

METHODS OF TREATING FOCAL SEGMENTAL GLOMERULOSCLEROSIS WITH ATRASENTAN

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority and benefit from U.S. Provisional Patent Application No. 63/343,574, filed May 19, 2022, the contents and disclosures of which are incorporated herein by reference in their entireties.

BACKGROUND

[002] Focal segmental glomerulosclerosis (FSGS) is a glomerular disease characterized by proteinuria, frequent progression to end-stage kidney disease (ESKD), and recurrence after kidney transplantation in ~25% of patients, which negatively impacts long-term allograft survival (Cravedi, 2013). It is a heterogeneous disorder that results from podocyte cell injury and depletion due to a variety of initiating causes. Primary (idiopathic) FSGS is the most common form of the disease and is presumed to be a result of an unknown circulating factor. Secondary FSGS includes virus-associated or drug-induced FSGS. Maladaptive forms of secondary FSGS result from adaptive structural-functional responses to excessive single nephron workload (Rosenberg, 2017). FSGS can also be caused by a number of genetic mutations in genes that encode for protein expressed mainly in the podocytes and their slit diaphragm. The genetic causes of FSGS may present as sporadic or familial disease, with autosomal dominant, autosomal recessive, X-linked, or mitochondrial inheritance patterns (Rood, 2012; Jefferson, 2014; Dummer, 2015; De Vriese, 2018). Apolipoprotein L1 (APOL1) genetic variants increases the risk for ESKD in FSGS patients with African ancestry (Dummer, 2015). The annual incidence rates of FSGS range from 0.2 to 1.8/100,000 population per year (McGrogan, 2011). Conservative management of FSGS includes blood pressure control, especially with RAS inhibitors along with dietary sodium restriction. Additional treatments are individualized on the basis of the particular form of FSGS, considering factors specific to the patient, such as age and comorbidities. Therapy for primary FSGS also involves the use of medications that are immunosuppressive that may also have direct effects on podocytes including prednisone, calcineurin inhibitors, cyclophosphamide, and mycophenolate mofetil plus high-dose dexamethasone (Korbet, 2012; Rosenberg, 2017).

[003] There are no approved therapies for FSGS, and for patients who fail conservative management with agents that block the renin angiotensin-aldosterone axis, there are no established safe and effective treatment options. As a result, there is an important unmet medical need to develop therapies for patients with FSGS who remain at risk for progressive renal failure.

SUMMARY

[004] Atrasentan is a selective endothelin A (ETA) receptor antagonist (ETA Ki ~ 34pM; ETB Ki ~ 63 nM, ETA selectivity ~1800x). *See, e.g.* Wu-Wong et al., Clin. Sci. (Lond.), 103(48), pp. 107s-111s (2002). Selective ETA receptor antagonists block ETA function, while minimally effecting the ETB receptor, providing beneficial renal effects including vasodilation and reduction of inflammation, while still enabling ET-1 clearance. *See e.g.*, Jandeleit-Dahm and Watson, Curr. Opin. Nephrol. Hypertens., 21(1), pp. 66-71 (2012); *see also*, Nakamura, et al., Nephron, Vol. 72, pp. 454-460 (1996). While ETA receptor antagonists increase sodium and water retention by the kidney, this is typically clinically manageable. *See, e.g.*, Saleh, et al., J. Pharm. Exp. Ther., 338(1), pp. 263-270 (2011).

[005] Atrasentan has been studied extensively as a once-daily treatment for diabetic kidney disease (DKD) in individuals with Type 2 diabetes in addition to optimized doses of renin-angiotensin system (RAS) inhibitors. ETA activation has been associated with the progression of many renal diseases as measured by proteinuria, kidney inflammation or fibrosis. (Dhaun, 2012; Vignon-Zellweger, 2012).

[006] Atrasentan has been shown to be effective in patients with diabetic kidney disease, significantly reducing the risk of renal events defined as a doubling of serum creatinine or end-stage kidney disease. *See, e.g.*, Heerspink, et al., The Lancet, 393, pp 1937-1947 (2019). DKD is considered a secondary glomerular disease, where kidney disease develops secondarily to an identified systemic cause, in the case of DKD as a microvascular complication to long-standing diabetes. *See, e.g.* Dattani and McAdoo, Medicine, 47(10), pp. 644-648 (2019). The pathogenesis of DKD is multifactorial and complex. Chronically elevated blood glucose levels due to diabetes which causes glucose toxicity to renal cells, especially kidney endothelial cells, and systemic and renal hemodynamic factors associated with hypertension that result in shear stress being transmitted to resident glomerular cells are the key pathogenic drivers of DKD. *See, e.g.* Thomas et al., Nat. Rev. Disease Primers. 1, pp. 15018-15026 (2015). Multiple factors dysregulated in

the diabetic milieu, including metabolic components such as hyperglycemia, dyslipidemia and oxidative stress, and hemodynamic factors such as vasoactive substances associated with hypertension, all stimulate renal ET-1 formation. In addition, DKD is typically observed in older populations due to the requirement for long-standing diabetes prior to the manifestation of DKD, and aging is also associated with increased ET-1 production in the kidney. *See, e.g.* Kohan, *Kidney Int.*, 86(5), pp. 896-904 (2014). Combined, this all provides a sound scientific rationale for the treatment of DKD with the ETA receptor blocker atrasentan. *See* Dhaun, et al., *Hypertension*, Vol. 57, pp. 772-779 (2011).

[007] Some embodiments provide a method of treating focal segmental glomerulosclerosis (FSGS) in a subject having FSGS, comprising administering to the subject a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[008] Some embodiments provide a method of decreasing renal inflammation and/or fibrosis in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[009] Some embodiments provide a method of reducing the rate of decline in estimated glomerular filtration rate (eGFR) in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0010] Some embodiments provide a method delaying the onset of ESKD in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0011] Some embodiments provide a method of decreasing proteinuria in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0012] Some embodiments provide a method of decreasing fatigue in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0013] Some embodiments provide a method of stabilizing functional podocyte mass in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[0014] Some embodiments provide a method of stabilizing or reducing renal inflammation and/or fibrosis. In some instances, the renal inflammation and/or fibrosis is tubulointerstitial inflammation. Some embodiments provide that the renal inflammation and/or fibrosis is tubulointerstitial fibrosis. Some embodiments provide that the renal inflammation and/or fibrosis includes glomerular inflammation and/or glomerulosclerosis. Some embodiments provide that the renal inflammation and/or fibrosis comprises one or more of tubulointerstitial inflammation, tubulointerstitial fibrosis, glomerular inflammation or glomerulosclerosis.

[0015] Some embodiments provide that the subject has biopsy-confirmed FSGS. Some embodiments provide that the subject has been diagnosed with biopsy-confirmed FSGS. Some embodiments provide that the subject has a genetic diagnosis of FSGS due to known podocyte protein mutation. Additional embodiments include subjects having mutations in APOL1.

[0016] Some embodiments provide that the FSGS comprises a nephrotic syndrome. Some embodiments provide that the nephrotic syndrome is selected from proteinuria, hypoalbuminemia, hypercholesterolemia, peripheral edema, or a combination of any of the foregoing.

[0017] Some embodiments provide that the FSGS is perihilar FSGS. Some embodiments provide that the FSGS is tip lesion FSGS. Some embodiments provide that the FSGS is cellular FSGS. Some embodiments provide that the FSGS is collapsing FSGS. Some embodiments provide that the FSGS is primary FSGS. Some embodiments provide that the FSGS is FSGS not otherwise specified (NOS).

[0018] Some embodiments provide that the FSGS is virus-associated FSGS. Some embodiments provide that the virus-associated FSGS is not HIV-associated FSGS. Some embodiments provide that the FSGS is toxin-associated FSGS. Some embodiments provide that the FSGS is adaptive FSGS.

[0019] Some embodiments provide that the subject is also being administered one or more additional agents. Some embodiments provide that the one or more additional agents are selected from calcineurin inhibitors, proteasome inhibitors, aminoquinolines, complement inhibitors, B-cell inhibitors, cytotoxic agents, mTOR inhibitors, steroids, and combinations thereof. Some embodiments provide that the one or more additional agents comprises a calcineurin inhibitor. Some embodiments provide that the calcineurin inhibitor is cyclosporin. Some embodiments provide that the one or more additional agents comprises an immunosuppressant. Some embodiments provide that the immunosuppressant is mycophenolate mofetil (MMF),

cyclophosphamide, or chlorambucil. Some embodiments provide that the one or more additional agents comprises steroids. Some embodiments provide that the steroids are selected from the group consisting of prednisone, dexamethasone, hydrocortisone, cyclosporin, adrenocorticotrophic hormone (ACTH), and combinations of any of the foregoing. Some embodiments provide that the one or more additional agents comprises aminoquinolines. Some embodiments provide that the one or more additional agents is hydroxychloroquine. Some embodiments provide that the subject is not currently receiving one or more immunosuppressants.

[0020] Some embodiments provide that the one or more additional agents is administered at a dosage that is stable for at least 12 weeks prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the dosage of the one or more additional agents is decreased after between about 15 days to about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0021] Some embodiments provide that the dosage of the one or more additional agents is reduced by about 25% to about 100% (to about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%). Some embodiments provide that the dosage of the one or more additional agents is reduced by about 50% to about 100%. Some embodiments provide that the dosage of the one or more additional agents is reduced by about 75% to about 100%.

[0022] Some embodiments provide that the subject is concomitantly receiving an ACE inhibitor, an ARB, a statin, a diuretic, a calcium channel blocker, a beta blocker, an aldosterone antagonist, fish oil, hydroxychloroquine, an SGLT2i, or a combination of any of the foregoing.

[0023] Some embodiments provide that the subject is concomitantly receiving an ACE inhibitor, an ARB, or a combination thereof. Some embodiments provide that the statin is selected from: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin. Some embodiments provide that the diuretic is selected from: hydrochlorothiazide, trichlormethiazide, hydroflumethiazide, quinethazone, metolazone, chlorothiazide, chlorthalidone, indapamide, methyclothiazide bumetanide, torsemide, piretanide, ethacrynic acid, bumetanide, furosemide, triamterene, spironolactone, eplerenone, and amiloride. Some embodiments provide that the ACE inhibitor is selected from: quinapril, fosinopril perindopril, captopril, enalapril, enalaprilat, ramipril, cilazapril, delapril, fosinopril, zofenopril, indolapril,

benazepril, lisinopril, spirapril, trandolapril, perindopril, pentopril, moexipril, rescinamine, and pivopril. Some embodiments provide that the ARB is selected from: candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan, olmesartan medoxomil, telmisartan, valsartan, azilsartan medoxomil, and BRA-657.

[0024] Some embodiments provide that the atrasentan is administered as a pharmaceutically acceptable salt. Some embodiments provide that the atrasentan is administered as atrasentan hydrochloride or atrasentan mandelate. Some embodiments provide that the atrasentan is administered as atrasentan hydrochloride. Some embodiments provide that the atrasentan is administered as the free base.

[0025] Some embodiments provide that the subject is at a high risk of progression to end-stage kidney disease (ESKD). Some embodiments provide that the subject has been diagnosed with FSGS. Some embodiments provide that the diagnosis of FSGS comprises a kidney biopsy, a genetic test for mutations in a podocyte protein associated with FSGS, or a combination of any of the foregoing. Some embodiments provide that the diagnosis of FSGS comprises examination of a kidney biopsy.

[0026] Some embodiments provide that the subject is excreting an average of about 0.75 g/g or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the subject is excreting an average of about 1.5 g/g or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the subject is excreting an average of about 3.5 g/g or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the subject is excreting an average of about 3.5 g/g to about 10 g/g of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0027] Some embodiments provide that the subject is excreting an average of about 0.75 grams to about 1.5 grams of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0028] Some embodiments provide that the subject is excreting an average of about 1 gram or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0029] Some embodiments provide that the subject has an average eGFR of about 20 to about 120 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0030] Some embodiments provide that the subject has an average eGFR of about 30 to about 90 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0031] Some embodiments provide that the subject has an average eGFR of about 20 to about 60 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0032] Some embodiments provide that the subject has a urine protein to creatinine ratio (UPCR) of greater than about 1.5 g/g to about 11 g/g (e.g., about 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 11 g/g) for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0033] Some embodiments provide that the subject has an average HbA1c of about 4% to about 6% for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0034] Some embodiments provide that the subject has an average fasting blood glucose level of about 125 mg/dL or less for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0035] Some embodiments provide that the subject maintains a potassium level within a normal physiologic range.

[0036] Some embodiments provide that the subject maintains a sodium level within a normal physiologic range.

[0037] Some embodiments provide that the subject has alanine transaminase/aspartate transaminase (ALT/AST) levels during the administration of atrasentan, or a pharmaceutically acceptable salt thereof, that are about the same as the ALT/AST levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0038] Some embodiments provide that the subject has bilirubin levels during the administration of atrasentan, or a pharmaceutically acceptable salt thereof, that are about the same as the bilirubin levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. Thus, in some embodiments, bilirubin levels can be utilized to assess liver function or effects of administration of one or more agents as described herein.

