD, identifying a sufficient number of patients who have ACEi/ARB-resistant proteinuria and are therefore most likely to progress has proven a significant challenge. Given the poor patient and physician awareness regarding the diagnosis of CKD^{4,132} it may not be surprising that enrollment rates (eg, 0.2 patients/site/mo) are less than a quarter of those for other disease indications (eg, diabetes mellitus or hyperlipidemia). Put another way, it may take four times longer to enroll a trial for CKD than for many other diseases, another competitive disadvantage for renal drug development in the resource-constrained pharmaceutical environment. Although some of these disparities are owing to real differences in disease prevalence, the lower prevalence should be more than offset by the disproportionate societal expense of caring for patients with kidney disease.^{2,133–135} For example, in 2011, although ESRD patients comprised only 1.4% of the Medicare population, they consumed more than 7% of Medicare resources.¹³⁶ Campaigns to increase patient and physician awareness are critical to streamline recruitment to trials of therapies for CKD. Therapeutic trial networks and patient registries also may provide a means to accelerate the development of treatments for chronic kidney disease.

In the coming decades a silent tsunami of renal failure is poised to emerge, fueled not only by the aging of the population, but also the increasing prevalence of type 2 diabetes mellitus and autoimmune disease in a younger demographic.¹¹ Not only is CKD extremely monetarily costly, but it is deadly. Neither the medical community at large, nor society in

general, seem prepared to deal with these events. New therapeutics offer the hope of staving off this unwelcome reality, however, their development will require more sophisticated scientific understanding of disease heterogeneity, better biomarkers predictive of disease progression, improved patient awareness, and streamlined patient enrollment to ensure success. Through concerted efforts on these fronts, the renal community will play a central role to help limit renal death.

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Figure 1.
Please provide.

Table 1
Selected Ongoing Phase 2 and Phase 3 Drug Development Programs for the Treatment of Diabetic Nephropathy

Drug	MOA Target	Hypothesized Benefit	Phase NCT	Trial Design	Notes	Reference
Atrasentan (AbbVie)	Endothelin Receptor A antagonist	hemodynamic	Phase 3 NCT01858532 SONAR	Phase 3 enrollment (est) n = 4148; completion (est): July 2018	Primary end point: time to the first occurrence of a component of the composite creatinine doubling or ESRD	60, 137
Canagliflozin (Janssen)	SGLT2 inhibitor	Hemodynamic	Phase 3 NCT02065791 CREDENCE	Phase 3 enrollment (est) n = 4200; completion (est): February 2019	Time to composite end point including end-stage kidney disease (ESRD), doubling of serum creatinine level, renal or cardiovascular death	59
Pyridoxin (Nephrogenex)	Vitamin B6 analog reducing advanced glycosylation end product; protein modification	Antioxidant	Phase 3 NCT02156843 Pioneer	Phase 3 enrollment (est) n = 600; study terminated	Time to the composite end point: >=100% serum creatinine increase or ESRD	138
Finenone BAY 94-8862 (Bayer)	Mineralocorticoid-receptor antagonist	Hemodynamic, anti-inflammatory	Phase 3 NCT02540933 FIDELIO-DKD	Phase 3 enrollment n = 4800; est completion May 2019	Time to the onset of kidney failure, a sustained decrease in eGFR > 40%, and renal death	139, 140
ASP8232 (Astellas)	Vascular adhesion protein 1 inhibitor	Anti-inflammatory	Phase 2 NCT02358096 (ALBUM)	Phase 2 enrollment (est) 110; completion (est) November 2016	Evaluate ASP8232 as add-on therapy to ACEi (or ARB) in reducing albuminuria in patients with T2DM and CKD	116
Baricitinib (Eli Lilly)	JAK1/2 inhibition	Anti-inflammatory	Phase 2 NCT01683409	Phase 2 enrollment 131; completed	Outcome showed ~30%–40% decrease in UACR	100, 141
CCX-140 (Chemocentryx)	CCR2 antagonist	Anti-inflammatory	Phase 2 NCT01447147	Phase 2 enrollment = 332;	Significant 24% reduction in first	(110, 142)

Drug	MOA Target	Hypothesized Benefit	Phase NCT	Trial Design	Notes	Reference
				completed	morning urinary ACR at 12 wk	
CTP-499 (CoNCErt)	Deuterium-containing pentoxifyl line metabolite, a multisubtype PDE inhibitor	Antifibrotic	Phase 2 NCT01487109	Phase 2 enrollment 170; completed January 2015	No reported significant change in UACR in CTP-499 compared with placebo at 24 wk	143
GKT13783.1 (Genkyotex)	NOX1/4 inhibitor	Anti-oxidant	NCT02010242	Phase 2 enrollment (est) n = 200; study completed March 2015	Failure to achieve primary outcome of ACR reduction in DN	144, 145
VPI-2690B	Monoclonal Ab to α V β 3 integrin	Inhibition of IGF1 signaling	NCT02256790	Phase 2 enrollment (Est) 300; est completion August 2017	Albuminuria reduction and eGFR preservati on 50 wk	118, 119
GS-4997 (Gilead)	ASK1 inhibitor	Protein kinase inhibitor anti-inflammatory	NCT02177786	Phase 2 enrollment (est) 300; estimated completion September 2016	Change in estimated glomerular filtration rate from baseline at week 48; UACR reduction	124

Abbreviations: est, estimated; IGF, insulin-like growth factor; SONAR, Study Of Diabetic Nephropathy With Atrasentan; UACR, urinary albumin creatinine ratio.