[0039] Some embodiments provide that fluid retention in the subject is manageable with diuretics.

[0040] Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 20% to about 80% after between about 15 day and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0041] Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 20% to about 80% after between about 4 weeks to about 10 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0042] Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 10 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 12 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0043] Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 35% to about 80% (about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80%).

[0044] Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0045] Some embodiments provide that the protein in the urine of the subject is reduced by about 100 mg/dL to about 500 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0046] Some embodiments provide that the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0047] Some embodiments provide that the UPCR of the subject is reduced to less than about 1.5 g/g to about 11 g/g after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the UPCR of the subject is reduced to less than about 1.5 g/g, about 2 g/g, about 3 g/g, about 4 g/g, about 5 g/g, about 6 g/g, about 7 g/g, about 8 g/g, about 9 g/g, about 10 g/g, or about 11 g/g after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the UPCR of the subject is reduced to less than about 1.5 g/g to about 11 g/g after between about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. Some embodiments provide that the UPCR of the subject is reduced to less than about 1.5 g/g, about 2 g/g, about 3 g/g, about 4 g/g, about 5 g/g, about 6 g/g, about 7 g/g, about 8 g/g, about 9 g/g, about 10 g/g, or about 11 g/g after between about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0048] Some embodiments provide that the risk of the subject developing ESKD is reduced by about 20% to about 99% after between about 6 months and about 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0049] Some embodiments provide that the risk of the subject developing ESKD is reduced by about 20% to about 99% after between about 12 months and about 60 months (about 6 months, about 9 months, about 12, months, about 15 months, about 18 months, about 21 months, about 24 months, about 27 months, about 30 months, about 33 month, about 36 months, about 39 months, about 42, months, about 45 months, about 48 months, about 51 months, about 54 months, about 57 months, or about 60 months) of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0050] Some embodiments provide that the average rate of decrease in eGFR is from about 0.75 mL/min/year to about 75 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0051] Some embodiments provide that the average rate of decrease in eGFR is from about 3 mL/min/year to about 6 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0052] Some embodiments provide that the average rate of decrease in eGFR is from about 4 mL/min/year to about 5 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[0053] Some embodiments provide that the average rate of decrease in eGFR is reduced by from about 15% to about 70% after between about 6 months and about 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[0054] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.20 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0055] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.25 mg to about 1.25 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0056] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0057] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is about 0.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0058] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.75 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0059] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.80 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0060] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 1.0 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0061] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 1.25 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0062] Some embodiments provide that the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[0063] Some embodiments provide that the method further includes administering a therapeutically effective amount of a SGLT-2 inhibitor. Some embodiments provide that the SGLT-2 inhibitor is selected from bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, licogliflozin, sotagliflozin, and tofogliflozin.

[0064] Some embodiments provide that the SGLT-2 inhibitor is canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin.

[0065] Some embodiments provide that the subject has been determined to have proteinuria of at least 1 g/day in at least two of three consecutive readings over the year prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[0066] Some embodiments provide that the subject has been administered a maximally tolerated stable dose of a RAS inhibitor for at least 12 weeks prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[0067] Some embodiments provide that the subject is concurrently administered a maximally tolerated stable dose of a RAS inhibitor and a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[0068] Some embodiments provide that the subject has been determined to have an eGFR of at least 30 mL/min/1.73 m² prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[0069] Some embodiments provide that the FSGS comprises non-nephrotic range proteinuria of less than 3.5 grams of protein in the urine per day for at least about 3 months prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[0070] Some embodiments provide that the FSGS is associated with one or more genetic mutations. Some embodiments provide that the one or more genetic mutations is in gene encoding a podocyte protein associated with FSGS. Some embodiments provide that the one or more genetic mutations is selected from one or more mutations in a gene selected from the group consisting of: NPHS1, NPHS2, CD2AP, TRPC6, ACTN4, INF2, MYO1E, ARHGAP24, ARHGDIA, PLCE1, PTPRO, WT1, LXMB1, tRNA^{Leu}, COQ2, COQ6, ITGB4, PDSS2, CD151, CUBN, LAMB2, APOL1, and a combination of any of the foregoing. Some embodiments provide that the one or more genetic mutations is in APOL1.

[0071] Some embodiments provide that the subject has been administered a prior therapy for FSGS and was not responsive to the prior therapy.

[0072] Some embodiments provide that the prior therapy is a standard of care therapy for FSGS. Some embodiments provide that the prior therapy is selected from: acthar, sparsentan, rituximab with plasmaphoresis, volcosporin, 10-nitro-9(E)-octadec-9-enoic acid (CXA-10), PF-06730512, 4-Chloro-N-[5-methyl-2-[7H-pyrrolo[2,3-d]pyrimidine-4-carbonyl]-3-pyridyl]-3-(trifluoromethyl)benzenesulfonamide (CCX140-B), abatacept, bardoxolone, or a combination of any of the foregoing

[0073] Some embodiments provide that the subject has not been treated or is not being treated with a sodium glucose co-transporter 2 (SGLT2) inhibitor.

[0074] Some embodiments provide that the subject has not been treated or is not being treated with antiretroviral therapy. Examples of antiretroviral therapy include, but are not limited to protease inhibitors, reverse transcription inhibitors, integrase inhibitors, and combinations thereof, such as HAART (highly active antiretroviral therapy).

[0075] Some embodiments provide that the subject has not been previously diagnosed with one or more of an acute kidney injury (e.g., due to hypoxia), diabetic nephropathy (also referred to as diabetic kidney disease or “DKD”), IgA nephropathy, sickle cell nephropathy, HIV/AIDS, or acute kidney failure.

[0076] Some embodiments provide that the subject has not been previously diagnosed with HIV-related nephropathy.

[0077] Some embodiments provide that the subject has not been previously diagnosed with HIV.

[0078] Some embodiments provide that the subject is not currently diagnosed with HIV.

[0079] Some embodiments provide that the subject is not currently being treated for HIV.

[0080] Some embodiments provide that the subject has not been previously diagnosed with renovascular hypertension.

[0081] Some embodiments provide that the subject is not currently being treated for renovascular hypertension.

BRIEF DESCRIPTION OF THE FIGURES

[0082] Figure 1 illustrates the overall study schema (all cohorts) for the Phase 2 study disclosed herein. Abbreviations: DKD = diabetic kidney disease; FSGS = focal segmental glomerulosclerosis; IgAN = immunoglobulin A nephropathy; PK = pharmacokinetics; QD = once a day. ^a: Subjects in Cohort 2 (FSGS) have the option to dose escalate at or after Week 12. These subjects will be transitioned to Cohort 2b.

[0083] Figure 2 illustrates the dose escalation for cohorts 2 (2b) and 5 for the Phase 2 study disclosed herein.

[0084] Figure 3 illustrates the baseline characteristics of patients having FSGS that were included in the Phase 2 study disclosed herein.

[0085] Figure 4 illustrates the urine protein to creatinine ratio (UPCR) measured at week 0, 6, 12, and 24 of the Phase 2 study disclosed herein.

BRIEF DESCRIPTION OF THE TABLES

[0086] Table 1: Objectives and endpoints for each cohort in the Phase 2 study disclosed herein.

[0087] Table 2: Information on Atrasentan used in the Phase 2 study disclosed herein.

[0088] Table 3: Protocol-required laboratory assessments in the Phase 2 study disclosed herein.

DETAILED DESCRIPTION

I. DEFINITIONS

[0089] In order that the present disclosure can be more readily understood, certain terms are first defined. As used in this application, except as otherwise expressly provided herein, each

of the following terms shall have the meaning set forth below. Additional definitions are set forth throughout the application.

[0090] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure is related. For example, the Concise Dictionary of Biomedicine and Molecular Biology, Juo, Pei-Show, 2nd ed., 2002, CRC Press; The Dictionary of Cell and Molecular Biology, 3rd ed., 1999, Academic Press; and the Oxford Dictionary Of Biochemistry And Molecular Biology, Revised, 2000, Oxford University Press, provide one of skill with a general dictionary of many of the terms used in this disclosure. For purposes of the present disclosure, the following terms are defined.

[0091] Units, prefixes, and symbols are denoted in their Système International de Unites (SI) accepted form. Numeric ranges are inclusive of the numbers defining the range. The headings provided herein are not limitations of the various aspects of the disclosure, which can be had by reference to the specification as a whole. Accordingly, the terms defined immediately below are more fully defined by reference to the specification in its entirety.

[0092] The terms “a,” “an,” or “the” as used herein not only include aspects with one member, but also include aspects with more than one member. For instance, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “a cell” includes a plurality of such cells and reference to “the agent” includes reference to one or more agents known to those skilled in the art, and so forth.

[0093] The term “or” as used herein should in general be construed non-exclusively. For example, a claim to “a composition comprising A or B” would typically present an aspect with a composition comprising both A and B. “Or” should, however, be construed to exclude those aspects presented that cannot be combined without contradiction (*e.g.*, a composition pH that is between 9 and 10 or between 7 and 8).

[0094] The group “A or B” is typically equivalent to the group “selected from the group consisting of A and B.”

[0095] The term “and/or” where used herein is to be taken as specific disclosure of each of the two specified features or components with or without the other. Thus, the term “and/or” as used in a phrase such as “A and/or B” herein is intended to include “A and B,” “A or B,” “A” (alone), and “B” (alone). Likewise, the term “and/or” as used in a phrase such as “A, B, and/or C”

is intended to encompass each of the following aspects: A, B, and C; A, B, or C; A or C; A or B; B or C; A and C; A and B; B and C; A (alone); B (alone); and C (alone).

[0096] The terms “about” and “approximately” as used herein shall generally mean an acceptable degree of error for the quantity measured given the nature or precision of the measurements. Typical, exemplary degrees of error are within 20 percent (%), within 10%, or within 5% of a given value or range of values. Any reference to “about X” specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Thus, “about X” is intended to provide written description support for a claim limitation of, *e.g.*, “0.98X.” The terms “about” and “approximately,” particularly in reference to a given quantity, encompass and describe the given quantity itself.

[0097] When “about” is applied to the beginning of a numerical range, it applies to both ends of the range. Thus, “from about 5 to 20%” is equivalent to “from about 5% to about 20%.” When “about” is applied to the first value of a set of values, it applies to all values in that set. Thus, “about 0.5, 0.75, or 1.0 mg” is equivalent to “about 0.5, about 0.75, or about 1.0 mg.”

[0098] As used herein, the term “about”, when preceding a series of peak positions for X-ray powder diffraction (*e.g.*, 2θ values), means that all of the peaks of the group which it precedes are reported in terms of angular positions with a variability of $\pm 0.1^\circ$. Accordingly, for example, the phrase about 8.3° , 9.7° , 10.0° , 13.0° , 15.6° , 17.2° or 19.5° means $8.3^\circ \pm 0.1^\circ$, $9.7^\circ \pm 0.1^\circ$, $10.0^\circ \pm 0.1^\circ$, $13.0^\circ \pm 0.1^\circ$, $15.6^\circ \pm 0.1^\circ$, $17.2^\circ \pm 0.1^\circ$, or $19.5^\circ \pm 0.1^\circ$.

[0099] “Treatment” or “therapy” of a subject refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of reversing, alleviating, ameliorating, inhibiting, or slowing down, the onset, progression, development, severity, or recurrence of a symptom, complication, condition, or biochemical indicia associated with a disease.

[00100] “Administering” or “administration” refer to the physical introduction of a therapeutic agent to a subject, using any of the various methods and delivery systems known to those skilled in the art. Routes of administration can include oral, intravenous, intramuscular, subcutaneous, intraperitoneal, spinal or other parenteral routes of administration, for example by injection or infusion (*e.g.*, intravenous infusion). Administration can also be performed, for example, once, a plurality of times, and/or over one or more extended periods.

[00101] The term "prophylactic" or "prophylactically" refers to any type of intervention or process performed on, or the administration of an active agent to, the subject with the objective of protecting or preventing a disease or condition from developing or at least not developing fully (e.g., to reduce the symptoms or severity of the disease or condition) such as in the development of a side effect.

[00102] A "subject" includes any human or non-human animal. The term "non-human animal" includes, but is not limited to, vertebrates such as non-human primates, sheep, dogs, and rodents such as mice, rats, and guinea pigs. In some embodiments, the subject is a human. The terms "subject" and "patient" and "individual" are used interchangeably herein.

[00103] In some instances, a subject with FSGS has one or more genetic mutations relating to FSGS. A genetic mutation as described herein includes a deletion, insertion, or substitution of at least one amino acid as compared to a wild type protein (and e.g., contributes to manifestation of FSGS); a mutation in a gene that results in the expression of a protein with one or more point mutations as compared to a wild type protein (and e.g., contributes to manifestation of FSGS), a mutation in a gene that results in the expression of a protein with at least one deletion, insertion, or substitution of at least one amino acid as compared to a wild type protein, a gene duplication that results in an increased level of a protein in a cell, or a mutation in a regulatory sequence (e.g., a promoter and/or enhancer) that results in an increased level of transcription or translation in a cell), an alternative spliced version of an mRNA molecule that results in a protein having a deletion of at least one amino acid as compared to the wild type version of the protein), or increased expression (e.g., increased levels) of a wild type version in a mammalian cell due to—for instance—aberrant cell signaling and/or dysregulated signaling (e.g., as compared to a control cell) (and e.g., contributes to manifestation of FSGS). As another example, a dysregulation of a gene, a protein, or expression or activity, or level of any of the same, can be a mutation in the gene that encodes a protein that is constitutively active or has increased activity as compared to a protein encoded by the gene that does not include the mutation.

[00104] The term "wild type" describes a nucleic acid (e.g., a DNA or mRNA sequence) or protein sequence that is typically found in a subject that does not have a disease or disorder (e.g., FSGS) related to the reference nucleic acid or protein.

[00105] An "effective amount" or "therapeutically effective amount" or "therapeutically effective dosage" of a drug or therapeutic agent is any amount of the drug that,

when used alone or in combination with another therapeutic agent, slowing down the onset of a disease or promotes disease regression evidenced by a decrease in severity of disease symptoms, an increase in frequency and duration of disease symptom-free periods, or a ameliorating an impairment or disability due to the disease affliction. The ability of a therapeutic agent to promote disease regression can be evaluated using a variety of methods known to the skilled practitioner, such as in human subjects during clinical trials, in animal model systems predictive of efficacy in humans, or by assaying the activity of the agent in *in vitro* assays.

[00106] The phrase "pharmaceutically acceptable" indicates that the substance or composition must be compatible chemically and/or toxicologically, with the other ingredients comprising a formulation, and/or the mammal being treated therewith.

[00107] As used herein, "polymorphs" refer to distinct solids sharing the same molecular formula, yet each polymorph may have distinct solid state physical properties. A single compound may give rise to a variety of polymorphic forms where each form has different and distinct solid state physical properties, such as different solubility profiles, melting point temperatures, flowability, dissolution rates and/or different X-ray diffraction peaks. These practical physical characteristics are influenced by the conformation and orientation of molecules in the unit cell, which defines a particular polymorphic form of a substance. Polymorphic forms of a compound can be distinguished in a laboratory by X-ray diffraction spectroscopy, such as X-ray powder diffraction ("XRPD"), and by other methods, such as infrared spectrometry. Additionally, polymorphic forms of the same drug substance or active pharmaceutical ingredient can be administered by itself or formulated as a drug product (pharmaceutical composition) and are well known in the pharmaceutical art to affect, for example, the solubility, stability, flowability, tractability and compressibility of drug substances and the safety and efficacy of drug products. For more, see Hilfiker, Rolf (ed.), *Polymorphism in the Pharmaceutical Industry*. Weinheim, Germany: Wiley-VCH 2006.

[00108] As used herein, the term "amorphous" means a solid in a solid state that is a non-crystalline state. Amorphous solids generally possess crystal-like short-range molecular arrangement, but no long-range order of molecular packing as found in crystalline solids. The solid state form of a solid may be determined by polarized light microscopy, X-ray powder diffraction ("XRPD"), differential scanning calorimetry ("DSC"), or other standard techniques known to those of skill in the art.

[00109] As used herein, the term “crystalline” means a solid in a solid state having a regularly repeating arrangement of molecules or external face planes. The solid state form of a solid may be determined by polarized light microscopy, X-ray powder diffraction (“XRPD”), differential scanning calorimetry (“DSC”), or other standard techniques known to those of skill in the art. Accordingly, the term “crystalline purity,” as used herein, means the percentage of a certain crystalline polymorph of atrasentan or pharmaceutically acceptable salt thereof in a sample that may contain amorphous atrasentan or a pharmaceutically acceptable salt thereof, one or more additional crystalline polymorphs of atrasentan or a pharmaceutically acceptable salt thereof, or mixtures thereof. When a crystalline polymorph of atrasentan or a pharmaceutically acceptable salt thereof is described as having “substantial crystalline purity”, it means the polymorph is substantially free (e.g., contains <10%, <5%, <2%, <1%, <0.5%, <0.1%, or <0.05%) of other polymorphs (amorphous and/or crystalline).

[00110] The term “chemical purity,” as used herein, means percentage of a particular compound (e.g., atrasentan or a pharmaceutically acceptable salt thereof) in a sample. Accordingly, atrasentan or a pharmaceutically acceptable salt thereof and compositions comprising or made therefrom may contain one or more impurity, including but not limited to: water, ethyl acetate, ethanol, (2*R*,3*R*,4*S*)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(*N*-(*n*-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, (2*R*,3*R*,4*S*)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-((*N*-(*n*-butyl)-*N*-ethyl)aminocarbonylmethyl)pyrrolidine-3-carboxylic acid, (2*R*,4*S*)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(*N*,*N*-di(*n*-butyl)aminocarbonylmethyl)pyrrolidine, or ethyl (2*R*,3*R*,4*S*)-2-(4-methoxyphenyl)-4-(1,3-benzodioxol-5-yl)-1-(*N*,*N*-di(*n*-butyl)aminocarbonylmethyl)pyrrolidine-3-carboxylate. When a sample of atrasentan or a pharmaceutically acceptable salt thereof is described as having “substantial purity”, the sample is substantially free of impurities (e.g., contains <10%, <5%, <2%, <1%, <0.5%, <0.1%, or <0.05%).

[00111] The term “diastereomeric excess,” as used herein, means the amount of one diastereomer of a compound (e.g., atrasentan or a pharmaceutically acceptable salt thereof) in a mixture which may have other diastereomers of the same compound in the mixture. The term “substantial diastereomeric purity,” as used herein, means diastereomeric excess greater than about 90%, 95%, 99%, 99.5%, 99.9%, or 100%.

[00112] As used herein, the term “pharmaceutically acceptable carrier” refers to a substance that aids the administration of an active agent to a cell, an organism, or a subject. “Pharmaceutically acceptable carrier” refers to a carrier or excipient that can be included in the compositions of the disclosure and that causes no significant adverse toxicological effect on the subject. Non-limiting examples of pharmaceutically acceptable carriers include water, NaCl, normal saline solutions, lactated Ringer’s, normal sucrose, normal glucose, binders, fillers, disintegrants, lubricants, coatings, sweeteners, flavors and colors, liposomes, dispersion media, microcapsules, cationic lipid carriers, isotonic and absorption delaying agents, and the like. The carrier may also be substances for providing the formulation with stability, sterility and isotonicity (*e.g.*, antimicrobial preservatives, antioxidants, chelating agents and buffers), for preventing the action of microorganisms (*e.g.* antimicrobial and antifungal agents, such as parabens, chlorobutanol, phenol, sorbic acid and the like) or for providing the formulation with an edible flavor *etc.* In some instances, the carrier is an agent that facilitates the delivery of a small molecule drug or antibody to a target cell or tissue. One of skill in the art will recognize that other pharmaceutical carriers are useful in the present disclosure.

[00113] The term “expression” as used herein refers to the level of protein or mRNA in a mammalian cell.

[00114] The term “activity” as used herein refers to one or more activities of a protein, such as binding or enzymatic activity (*e.g.*, one or more of phosphorylation, dephosphorylation, nuclear import, transcriptional activation, transcriptional repression, and/or binding activity to a substrate or a binding partner).

[00115] The term “IL-6 signaling” as used herein means the expression and/or activity of one or more protein in a signaling pathway beginning with activation of an IL-6 receptor and ending in gene expression. Non-limiting examples of protein in a signaling pathway beginning with activation of an IL-6 receptor and ending in gene expression include an IL-6 receptor, JAK, STAT3, PI3K, Akt/PKB, IKKs, IκBs, NF-κB, MAPK, Ras, Raf, MEK, and ERK.

[00116] The term “NF-κB signaling” as used herein means the expression and/or activity of one or more of IKKα, IKKβ, IκB, and NF-κB, and/or one or more genes upregulated by activity of NF-κB (*e.g.*, one or more of TNF-α, IL-1, CAM, COX-2, and iNOS).

[00117] The term “PDGF signaling” as used herein means the expression and/or activity of one or more of PDGF receptor, PKC, PI3K, Src, Ras, ERK1/2, Rho, Rac, Akt, mTOR, NADPH oxidase, MAPK, and cPLA₂.

[00118] The term “SGLT-2 inhibitor” as used herein refers to a compound that inhibits the Sodium Glucose Co-Transporter-2 (SGLT-2). SGLT-2 inhibitors disrupt reabsorption of glucose by the kidneys and thus exert a glucose-lowering effect. By enhancing glucosuria, independently of insulin, SGLT-2 inhibitors have been shown to treat Type 2 diabetes and to improve cardiovascular outcomes. *See* Wright, 2001, *Am. J. Physiol. Renal Physiol.* 280:F10; and Scheen, 2018, *Circ. Res.* 122:1439. In some embodiments, the term “SGLT-2 inhibitor” refers to compounds whose primary effect is inhibition of SGLT-2, but is not limited to compounds that only inhibit SGLT-2, thus including compounds that have other activities in addition to SGLT-2 inhibition (e.g., SGLT-1 inhibition).

[00119] In some embodiments, SGLT-2 inhibitors include compounds of a class of drugs known as gliflozins. In some embodiments, SGLT-2 inhibitors include compounds that are approved as SGLT-2 inhibitors by a regulatory agency such as the FDA or EMA. Non-limiting examples of SGLT-2 inhibitors include bexagliflozin, canagliflozin (INVOKANA®), dapagliflozin (FARXIGA®), empagliflozin (JARDIANCE®), ertugliflozin (STEGLATRO™), ipragliflozin (SUGLAT®), luseogliflozin (LUSEFI®), remogliflozin, sergliflozin, licogliflozin, sotagliflozin (ZYNQUISTA™), and tofogliflozin.

[00120] In some embodiments, the SGLT-2 inhibitors include, but are not limited to dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, bexagliflozin, licogliflozin, janagliflozin (XZP-5695), tofogliflozin, ertugliflozin, henagliflozin (SHR-3824), enavogliflozin (DWP-16001), TA-1887 (3-(4-cyclopropylbenzyl)-4-fluoro-1-(β-D-glucopyranosyl)-1H-indole), indole-N-glycoside 18 (3-(4-ethylbenzyl)-1-(β-D-glucopyranosyl)-1H-indole), sotagliflozin, luseogliflozin, sergliflozin etabonate (ethyl carbonate), remogliflozin, remogliflozin etabonate, and T-1095 (((2R,3S,4S,5R,6S)-6-(2-(3-(benzofuran-5-yl)propanoyl)-3-hydroxy-5-methylphenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl) etabonate).

[00121] In some embodiments, the SGLT-2 inhibitors include C-glycosides such as dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, bexagliflozin, licogliflozin, janagliflozin (XZP-5695), tofogliflozin, ertugliflozin, henagliflozin (SHR-3824), enavogliflozin (DWP-16001). In some embodiments, the SGLT-2 inhibitors include C-glycosides with a bicyclic or spiro pyran

group, such as tofogliflozin, ertugliflozin, and henagliflozin (SHR-3824). In some embodiments, the SGLT-2 inhibitors include C-glycosides that do not have a bicyclic or spiro pyran group, such as dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, bexagliflozin, licogliflozin, janagliflozin (XZP-5695), and enavogliflozin (DWP-16001).

[00122] In some embodiments, the SGLT-2 inhibitors include N-glycosides such as TA-1887 (3-(4-cyclopropylbenzyl)-4-fluoro-1-(β -D-glucopyranosyl)-1H-indole) and indole-N-glycoside 18 (3-(4-ethylbenzyl)-1-(β -D-glucopyranosyl)-1H-indole).

[00123] In some embodiments, the SGLT-2 inhibitors include 2-methylthio-C-glycosides, such as sotagliflozin.

[00124] In some embodiments, the SGLT-2 inhibitors include thiopyran-C-glycosides, such as luseogliflozin.

[00125] In some embodiments, the SGLT-2 inhibitors include O-glycosides and O-glycoside prodrugs, such as sergliflozin etabonate (ethyl carbonate), remogliflozin, remogliflozin etabonate, and T-1095 (((2R,3S,4S,5R,6S)-6-(2-(3-(benzofuran-5-yl)propanoyl)-3-hydroxy-5-methylphenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl) etabonate).

[00126] In some embodiments, an SGLT-2 inhibitor, as defined herein, includes any compound exhibiting SGLT-2 inhibition activity. In some embodiments, an SGLT-2 inhibitor is selective for SGLT-2 over SGLT-1, for example, by having about 2-fold, about 5-fold, about 10-fold, about 20-fold, about 50-fold, about 100-fold, about 200-fold, about 300-fold, about 400-fold, about 500-fold, about 750-fold, about 1,000-fold, about 1,250-fold, about 1,500-fold, about 1,750-fold, about 2,000-fold, about 2,500-fold, or any value in between, greater activity against SGLT-2 than against SGLT-1. Exemplary SGLT-2 inhibitors can exhibit inhibition activity (IC_{50}) against SGLT-2 of less than about 1000 nM, less than about 500 nM, less than about 200 nM, less than about 100 nM, less than about 50 nM, less than about 25 nM, less than about 10 nM, or less than about 1 nM as measured in an assay as described herein. In some embodiments, SGLT-2 inhibitors can exhibit inhibition activity (IC_{50}) against SGLT-2 of less than about 25 nM, less than about 10 nM, less than about 5 nM, or less than about 1 nM as measured in an assay as provided herein. An exemplary assay for determining SGLT-2 inhibitory activity is described in Ryan, et al., *Kidney International*, Vol. 45, pp. 48-57 (1994). Briefly, CHO cells are stably transfected with cDNA encoding human SGLT-2 (GenBank #M95549). Cells are washed and then incubated with 10 μ M [14 C]alpha-methyl glucopyranoside (AMG), and 10 μ M inhibitor. The uptake of [14 C]AMG is

quenched with cold buffer containing phlorizin, and cells are lysed. Suitable reagents are then used to quantify the uptake of [^{14}C]AMG.

[00127] SGLT-2 inhibitors include pharmaceutically acceptable salts, solvates, complexes, and salts of solvates thereof, for example, “dapagliflozin” includes salts of dapagliflozin (such as the hydrochloride salt) as well as solvates (such as the propylene glycol hydrate); likewise, “canagliflozin” includes solvates (such as canagliflozin hemihydrate) and salts of solvates (such as the hydrochloride salt of the hydrate). Similarly, henagliflozin (SHR-3824) and dapagliflozin include complexes (such as the complexes henagliflozin proline and dapagliflozin proline, respectively).

[00128] As used herein, when a subject is described as having “controlled serum glucose levels”, it means the subject has a serum glucose level within the normal or healthy ranges. In some embodiments, the subject has a fasting serum glucose level of between about 70 mg/dL and about 130 mg/dL. For example, the subject has been determined to have a fasting serum glucose level of below about 130 mg/dL, 125 mg/dL, 120 mg/dL, 115 mg/dL, 110 mg/dL, 105 mg/dL, 100 mg/dL, 95 mg/dL, 90 mg/dL, 85 mg/dL, 80 mg/dL, or 75 mg/dL.

[00129] As used in the methods described herein, the term “reducing” refers to a reduction in the indicated parameter relative to the baseline measurement (or measurements) of the same parameter in the subject taken prior to the initiation of administration with atrasentan or a pharmaceutically acceptable salt thereof, or a reduction in the indicated parameter relative to the baseline measurement (or measurements) of the same parameter in a healthy subject (for example, a subject that does not have FSGS). Similarly, the term “increasing,” as used herein, refers to an increase in the indicated parameter relative to the baseline measurement (or measurements) of the same parameter in the subject taken prior to the initiation of administration with atrasentan or a pharmaceutically acceptable salt thereof, or an increase in the indicated parameter relative to the baseline measurement (or measurements) of the same parameter in a healthy subject (for example, a subject that does not have FSGS).

[00130] The term “glomerular filtration rate” (GFR) is defined as the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman's capsule per unit time. It is indicative of overall kidney function. The glomerular filtration rate (GFR) can be calculated by measuring any chemical that has a steady level in the blood, and is freely filtered but neither reabsorbed nor secreted by the kidneys. The rate therefore measured is the quantity of the

substance in the urine that originated from a calculable volume of blood. The GFR is typically recorded in units of volume per time, e.g., milliliters per minute and the formula below can be used: $GFR = (\text{Urine Concentration} \times \text{Urine Volume}) / \text{Plasma Concentration}$. The GFR can be determined by injecting inulin into the plasma. Since inulin is neither reabsorbed nor secreted by the kidney after glomerular filtration, its rate of excretion is directly proportional to the rate of filtration of water and solutes across the glomerular filter. A normal value is: $GFR = 90\text{--}125 \text{ mL/min/1.73m}^2$, in particular $GFR = 100\text{--}125 \text{ mL/min/1.73 m}^2$. Other principles to determine GFR involve measuring $^{51}\text{Cr-EDTA}$, ^{125}I iothalamate or iohexol. The “estimated glomerular filtration rate (eGFR)” is defined as derived at screening from serum creatinine values based on e.g., the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, the Cockcroft-Gault formula or the Modification of Diet in Renal Disease (MDRD) formula, which are all known in the art. “Reducing the rate of decline in eGFR” as used herein means reducing the rate of decrease in eGFR and/or attenuating the rate of decline in eGFR. As indicated herein, eGFR is an art-recognized measurement of disease or disease progression. For example, the rate of decline in eGFR can be attenuated by at least about 20%; by at least about 30%; by at least about 40%; by at least about 50%; by at least about 60%; by at least about 70%; by at least about 80%; by at least about 90%; or by at least about 95%; or any value in between after treatment with atrasentan, or a pharmaceutically acceptable salt thereof. This attenuation can be after treatment, for example, for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between. In some embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In some embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 6 months and about 1 year.

[00131] “ESKD” is the abbreviation for end-stage kidney disease. As used herein, the onset of ESKD is defined as the time point when the subject has an eGFR of below about $15 \text{ mL/min/1.73m}^2$ and/or when the subject has initiated chronic dialysis. When a subject is defined to be “at a high risk of progression to ESKD”, the subject has $>1 \text{ g/day}$ protein in the urine and/or

eGFR < 60 for at least about 3 months before the first administration of atrasentan or a pharmaceutically acceptable salt thereof. As used herein, and as recognized by one of skill in the art, any historical or inadvertent reference to ESRD (end-stage renal disease) is used interchangeably in the art to refer to ESKD (end-stage kidney disease), which is the more current term for the condition.

[00132] As used herein, when a subject is described to “maintain a potassium level within the normal physiologic range”, the subject has a blood potassium level of from about 3.5 mEq/L to about 5.2 mEq/L.

[00133] As used herein, when a subject is described to “maintain a sodium level within the normal physiologic range”, the subject has a blood sodium level of from about 135 to about 145 mEq/L.

[00134] As used herein, the term "proteinuria" refers to the presence of protein in the urine in excess of normal levels. "Proteinuria" includes "albuminuria" and "microalbuminuria". Normal human levels of protein appear in the urine in the range of about 0 to 30 mg/L, although for any given urine sample, the level may reach about 80 mg/L. For a 24 hour urine collection, normal human levels of urinary protein are in the range of about 0 to 150 mg. Proteinuria can be indicated by the ratio of total protein/creatinine in the urine (UPCR), or by the ration of a specific protein, such as a urinary albumin/creatinine ratio (ACR) of greater than about 30 mg/g. Typically, the urinary UACR value in mg/g approximately equals to the albumin excretion by the subject in mg/day. Proteinuria, including albuminuria and microalbuminuria, often leads to or is indicative of a disease, but is not limited to production of a disease. Proteinuria is intended to encompass all forms of proteinuria, including but not limited to physiological proteinuria; functional proteinuria; and athletic proteinuria, which relates to a form of functional proteinuria following excessive muscular exertion. Further, proteinuria covers benign proteinuria (also known as "essential" proteinuria), which refers to types or proteinuria that are not the result of pathologic changes in the kidneys. Proteinuria also covers pathologic proteinuria, for example levels of protein in the urine greater than normal physiological levels.

[00135] As used herein, the term "albuminuria" (also known as "macroalbuminuria") refers to the presence of albumin in the urine in excess of normal levels. Since urinary protein is predominantly albumin, normal human levels of urinary UACR are in the range of about 0 to 30 mg/mmol. As used herein, the term "microalbuminuria" refers to the

presence of albumin in the urine, excreted at a rate of about 20 to 200 $\mu\text{g}/\text{min}$ or at a level of about 30 to 300 mg/L in humans. When defined by the urinary ACR, "microalbuminuria" refers to a urinary UACR of greater than about 30 mg/g , or a urinary UACR of about 3.5 mg/mmol or greater for women and about 2.5 mg/mmol or greater for men. Microalbuminuria is often an early warning of kidney disease, but can also be present for other reasons.

[00136] "ALT" as used herein refers to alanine transaminase. "AST" as used herein refers to aspartate transaminase.

[00137] The term "synergy" or "synergistic" is used herein to mean that the effect of a combination of two or more therapeutic agents is greater than the sum of the effect of each agent when administered alone. *See, e.g.*, Chou and Talalay, *Advances in Enzyme Regulation* (1984), 22, 27-55. A "synergistically effective amount" is an amount of the combination of the two or more therapeutic agents that results in a synergistic effect (as "synergistic" is defined herein). In some embodiments, a synergistically effective amount of a combination may be therapeutically effective even when one or more of the compounds in the combination is administered at a dose that would be sub-therapeutic when the compound is administered alone.

[00138] It will be appreciated that different concentrations of each compound may be employed for various art-recognized factors, for example, the patient's height, weight, sex, age and medical history. Exemplary synergistic effects includes, but are not limited to, enhanced therapeutic efficacy, decreased dosage at equal or increased level of efficacy, reduced or delayed development of drug resistance, and simultaneous enhancement or equal therapeutic actions (e.g., the same therapeutic effect as at least one of the therapeutic agents) and a reduction of unwanted drug effects (e.g. side effects and adverse events) of at least one of the therapeutic agents.

[00139] In some embodiments, "synergistic effect" as used herein refers to a combination of atrasentan, or a pharmaceutically acceptable salt thereof, and one or more additional therapeutic agents (for example, a SGLT-2 inhibitor), producing an effect, for example, any of the beneficial or desired results including clinical results as described herein, which is greater than the sum of effect observed when the atrasentan, or a pharmaceutically acceptable salt thereof, and the SGLT-2 inhibitor are administered alone. Such clinical results include, but are not limited to treating FSGS, decreasing renal inflammation and/or fibrosis, decreasing proteinuria (e.g., albuminuria), decreasing fatigue, reducing the rate of decline in eGFR, delaying the onset of ESKD, decreasing fatigue, reducing activation of a mesangial cell.

[00140] In some embodiments, “synergistic effect” as used herein refers to a combination of atrasentan, or a pharmaceutically acceptable salt thereof and a SGLT-2 inhibitor, providing a greater reduction in proteinuria, such as albuminuria, than the sum of effect observed when the atrasentan, or a pharmaceutically acceptable salt thereof, and the SGLT-2 inhibitor are administered alone.

[00141] In some embodiments, “synergistic effect” as used herein refers to a combination of atrasentan, or a pharmaceutically acceptable salt thereof, and an SGLT-2 inhibitor, producing a desired therapeutic effect and a reduction in the occurrence and/or severity of an unwanted drug effect, side effect, or adverse event. In some embodiments, the unwanted drug effect, side effect, or adverse event is associated with or observed in monotherapy of atrasentan, or a pharmaceutically acceptable salt thereof, or a SGLT-2 inhibitor. In some embodiments, the unwanted drug effect, side effect, or adverse event is one or more of fluid retention, anemia, nausea, constipation, thirst, bone fractures, increased urination, urinary tract infection, yeast infection, vaginal itching, increased LDL cholesterol levels, increased brain natriuretic peptide (BNP) levels, acute sodium retention, and acute increases in creatinine levels. In some embodiments, the fluid retention is associated with a weight gain of greater than about 3 kg. In some embodiments, the increased BNP levels are greater than about 300 pg/mL.

[00142] An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease temporally associated with the subject’s participation in the research, whether or not considered related to the subject’s participation in the research. Any medical condition or clinically significant laboratory abnormality with an onset date before first dose is a pre-existing condition that must be captured as part of the Medical History and should not be considered an AE unless the condition worsens in intensity or frequency after enrollment. Events meeting the AE definition include one or more of the events in the following paragraphs.

[00143] An AE can be any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) requiring intervention or other safety assessments (e.g., ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). An AE can include exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions

detected or diagnosed after study drug administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se is not considered as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

[00144] A “serious adverse event” (SAE) is any AE that results in the following: death; life-threatening condition (places the subject at immediate risk of death); subject hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect; or any other AE that, based upon the Investigators medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse).

[00145] An “adverse events of special interest” (AESI) includes fluid retention, dilutional anemia, vasodilation/hypotension/acute kidney injury, or cardiac failure

[00146] As described herein, any concentration range, percentage range, ratio range, or integer range is to be understood to include the value of any integer within the recited range and, when appropriate, fractions thereof (such as one tenth and one hundredth of an integer), unless otherwise indicated.

[00147] Unless otherwise stated, any reference to an amount of atrasentan in this disclosure is based on the free equivalent weight of atrasentan. For example, 0.75 mg of atrasentan refers to 0.75 mg of atrasentan in the free form or an equivalent amount of a salt form of atrasentan.

[00148] Various aspects of the disclosure are described in further detail in the following subsections.

II. METHODS OF TREATMENT

[00149] In a normal and healthy human kidney, expressions of endothelin-1 (ET-1) and endothelin A receptor (ET-RA) are more intense in vascular tissue and less intense in glomerular structures. In contrast, subjects with FSGS show increased expressions of ET-1 and ET-RA in the kidney. In that population, ET-1 expression positively correlates with proteinuria,

which is at least partially ameliorated by administration of ACE inhibitors. Indeed, the currently therapy for FSGS is optimization of antihypertensive and antiproteinuric agents (e.g., angiotensin converting enzyme inhibitors and/or angiotensin II receptor blockers), along with a course of corticosteroids, to inhibit disease progression. *See, e.g.,* Penfold et al., *Int. J. Nephrol. and Renovascular Dis.* 11, pp. 137-148 (2017). However, these combinations of agents may exhibit significant dose-limiting side effects such as hyperkalemia, and further immunosuppression may be necessary in more serious cases.

[00150] Clinically, FSGS is diagnosed by kidney biopsy indicating the presence of mesangial cell proliferation and/or matrix expansion (or focal segmental glomerular sclerosis in advanced stages) with predominant mesangial granular deposits of IgA (2+ or more) on immunofluorescence. This pathology is distinct from other progressive kidney diseases such as diabetic nephropathy, which typically present with a diffuse capillary basement membrane thickening with peripheral hyaline PAS-positive nodules, with segmental or global glomerular sclerosis at advanced stages, and thickened arterioles with hyaline deposits. *See, e.g.,* Zanatta, et al., *Renal Failure*, 34(3), pp. 308-315 (2012).

[00151] Accordingly, in one aspect, provided herein is a method of treating FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In another aspect, provided herein is a method of decreasing renal inflammation and/or fibrosis in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In another aspect, provided herein is a method of reducing the rate of decline in eGFR in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In another aspect, provided herein is a method of delaying the onset of ESKD in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In another aspect, provided herein is a method of decreasing proteinuria in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In another aspect, provided herein is a method of decreasing fatigue in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In another aspect,

provided herein is a method of stabilizing functional podocyte mass in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. As indicated herein, in some embodiments, disease progression is stabilized, reduced, or slowed according to certain methods disclosed herein and including as measured by art-accepted parameters, examples of which are provided herewith.

[00152] In some instances, the FSGS has been diagnosed with biopsy-confirmed FSGS. Some embodiments provide that the subject has a genetic diagnosis of FSGS due to known podocyte protein mutation. Additional embodiments include subjects having mutations in APOL1. In some instances, the FSGS comprises a nephrotic syndrome. In some instances, the nephrotic syndrome is selected from proteinuria, hypoalbuminemia, hypercholesterolemia, peripheral edema, or a combination of any of the foregoing. In some instances, the FSGS is perihilar FSGS, tip lesion FSGS, cellular FSGS, collapsing FSGS, primary FSGS, virus-associated FSGS, not HIV-associated FSGS, toxin-associated FSGS, adaptive FSGS, or combinations thereof. In some instances, the FSGS is FSGS not otherwise specified (NOS).

[00153] In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with any of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with diabetic nephropathy. In some embodiments, the subject has not been previously diagnosed with HIV/AIDS. In some embodiments, the subject has not been previously diagnosed with HIV-related nephropathy. In some embodiments, the subject has not been previously diagnosed with prostate cancer. In some embodiments, the subject has not been previously diagnosed with acute kidney failure. In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, cancer, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject has been previously diagnosed with diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject has been previously diagnosed with diabetes, and has not been previously diagnosed with diabetic nephropathy. In some embodiments, the subject has not been previously diagnosed with Type 2 diabetes. In some embodiments, the subject has been previously diagnosed with Type 2 diabetes.

In some embodiments, the subject has been previously diagnosed with Type 2 diabetes, and has not been previously diagnosed with diabetic nephropathy.

[00154] In some embodiments, the subject is not currently diagnosed with cancer. In some embodiments, the subject is not currently being treated for cancer. In some embodiments, the cancer is lung cancer or prostate cancer.

[00155] In some embodiments, the subject does not have one or more of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject does not have any of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject does not have diabetic nephropathy. In some embodiments, the subject does not have HIV/AIDS. In some embodiments, the subject does not have HIV-related nephropathy. In some embodiments, the subject does not have cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is lung cancer. In some embodiments, the subject does not have acute kidney failure. In some embodiments, the subject does not have one or more of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, cancer, or acute kidney failure. In some embodiments, the cancer is lung cancer or prostate cancer. In some embodiments, the subject has diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject does not have diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject has diabetes, and does not have diabetic nephropathy. In some embodiments, the subject has Type 2 diabetes. In some embodiments, the subject does not have Type 2 diabetes. In some embodiments, the subject has Type 2 diabetes, and does not have diabetic nephropathy.

[00156] In some embodiments, the subject does not suffer from one or more of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject does not suffer from any of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject does not suffer from diabetic nephropathy. In some embodiments, the subject does not suffer from HIV/AIDS. In some embodiments, the subject does not suffer from HIV-related nephropathy. In some embodiments, the subject does not suffer from cancer. In some embodiments, the cancer is prostate cancer. In some embodiments, the cancer is lung cancer. In some embodiments, the subject does not suffer from acute kidney failure. In some embodiments, the subject does not suffer from one or more of diabetic nephropathy, HIV/AIDS, HIV-related

nephropathy, cancer, or acute kidney failure. In some embodiments, the cancer is lung cancer or prostate cancer. In some embodiments, the subject does not suffer from diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject does suffer from diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject does suffer from diabetes, such as Type 1 diabetes or Type 2 diabetes, but does not suffer from diabetic nephropathy. In some embodiments, the subject does not suffer from Type 2 diabetes. In some embodiments, the subject does suffer from Type 2 diabetes. In some embodiments, the subject does suffer from Type 2 diabetes, but does not suffer from diabetic nephropathy.

[00157] In some embodiments, the subject is not being treated for one or more of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject is not being treated for any of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject is not being treated for diabetic nephropathy. In some embodiments, the subject is not being treated for HIV/AIDS. In some embodiments, the subject is not being treated for HIV-related nephropathy. In some embodiments, the subject is not being treated for prostate cancer. In some embodiments, the subject is not being treated for acute kidney failure. In some embodiments, the subject is not being treated for one or more of diabetic nephropathy, HIV/AIDS, HIV-related nephropathy, cancer, or acute kidney failure. In some embodiments, the cancer is lung cancer or prostate cancer. In some embodiments, the subject is not being treated for diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject is being treated for diabetes (i.e., Type 1 or Type 2 diabetes). In some embodiments, the subject is being treated for diabetes, such as Type 1 diabetes or Type 2 diabetes, but is not being treated for diabetic nephropathy. In some embodiments, the subject is not being treated for Type 2 diabetes. In some embodiments, the subject is being treated for Type 2 diabetes. In some embodiments, the subject is being treated for Type 2 diabetes, but is not being treated for diabetic nephropathy.

[00158] In certain embodiments, the subject has been determined to have controlled serum glucose levels. In some embodiments, the subject with controlled serum glucose levels is not being treated for diabetes. In some embodiments, the subject with controlled serum glucose levels is being treated for diabetes. In some embodiments, the subject with controlled serum glucose levels is not being treated for Type 2 diabetes. In some embodiments, the subject with controlled serum glucose levels is being treated for Type 2 diabetes. In some embodiments, the

subject has been determined to have controlled serum glucose levels; where the subject has not been diagnosed with one or more of HIV-related nephropathy or acute kidney failure. For example, the subject has been determined to have a fasting serum glucose level of below about 130 mg/dL, about 125 mg/dL, about 120 mg/dL, about 115 mg/dL, about 110 mg/dL, about 105 mg/dL, about 100 mg/dL, about 95 mg/dL, about 90 mg/dL, about 85 mg/dL, about 80 mg/dL, or about 75 mg/dL, or any value in between. In certain embodiments, the subject has not been diagnosed with one or more of HIV-related nephropathy or acute kidney failure. In certain embodiments, the subject has been determined to have controlled serum glucose levels as described anywhere herein; and the subject has not been diagnosed with one or more of HIV-related nephropathy or acute kidney failure. In certain embodiments, the subject has been determined to have controlled serum glucose levels; and the subject has not been diagnosed with one or more of HIV-related nephropathy or acute kidney failure.

[00159] In another aspect, provided herein is a method of stabilizing or decreasing renal inflammation and/or fibrosis in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some instances, the renal inflammation and/or fibrosis is tubulointerstitial inflammation. In some instances, the renal inflammation and/or fibrosis is tubulointerstitial fibrosis. In some instances, the renal inflammation and/or fibrosis includes glomerular inflammation and/or glomerulosclerosis. In some instances, the renal inflammation and/or fibrosis includes tubulointerstitial inflammation, tubulointerstitial fibrosis, glomerular inflammation, and/or glomerulosclerosis.

[00160] In some embodiments, the renal inflammation in the subject having FSGS is decreased by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the renal inflammation in the subject is decreased by at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95%, or any value

in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00161] In some embodiments, renal fibrosis in the subject having FSGS is decreased by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the renal fibrosis in the subject is decreased by at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95%, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00162] In some embodiments, renal fibrosis in the subject having FSGS is decreased to less than about 50% of the cortical area of the affected kidney(s) after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, about renal fibrosis in the subject is decreased to less than about 40% of the cortical area. For example, in some embodiments, renal fibrosis in the subject is decreased to less than about 35%, about 30%, about 25%, about 20%, about 15%, or about 10%, or any value in between, of the cortical area. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00163] In some embodiments, the number of urinary red blood cells per high powered (microscope) field (rbc/hpf) in the subject having FSGS is decreased by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after

treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the urinary rbc/hpf in the subject is decreased by at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95%, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00164] In another aspect, provided herein is a method of reducing the rate of decline in eGFR, in a subject having FSGS comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[00165] In some embodiments, provided herein is a method for reducing the rate of decrease in eGFR in a subject having FSGS, the method comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, the rate of decrease in eGFR of the subject is reduced by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In some embodiments, the rate of decrease in eGFR of the subject is reduced by at least about 20%; by at least about 30%; by at least about 40%; by at least about 50%; by at least about 60%; by at least about 70%; by at least about 80%; by at least about 90%; or by at least about 95%; or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 6 months and about 1 year.

[00166] In some embodiments, the rate of decrease in eGFR of the subject having FSGS is reduced to below about 10 mL/min/1.73m² after treatment with atrasentan or a pharmaceutically acceptable salt thereof. For example, after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between. In certain embodiments, the rate of decrease in eGFR of the subject is reduced to below about 9 mL/min/1.73m², about 8 mL/min/1.73m², about 7 mL/min/1.73m², about 6 mL/min/1.73m², about 5 mL/min/1.73m², about 4 mL/min/1.73m², about 3 mL/min/1.73m², about 2 mL/min/1.73m², about 1 mL/min/1.73m², or about 0.75 mL/min/1.73m², or any value in between after treatment with atrasentan, or a pharmaceutically acceptable salt thereof, for between about 6 months to about 1 year. The typical decline in eGFR with age, for example, in a subject between about 20 to about 30 years of age, is about 1 mL/min/1.73m² per year.

[00167] In another aspect, provided herein is a method of delaying the onset of ESKD in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[00168] In some embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below 15 mL/min/1.73m². In certain embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below 15 mL/min/1.73m² by at least about 10%. For example, in some embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below 15 mL/min/1.73m² by at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 100%, about 150%, about 200%, about 250%, about 300%, about 350%, about 400%, about 450%, or about 500%, or any value in between. Thus, in some embodiments, the method slows the progression of FSGS-related disease as measured by industry-accepted benchmarks.

[00169] In certain embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below 15 mL/min/1.73m² by at least about 1 year. For example, the method can delay the time when eGFR

of the subject falls below 15 mL/min/1.73m² by at least about 1.5 years, 2 years, 2.5 years, 3 years, 3.5 years, 4 years, 4.5 years, 5 years, 5.5 years, 6 years, 6.5 years, 7 years, 7.5 years, 8 years, 8.5 years, 9 years, 9.5 years, 10 years, 11 years, 12 years, 13 years, 15 years, 16 years, 17 years, 18 years, 19 years, or 20 years.

[00170] In another aspect, provided herein is a method of decreasing proteinuria in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. As used throughout, it is understood that proteinuria measures protein in urine. While typically albumin is the primary protein in urine, other and multiple proteins can be tested as part of one or methods described herein. Referring to “protein” may refer to albumin or one or more other proteins typically detected in urine in some embodiments described herein, as would be appreciated by one of skill in the art.

[00171] In some embodiments, the amount of protein (e.g., albumin) in the urine of the subject having FSGS is reduced by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In some embodiments, the amount of protein in the urine of the subject is reduced by at least about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 95%, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00172] In certain embodiments, the amount of protein (e.g., albumin) in the urine of the subject having FSGS is reduced by about 20% to about 80% after between about 2 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein (e.g., albumin) in the urine of the subject having FSGS is reduced by about 20% to about 80% after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain of these embodiments,

the amount of protein in the urine of the subject is reduced by about 25% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 30% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 35% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 40% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 45% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 50% to about 80%. In the aforementioned embodiments, the reduction of the amount of protein (e.g., albumin) in the urine of the subject having FSGS is relative to the amount of protein (e.g., albumin) in the urine prior to initiation of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00173] In some embodiments, the amount of protein (e.g., albumin) in the urine of the subject having FSGS is reduced by about 100 mg/dL to about 3,000 mg/dL after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 2,500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 2,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 1,500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 1,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 400 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 300 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 200 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 2,500 mg/dL.

In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 2,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 1,500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 1,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 900 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 800 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 600 mg/dL to about 900 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 700 mg/dL to about 900 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 1,000 mg/dL to about 2,000 mg/dL. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In the aforementioned embodiments, the reduction of the amount of protein (e.g., albumin) in the urine of the subject having FSGS is relative to the amount of protein (e.g., albumin) in the urine prior to initiation of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00174] In certain embodiments, the amount of protein (e.g., albumin) in the urine of the subject having FSGS is reduced by about 100 mg/dL to about 500 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 200 mg/dL to about 500 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 300 mg/dL to about 500 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In the aforementioned embodiments, the reduction of the amount of protein (e.g., albumin) in the urine of the subject having FSGS is relative to the amount of protein (e.g., albumin) in the urine prior to initiation of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00175] In certain embodiments, the amount of protein (e.g., albumin) in the urine of the subject having FSGS is reduced by about 500 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable

salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 600 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 700 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In the aforementioned embodiments, the reduction of the amount of protein (e.g., albumin) in the urine of the subject having FSGS is relative to the amount of protein (e.g., albumin) in the urine prior to initiation of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00176] In some embodiments, the subject having FSGS has a reduced level of protein (e.g., albumin) in the urine of below about 1.0 gram/day after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 20 weeks, 30 weeks, 40 weeks, 50 weeks, 60 weeks, 70 weeks, 80 weeks, 90 weeks, 100 weeks, 110 weeks, 120 weeks, 130 weeks, 140 weeks, 150 weeks, 160 weeks, 170 weeks, 180 weeks, 190 weeks, or 200 weeks). In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.9 gram/day. In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.8 gram/day. In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.7 gram/day. In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.6 gram/day. In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.5 gram/day. In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.4 gram/day. In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.3 gram/day. In certain embodiments, the subject has a reduced level of protein in the urine of below about 0.2 gram/day. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In the aforementioned embodiments, the reduction of the amount of protein (e.g., albumin) in the urine of the subject having FSGS is relative to the amount of protein (e.g., albumin) in the urine prior to initiation of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00177] In another aspect, provided herein is a method of decreasing fatigue in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan,

or a pharmaceutically acceptable salt thereof, to a subject in need thereof. In some embodiments, the subject has been determined not to suffer from one or more of diabetic nephropathy, HIV-related nephropathy, prostate cancer, or acute kidney failure. In certain embodiments, the subject has been determined not to suffer from diabetic nephropathy. In certain embodiments, the subject has been determined not to suffer from HIV-related neuropathy. In certain embodiments, the subject has been determined not to suffer from prostate cancer. In certain embodiments, the subject has been determined not to suffer from acute kidney failure.

[00178] In some embodiments, the fatigue of the subject having FSGS is reduced by about 5% to about 80% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the fatigue is reduced by about 10% to about 75%. In certain embodiments, the fatigue is reduced by about 10% to about 70%. In certain embodiments, the fatigue is reduced by about 10% to about 65%. In certain embodiments, the fatigue is reduced by about 10% to about 60%. In certain embodiments, the fatigue is reduced by about 10% to about 55%. In certain embodiments, the fatigue is reduced by about 10% to about 50%. In certain embodiments, the fatigue is reduced by about 10% to about 45%. In certain embodiments, the fatigue is reduced by about 10% to about 40%. In certain embodiments, the fatigue is reduced by about 10% to about 35%. In certain embodiments, the fatigue is reduced by about 10% to about 30%. In certain embodiments, the fatigue is reduced by about 10% to about 25%. In certain embodiments, the fatigue is reduced by about 10% to about 20%. In certain embodiments, the fatigue is reduced by about 10% to about 15%. In certain embodiments, the fatigue is reduced by about 20% to about 75%. In certain embodiments, the fatigue is reduced by about 20% to about 70%. In certain embodiments, the fatigue is reduced by about 20% to about 65%. In certain embodiments, the fatigue is reduced by about 20% to about 60%. In certain embodiments, the fatigue is reduced by about 20% to about 55%. In certain embodiments, the fatigue is reduced by about 20% to about 50%. In certain embodiments, the fatigue is reduced by about 20% to about 45%. In certain embodiments, the fatigue is reduced by

about 20% to about 40%. In certain embodiments, the fatigue is reduced by about 20% to about 35%. In certain embodiments, the fatigue is reduced by about 20% to about 30%. In certain embodiments, the fatigue is reduced by about 30% to about 75%. In certain embodiments, the fatigue is reduced by about 30% to about 70%. In certain embodiments, the fatigue is reduced by about 30% to about 65%. In certain embodiments, the fatigue is reduced by about 30% to about 60%. In certain embodiments, the fatigue is reduced by about 30% to about 55%. In certain embodiments, the fatigue is reduced by about 30% to about 50%. In certain embodiments, the fatigue is reduced by about 30% to about 45%. In certain embodiments, the fatigue is reduced by about 30% to about 40%. In certain embodiments, the fatigue is reduced by about 40% to about 75%. In certain embodiments, the fatigue is reduced by about 40% to about 70%. In certain embodiments, the fatigue is reduced by about 40% to about 65%. In certain embodiments, the fatigue is reduced by about 40% to about 60%. In certain embodiments, the fatigue is reduced by about 40% to about 55%. In certain embodiments, the fatigue is reduced by about 40% to about 50%. In certain embodiments, the fatigue is reduced by about 50% to about 75%. In certain embodiments, the fatigue is reduced by about 50% to about 70%. In certain embodiments, the fatigue is reduced by about 50% to about 65%. In certain embodiments, the fatigue is reduced by about 50% to about 60%. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In certain embodiments, the decrease in fatigue comprises a decrease in the score on one or more of the Fatigue Severity Scale, the Chalder Fatigue Scale, the FACIT Fatigue Scale, the Brief Fatigue Inventory, the FACT-F Subscale, Global Vigor and Affect, the May and Kline Adjective Checklist, the Pearson-Byars Fatigue Feeling Checklist, the Rhoten Fatigue Scale, the Schedule of Fatigue and Anergia, the Visual Analog Scale, or the Checklist Individual Strength. In the aforementioned embodiments, the reduction of fatigue experienced by the subject having FSGS is relative to the fatigue experienced by the subject prior to initiation of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the decrease in fatigue comprises a decrease in the score on the Brief Fatigue Inventory.

III. SUBJECT SELECTION

[00179] The subject having FSGS as described anywhere herein can be diagnosed using one or more methods known in the art. Non-limiting examples include: kidney biopsy,

detecting anti-glycan antibodies, detecting deposition fibrosis in the kidney, or a combination of any of the foregoing.

[00180] In some embodiments, the presence and/or level of a particular protein in a subject is determined prior to administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, serum levels of Gd-IgA1, serum levels of autoantibodies specific for Gd-IgA1, and/or serum and/or urine levels of IgA1-containing immune complexes. *See, e.g.,* Knoppova, *et al.*, *Front. Immunol.*, Vol. 17, Art. 117 (2016), which is hereby incorporated by reference in its entirety. In some embodiments, the subject has Gd-IgA levels in the 90th percentile or above prior to administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has Gd-IgA levels in the 95th percentile or above prior to administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject's Gd-IgA levels decrease to below the 90th percentile after treatment with atrasentan, or a pharmaceutically acceptable salt thereof, for between about 6 months to 1 year.

[00181] In certain embodiments, the subject has mesangial cellularity in about $\geq 50\%$ (e.g., about $\geq 60\%$, about $\geq 70\%$, or about $\geq 80\%$) of the glomeruli, wherein mesangial cellularity is defined as more than four mesangial cells in any mesangial area of a glomerulus. In certain embodiments, endocapillary hypercellularity is present in the subject, wherein endocapillary hypercellularity is defined as hypercellularity due to an increased number of cells within glomerular capillary lumina. In certain embodiments, segmental sclerosis is present in the subject, wherein segmental sclerosis is defined as adhesion or sclerosis (obliteration of capillary lumina by matrix) in part of but not the whole glomerular tuft. In certain embodiments, the subject has tubular atrophy/interstitial fibrosis in about $\geq 50\%$ (e.g., about $\geq 60\%$, about $\geq 65\%$, about $\geq 70\%$, about $\geq 75\%$, or about $\geq 80\%$) of the cortical area, wherein tubular atrophy/interstitial fibrosis is defined as the estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis. In certain embodiments, the subject has crescents present on the glomeruli. In certain of these embodiments, the subject has crescents present on below about 25% (e.g., below about 20%, about 15%, about 10%, or about 5%) of the glomeruli. In certain embodiments, the subject has a MEST-C score of M1; E1; S1; T1 or T2; and/or C0 or C1 under the Oxford MEST-C classification system. The Oxford MEST-C classification system is defined in *Kidney International* (2009) 76, 546–556 and *Nature Reviews Nephrology* (2017) 13, 385–386, each of which is incorporated herein by

reference in its entirety (Also see: *Kidney Research and Clinical Practice* (2016) 35, 197-203, which is incorporated herein by reference in its entirety)).

[00182] In some embodiments, the subject is at a high risk of progression to ESKD. In certain of these embodiments, the subject is excreting an average of about 1 gram or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In certain of these embodiments, the subject is excreting an average of about 0.75 grams or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In certain of these embodiments, the subject is excreting an average of about 0.75 grams to about 1.5 grams of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In certain of these embodiments, the subject is excreting an average of about 1 gram or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[00183] In certain embodiments, the subject has an average eGFR of about 20 to about 120 mL/min/1.73m² (about 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, or 120) for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject has an average eGFR of about 20 to about 90 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject has an average eGFR of about 20 to about 60 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[00184] In certain embodiments, the subject has an average eGFR ≤ 60 mL/min/1.73m² (e.g., about ≤ 55 , about ≤ 50 , about ≤ 45 , about ≤ 40 , about ≤ 35) for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In certain of these embodiments, the subject has eGFR > 30 mL/min/1.73m² prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof.

[00185] In some embodiments, the subject is excreting an average of about 1 gram or more of protein in the urine per day for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at

least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, the subject can be excreting an average of about 1.1 gram, 1.2 grams, 1.3 grams, 1.4 grams, 1.5 grams, 1.6 grams, 1.7 grams, 1.8 grams, 1.9 grams, 2.0 grams, 2.1 grams, 2.2 grams, 2.3 grams, 2.4 grams, 2.5 grams, 2.6 grams, 2.7 grams, 2.8 grams, 2.9 grams, 3.0 grams, 3.1 grams, 3.2 grams, 3.3 grams, 3.4 grams, 3.5 grams, 5 grams, or 7.5 grams, or 10 grams, or any value in between, of protein in the urine per day for at least 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[00186] In some embodiments, the subject is excreting an average of from about 0.3 grams to about 2 grams of protein in the urine per day for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, the subject can be excreting from about 0.3 grams to 0.5 grams, 0.5 grams to 1 gram, from about 0.5 grams to 1.5 grams, from about 1 gram to 1.5 grams, or from about 1.5 grams to 2 grams of protein in the urine per day for at least 3 months.

[00187] In some embodiments, the subject is excreting at least about 1 gram of protein in the urine per day on at least two of three consecutive measurements a year prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. For example, the subject can be excreting about 1.1 grams, 1.2 grams, 1.3 grams, 1.4 grams, 1.5 grams, 1.6 grams, 1.7 grams, 1.8 grams, 1.9 grams, 2.0 grams, 2.1 grams, 2.2 grams, 2.3 grams, 2.4 grams, 2.5 grams, 2.6 grams, 2.7 grams, 2.8 grams, 2.9 grams, 3.0 grams, 3.1 grams, 3.2 grams, 3.3 grams, 3.4 grams, 3.5 grams, 5 grams, or 7.5 grams, or 10 grams of protein, or any value in between, in the urine per day on at least two of three consecutive measurements a year prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof.

[00188] In some embodiments, the subject has an UACR value of at least about 300 mg/g for at least three months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof, for example, 300 mg/g to about 5,000 mg/g. In some embodiments, the subject has an UACR value of about 800 mg/g for at least three months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof, for example, 800 mg/g

to about 5,000 mg/g. In some embodiments, the subject has an UACR value of at least about 500 mg/g, about 600 mg/g, about 700 mg/g, about 800 mg/g, about 900 mg/g, about 1,000 mg/g, about 1,500 mg/g, about 2,000 mg/g, about 2,500 mg/g, about 3,000 mg/g, about 3,500 mg/g, about 4,000 mg/g, about 4,500 mg/g, or about 5,000 mg/g, or any value in between, for at least three months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof.

[00189] In some embodiments, the subject has a decrease in UACR value of at least about 30% relative to the subject's average UACR value for at least three months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof, for example, a decrease of about 30% to about 100%, relative to the subject's average UACR value for at least three months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has a decrease in UACR value of at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 100%, or any value in between, relative to the subject's average UACR value for at least three months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject having a decrease in UACR value does not also experience significant sodium retention and/or significant fluid retention. In some embodiments, significant fluid retention can be about 1 kg to about 4 kg over six weeks, for example, about 4 kg, about 3.5 kg, about 3 kg, about 2.5 kg, about 2 kg, about 1.5 kg, or about 1 kg, or any value in between over 6 weeks. In some embodiments, a subject having significant fluid retention exhibits clinical symptoms of edema.

[00190] In certain embodiments, the subject has an average eGFR of about 20 to about 90 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof (e.g., about 3 months, about 4 months, about 5 months, about 6 months, about 7 months, about 8 months, about 9 months, about 10 months, about 11 months, about 12 months, about 1.5 years, or about 2 years). For example, about 20 to about 50 mL/min/1.73m²; about 30 to about 60 mL/min/1.73m²; about 40 to about 70 mL/min/1.73m²; about 50 to about 80 mL/min/1.73m²; or about 60 to about 90 mL/min/1.73m²; for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has an average eGFR $\leq$ 60 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject has an average eGFR $\leq$ 55 mL/min/1.73m² for at least about 3 months. In certain embodiments, the subject has an average eGFR $\leq$ 50 mL/min/1.73m² for at

least about 3 months. In certain embodiments, the subject has an average eGFR ≤ 45 mL/min/1.73m² for at least about 3 months. In certain embodiments, the subject has an average eGFR ≤ 40 mL/min/1.73m² for at least about 3 months. In certain embodiments, the subject has an average eGFR ≤ 35 mL/min/1.73m² for at least about 3 months. In certain embodiments, the subject has an average eGFR ≤ 25 mL/min/1.73m² for at least about 3 months. In certain embodiments, the subject has an average eGFR ≤ 20 mL/min/1.73m² for at least about 3 months. In certain of the foregoing embodiments, the subject has an average eGFR between about 30 mL/min/1.73m² and about 60 mL/min/1.73m² for at least 3 months before the administration of atrasentan or a pharmaceutically acceptable salt thereof. For example, the subject can have an average eGFR of between about 30 mL/min/1.73m² and about 55 mL/min/1.73m², between about 30 mL/min/1.73m² and about 50 mL/min/1.73m², between about 30 mL/min/1.73m² and about 45 mL/min/1.73m², or between about 30 mL/min/1.73m² and about 40 mL/min/1.73m².

[00191] In certain embodiments, the subject has an average eGFR of about 30 mL/min/1.73m² to about 45 mL/min/1.73m², for example, about ≤ 45 , about ≤ 40 , about ≤ 35 or about ≤ 30 , for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has an average eGFR of about 25 mL/min/1.73m² to about 75 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, about 25 mL/min/1.73m², about 30 mL/min/1.73m², about 35 mL/min/1.73m², about 40 mL/min/1.73m², about 45 mL/min/1.73m², about 50 mL/min/1.73m², about 55 mL/min/1.73m², about 60 mL/min/1.73m², about 65 mL/min/1.73m², about 70 mL/min/1.73m², about 75 mL/min/1.73m², or any value in between, for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[00192] In some embodiments, the subject has an average HbA1c of about 4% to about 6% for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan, or a pharmaceutically acceptable salt

thereof. For example, the subject can have an average HbA1c of about 4.2%, about 4.4%, about 4.6%, about 4.8%, about 5.0%, about 5.2%, about 5.4%, about 5.6%, about 5.8%, or about 6%, or any value in between.

[00193] In some embodiments, the subject has an average fasting blood glucose level of about 125 mg/dL or less for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, the subject can have an average fasting blood glucose level of about 120 mg/dL, about 115 mg/dL, about 110 mg/dL, about 105 mg/dL, about 100 mg/dL, about 95 mg/dL, about 90 mg/dL, about 85 mg/dL, about 80 mg/dL, or about 75 mg/dL, or any value in between.

[00194] In some embodiments, the subject maintains a potassium level within the normal physiologic range. In certain embodiments, the subject maintains a potassium level within the normal physiologic range for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject maintains a potassium level within 3.5 to 5.2 mEq/L. For example, the subject maintains an average potassium level at about 3.5 mEq/L, about 3.6 mEq/L, about 3.7 mEq/L, about 3.8 mEq/L, about 3.9, about mEq/L, about 4.0 mEq/L, about 4.1 mEq/L, about 4.2 mEq/L, about 4.3 mEq/L, about 4.4 mEq/L, about 4.5 mEq/L, about 4.6 mEq/L, about 4.7 mEq/L, about 4.8 mEq/L, about 4.9 mEq/L, about 5.0 mEq/L, about 5.1 mEq/L, or about 5.2 mEq/L, or any value in between.

[00195] In some embodiments, the subject maintains a sodium level within the normal physiologic range. In certain embodiments, the subject maintains a potassium level within the normal physiologic range for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In certain embodiments, the subject maintains a sodium

level within 135 to 145 mEq/L. For example, the subject maintains an average sodium level of about 135 mEq/L, about 136 mEq/L, about 137 mEq/L, about 138 mEq/L, about 139 mEq/L, about 140 mEq/L, about 141 mEq/L, about 142 mEq/L, about 143 mEq/L, about 144 mEq/L, about or 145 mEq/L, or any value in between.

[00196] In some embodiments, the subject has ALT/AST levels during the administration of atrasentan, or a pharmaceutically acceptable salt thereof, that are about the same as the ALT/AST levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, the subject has ALT/AST levels during the administration of atrasentan or a pharmaceutically acceptable salt thereof within about 25%, about 20%, about 15%, about 10%, about 5%, about or 2.5%, or any value in between, of the levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[00197] In some embodiments, the subject has bilirubin levels during the administration of atrasentan, or a pharmaceutically acceptable salt thereof, that are about the same as the bilirubin levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, the subject has bilirubin levels during the administration of atrasentan or a pharmaceutically acceptable salt thereof within about 25%, about 20%, about 15%, about 10%, about 5%, or about 2.5%, or any value in between, of the levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

[00198] In some embodiments, the fluid retention in the subject is manageable with diuretics (e.g., during the treatment with atrasentan or a pharmaceutically acceptable salt thereof and/or prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof). For example, the fluid retention can be less than about 3 kilograms (kg) of weight gain over 6 weeks. In some embodiments, the fluid retention is less than about 4 kg, about 3.5 kg, about 3 kg, about 2.5 kg, about 2 kg, about 1.5 kg, or about 1 kg, or any value in between over 6 weeks.

[00199] In some embodiments, the subject undergoes surgery, and/or other regimens prior to, substantially at the same time as, or following the administration of atrasentan, or a pharmaceutically acceptable salt thereof, as disclosed herein. In some embodiments, the subject is administered other chemical and/or biological therapeutic agents prior to, substantially at the same time as, or following the administration of atrasentan, or a pharmaceutically acceptable salt thereof, as disclosed herein.

[00200] In some embodiments, the subject has one or more genetic mutations that are associated with FSGS. In some embodiments, the subject has been previously determined to have one or more genetic mutations that are associated with FSGS. In some embodiments, the methods described herein further comprise determining that the subject has one or more genetic mutations that are associated with FSGS. A genetic mutation can include, for instance, a point mutation, a substitution, or a deletion. In some instances, the genetic mutation results in a mutation in the protein coding sequence of a gene. In some instances, the genetic mutation results in a mutation in the non-coding sequence of a gene. In some embodiments, the subject has a mutation in one or more of the following genes: APOL1, NPHS1, NPHS2, CD2AP, TRPC6, ACTN4, INF2, MYO1E, ARHGAP24, PLCE1, WT1, LMX1B, COQ6, LAMB2, PAX2, ANLN, and/or CRB2.

[00201] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in APOL1. In some instances, the mutation includes expression of the G1 or G2 risk allele. *See e.g.*, Genovese G, et al. *Science*. 2010 Aug 13;329(5993):841-5.; *see also*, Parsa A, et al., *N Engl J Med*. 2013 Dec 5;369(23):2183-96; and Daneshpajouhnejad P, et al. *Nat Rev Nephrol*. 2022 Feb 25:1-14. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from S342G, I384M, and/or 6 bp del N388/Y389.

[00202] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in NPHS1. *See e.g.*, Kestilä M, et al. *Mol Cell*. 1998 Mar;1(4):575-82; and Koziell A, et al. *Hum Mol Genet*. 2002 Feb 15;11(4):379-88. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from 121delCT (frameshift and truncation), R1109X (where X is any amino acid other than R), I306_1308insAC (frameshift and truncation), 3250insG (frameshift and truncation), and/or R1160X (where X is any amino acid other than R).

[00203] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in NPHS2. *See e.g.*, Boute N, et al. *Nat Genet*. 2000 Apr;24(4):349-54; Caridi G, et al. *J Am Soc Nephrol*. 2001 Dec;12(12):2742-2746; and Tsukaguchi H, et al. *J Clin Invest*. 2002 Dec;110(11):1659-66. Each of the foregoing references

in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from R138Q; R138X; 104insG (frameshift and truncation); 419delG; P20L; G92C; D160G; V180M; R291W; R138Q; 419delG; P20L; and/or R229Q.

[00204] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in CD2AP. *See e.g.*, Kim JM, et al. *Science*. 2003 May 23;300(5623):1298-300; and Löwik MM, et al. *Kidney Int*. 2007 Nov;72(10):1198-203. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from a mutation in a splice site acceptor and/or in R612X.

[00205] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in TRPC6. *See e.g.*, Winn MP, et al. *Science*. 2005 Jun 17;308(5729):1801-4; and Reiser J, et al. *Nat Genet*. 2005 Jul;37(7):739-44. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from P112Q; N143S; S270T; K874X; R895C; and/or E897K.

[00206] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in ACTN4. *See e.g.*, Kaplan JM, et al. *Nat Genet*. 2000 Mar;24(3):251-6; Bartram MP, et al. *Hum Mol Genet*. 2016 Mar 15;25(6):1152-64; Shao H, et al. *Sci Rep*. 2019 Oct 29;9(1):15517; and Weins A, et al. *J Am Soc Nephrol*. 2005 Dec;16(12):3694-701. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from K228G; T232I; S235P; K255E; T259I; S262P; G195D; W59R; I149del; K255E; T259I; and/or S262P.

[00207] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in INF2. *See e.g.*, Brown EJ, et al. *Nat Genet*. 2010 Jan;42(1):72-6. doi: 10.1038/ng.505. Epub 2009 Dec 20. Erratum in: *Nat Genet*. 2010 Apr;42(4):361; and Boyer O, et al. *J Am Soc Nephrol*. 2011 Feb;22(2):239-45. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from S186P; L198R; R218Q; R218W; R214H; L42P; A13T; E184K; E220K; L76P; R177H; Y193H; and/or R214C.

[00208] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in MYO1E. *See e.g.*, Mele C, et al. N Engl J Med. 2011 Jul 28;365(4):295-306, which is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from A159P and/or Y695X.

[00209] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in ARHGAP24. *See e.g.*, Akilesh S, et al. J Clin Invest. 2011 Oct;121(10):4127-37, which is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations includes Q158R.

[00210] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in PLCE1. *See e.g.*, Hinkes B, et al. Nat Genet. 2006 Dec;38(12):1397-405; and Boyer O, et al. J Med Genet. 2010 Jul;47(7):445-52. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from R493X (where X is an amino acid other than R); R1116X (where X is an amino acid other than R); Q1616X (where X is an amino acid other than Q); Q1854X (where X is an amino acid other than Q); S1484L; R2150X (where X is an amino acid other than R); R321X (where X is an amino acid other than R); and/or R1246X (where X is an amino acid other than R).

[00211] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in WT1. *See e.g.*, Hall G, et al. J Am Soc Nephrol. 2015 Apr;26(4):831-43, which is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations includes R458Q.

[00212] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in LMX1B. *See e.g.*, Boyer O, et al. J Am Soc Nephrol. 2013 Jul;24(8):1216-22; Isojima T, et al. Nephrol Dial Transplant. 2014 Jan;29(1):81-8; Hall G, et al. Sci Rep. 2017 Jan 6;7:39933; and Pinto E et al. BMC Nephrol. 2020 Aug 13;21(1):341. Each of the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from R246P and/or R246Q.

[00213] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in COQ6. *See e.g.*, Heeringa SF, et al. J Clin Invest. 2011 May;121(5):2013-24; *see also*, Park E, et al. Am J Kidney Dis. 2017 Jul;70(1):139-144. Each of

the foregoing references in this paragraph is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from G255R; A353D; Q447X (where X is any amino acid other than Q); R162X (where X is any amino acid other than R); W188X (where X is any amino acid other than W); P261L; and/or Q229P.

[00214] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in LAMB2. *See e.g.*, Hasselbacher K, et al. Kidney Int. 2006 Sep;70(6):1008-12, which is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from R264Q; N1380K; L1393F; and/or C321R.

[00215] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in PAX2. *See e.g.*, Barua M, et al. J Am Soc Nephrol. 2014 Sep;25(9):1942-53, which is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from R56Q and/or G189R.

[00216] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in ANLN. *See e.g.*, Gbadegesin RA, et al. J Am Soc Nephrol. 2014 Sep;25(9):1991-2002, which is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from R431C and/or G618C.

[00217] In some instances, the subject has, has previously been determined to have, or is determined to have, a mutation in CRB2. *See e.g.*, Ebarasi L, et al. Am J Hum Genet. 2015 Jan 8;96(1):153-61, which is hereby incorporated by reference in its entirety. In some instances, a subject with FSGS has one or more mutations selected from C620S; R628C; c.3089_3104dup (16-bp duplication); C629S; and/or R1249Q.

[00218] It is appreciated that a subject can present with one or more mutations (i.e., any combination) described herein.

[00219] In some embodiments, the subject has been receiving one or more inhibitors of the renin-angiotensin system for at least about 60 weeks prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. For example, in some embodiments, the subject has been receiving one or more inhibitors of the renin-angiotensin system for at least about 12 weeks, about 24 weeks, about 48 weeks, or about 60 weeks, or any value in between, prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof.

[00220] In some embodiments, the subject has been receiving a maximally tolerated stable dose of the one or more renin-angiotensin system inhibitors. For example, the subject can be receiving a maximally tolerated stable dose of the one or more renin-angiotensin system inhibitor for at least about 12 weeks, about 14 weeks, about 16 weeks, about 18 weeks, about 20 weeks, about 25 weeks, about 30 weeks, about 35 weeks, about 40 weeks, about 45 weeks, or about 50 weeks, or any value in between, prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more inhibitors of the renin-angiotensin system is selected from the group consisting of angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), renin inhibitors, and aldosterone antagonists. For example, the one or more inhibitors of the renin-angiotensin system can be ACE inhibitor, ARB, or a combination thereof, wherein the ACE inhibitor or ARB can be described anywhere herein. For example, the ACE inhibitor can be selected from: quinapril, fosinopril, perindopril, captopril, enalapril, enalaprilat, ramipril, cilazapril, delapril, fosinopril, zofenopril, indolapril, benazepril, lisinopril, spirapril, trandolapril, perindopril, pentopril, moexipril, rescinamine, and pivopril. For example, the ARB can be selected from: candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan, olmesartan medoxomil, telmisartan, valsartan, azilsartan medoxomil, and BRA-657.

[00221] In some embodiments, the subject is also being administered one or more additional agents. In some embodiments, the one or more additional agents are selected from calcineurin inhibitors, proteasome inhibitors, aminoquinolines, complement inhibitors, B-cell inhibitors, cytotoxic agents, mTOR inhibitors, sodium/glucose cotransporter-2 inhibitors (SGLT2i), and steroids. In some embodiments, the dosage of the one or more additional agents is decreased after between about 15 days to about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the one or more additional agents are immunosuppressants.

[00222] In some embodiments, the subject is not currently receiving one or more additional agents. In certain embodiments, the subject has not used one or more additional agent for two or more weeks within the 6 months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof.

[00223] In some embodiments, the one or more additional agents are selected from calcineurin inhibitors, proteasome inhibitors, aminoquinolines, complement inhibitors, B-cell inhibitors, cytotoxic agents, mTOR inhibitors, steroids, and combinations thereof.

[00224] In certain embodiments, the one or more additional agents are steroids. For example, the one or more additional agents can be selected from the group consisting of prednisone, dexamethasone, hydrocortisone, ciclosporin, and combinations of any of the foregoing.

[00225] In certain embodiments, the one or more additional agents are aminoquinolines. For example, the one or more additional agents can be hydroxychloroquine.

[00226] In some embodiments, the subject is receiving one or more additional agents at the time of treatment with atrasentan. In certain embodiments, the dosage of the one or more additional agents is decreased after treatment with atrasentan, or a pharmaceutically acceptable salt thereof (e.g., after 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 7 weeks, 8 weeks, 9 weeks, 10 weeks, 20 weeks, 30 weeks, 40 weeks, 50 weeks, 60 weeks, 70 weeks, 80 weeks, 90 weeks, 100 weeks, 110 weeks, 120 weeks, 130 weeks, 140 weeks, 150 weeks, 160 weeks, 170 weeks, 180 weeks, 190 weeks, or 200 weeks of treatment). In certain of these embodiments, the dosage of the one or more additional agents is decreased after between about 15 days to about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain of the foregoing embodiments, the additional agent dosage is decreased by about 10% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 15% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 20% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 25% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 30% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 35% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 40% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 45% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 50% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 55% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 60% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 65% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 70% to about 100%. In

certain embodiments, the additional agent dosage is decreased by about 75% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 80% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 85% to about 100%. In certain embodiments, the additional agent dosage is decreased by about 90% to about 100%. In certain of the foregoing embodiments, the dosage of the one or more additional agents is decreased after between about 15 days to about 30 days (e.g., about 15 days, about 20 days, about 25 days, or about 30 days) of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. When the dosage of additional agent is decreased by 100% as described herein, the subject is no longer needing additional agent.

[00227] In certain embodiments, the dosage of one or more steroids is decreased after treatment with atrasentan, or a pharmaceutically acceptable salt thereof, for example, after between about 15 days to about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the steroid dosage is decreased by about 10% to about 100%, as described herein. In some embodiments, the dosage of prednisone, dexamethasone, hydrocortisone, ciclosporin, or a combination of any of the foregoing is reduced by about 10% to about 100% after treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00228] In certain embodiments, the dosage of one or more aminoquinolines is decreased after treatment with atrasentan, or a pharmaceutically acceptable salt thereof, for example, after between about 15 days to about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the aminoquinoline dosage is decreased by about 10% to about 100%, as described herein. In some embodiments, the dosage of hydroxychloroquine is reduced by about 10% to about 100% after treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00229] In some embodiments, the subject is concomitantly receiving one or more additional therapeutic agents. The one or more additional therapeutic agents are described herein. For example, the subject is concomitantly receiving an inhibitor of one or more elements of the renin-angiotensin-aldosterone system. In certain embodiments, the subject is concomitantly receiving a SGLT-2 inhibitor, an ACE inhibitor, an ARB, a statin, a diuretic, a calcium channel blocker, a beta blocker, an aldosterone antagonist, fish oil, hydroxychloroquine, or a combination of any of the foregoing. In certain of these embodiments, the subject is concomitantly receiving a

SGLT-2 inhibitor. In certain of these embodiments, the subject is concomitantly receiving an ACE inhibitor, an ARB, or a combination thereof. In certain embodiments, the subject is concomitantly receiving one or more statins, such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin. In certain embodiments, the subject is concomitantly receiving one or more diuretics, such as hydrochlorothiazide, trichlormethiazide, hydroflumethiazide, quinethazone, metolazone, chlorothiazide, chlorthalidone, indapamide, methyclothiazide, bumetanide, torsemide, piretanide, ethacrynic acid, bumetanide, furosemide, triamterene, spironolactone, eplerenone, and amiloride. In certain embodiments, the subject is concomitantly receiving a SGLT-2 inhibitor, such as canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin. In certain embodiments, the subject is concomitantly receiving one or more ACE inhibitors, such as quinapril, fosinopril, perindopril, captopril, enalapril, enalaprilat, ramipril, cilazapril, delapril, fosinopril, zofenopril, indolapril, benazepril, lisinopril, spirapril, trandolapril, perindopril, pentopril, moexipril, rescinamine, and pivopril. In certain embodiments, the subject is concomitantly receiving an ARB, such as candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan, olmesartan medoxomil, telmisartan, valsartan, azilsartan medoxomil, and BRA-657. In certain embodiments, the subject is concomitantly receiving a diuretic and an ACE inhibitor or an ARB. In certain embodiments, the subject is concomitantly receiving a diuretic, an ACE inhibitor, and an ARB. In certain embodiments, the subject is concomitantly receiving a diuretic and a SGLT-2 inhibitor, and an ACE inhibitor or an ARB. In certain embodiments, the subject is concomitantly receiving a diuretic, a SGLT-2 inhibitor, an ACE inhibitor, and an ARB. In certain embodiments, the subject concomitantly receiving one or more additional therapeutic agents has not previously received the one or more therapeutic agents. For example, a subject that is concomitantly receiving a SGLT-2 inhibitor that has not previously received a SGLT-2 inhibitor.

[00230] In some embodiments, the subject has previously received, but is not concomitantly receiving, one or more additional therapeutic agents such as those described herein. For example, the subject is has previously received, but is not concomitantly receiving a SGLT-2 inhibitor, an ACE inhibitor, an ARB, a statin, a diuretic, a calcium channel blocker, a beta blocker, an aldosterone antagonist, fish oil, hydroxychloroquine, or a combination of any of the foregoing, as described herein. In certain of these embodiments, the subject has previously received, but is not concomitantly receiving a SGLT-2 inhibitor.

[00231] In some embodiments, the subject has cellular glomerular crescents present in about $\leq 25\%$ of glomeruli within 6 months prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. For example, the subject can have cellular glomerular crescents present in about 25%, about 20%, about 15%, about 10%, about 5%, or about 1%, or any value in between, of glomeruli. In some embodiments, the subject does not have cellular glomerular crescents present in the glomeruli. In certain embodiments, the subject is not under clinical suspicion of rapidly progressive glomerulonephritis (RPGN).

[00232] In some embodiments, the subject has not undergone organ transplantation prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof.

[00233] In some embodiments, the subject has a systolic blood pressure of below about 160 mmHg prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. For example, the subject can be a systolic blood pressure of below about 155 mmHg, below about 150 mmHg, below about 145 mmHg, or below about 140 mmHg. In some embodiments, the subject has a diastolic blood pressure of below about 100 mmHg prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. For example, the subject can have a diastolic blood pressure of below about 100 mmHg, below about 95 mmHg, or below about 90 mmHg. In some embodiments, the subject has a systolic blood pressure of between about 100 mm Hg and about 130 mm Hg and a diastolic blood pressure of about 70 mm Hg to about 90 mm Hg.

[00234] In some embodiments, the subject has not been diagnosed with heart failure prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has not been previously admitted to hospital for conditions relating to fluid overload prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. Non-limiting examples of conditions include uncontrolled peripheral edema, pleural effusion, or ascites. In some embodiments, the subject has not been diagnosed with clinically significant liver disease prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the transaminase or bilirubin values of the subject are no more than twice the normal upper limit prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. For example, the ALT level of the subject is below about 110 U/L (e.g., below about 100 U/L, below 90 U/L, below about 80 U/L, below about 70 U/L, below about 60 U/L, below about 50 U/L, or below about 40 U/L, or any value in between). As

another example, the AST level of the subject is below 100 U/L (e.g., below 90 U/L, below about 80 U/L, below about 70 U/L, below about 60 U/L, below about 50 U/L, or below about 40 U/L, or any value in between). As yet another example, the bilirubin level of the subject is below about 2.5 mg/dL (e.g., below about 2 mg/dL, below about 1.5 mg/dL, below about 1.4 mg/dL, below about 1.3 mg/dL, below about 1.2 mg/dL, below about 1.1 mg/dL, below about 1.0 mg/dL, or below about 0.9 mg/dL, or any value in between).

[00235] In some embodiments, the subject has a hemoglobin level of above about 9 g/dL (e.g., above about 10 g/dL, about 11 g/dL, about 12 g/dL, or about 13 g/dL, or any value in between) prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has not received blood transfusion for anemia for at least about 3 months (e.g., at least about 4 months, about 5 months, about 6 months, or about one year) prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has not been diagnosed with cancer for at least 5 years prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has not been diagnosed with cancer (e.g., lung cancer or prostate cancer) for at least 5 years prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has not been diagnosed with cancer for at least 5 years prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof, unless the cancer is nonmelanoma skin cancer not requiring ongoing treatment. In some embodiments, the subject does not have cancer prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof, unless the cancer is nonmelanoma skin cancer not requiring ongoing treatment. In some embodiments, the subject does not suffer from cancer prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof, unless the cancer is nonmelanoma skin cancer not requiring ongoing treatment. In some embodiments, the subject is not being treated for cancer for at least 5 years prior to the first administration of atrasentan or a pharmaceutically acceptable salt thereof, unless the cancer is nonmelanoma skin cancer not requiring ongoing treatment.

[00236] In some embodiments of the methods, uses, or product for uses herein, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure. In some embodiments of the methods, uses, or product for uses herein, the subject has not been previously diagnosed with one or more of diabetic nephropathy,

HIV/AIDS, cancer (e.g., prostate cancer or lung cancer), or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, prostate cancer, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV-related nephropathy, cancer (e.g., lung cancer, or prostate cancer), or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV-related nephropathy, or acute kidney failure. In certain embodiments, the subject has not been previously diagnosed with diabetic nephropathy. In certain embodiments, the subject has not been previously diagnosed with HIV/AIDS. In certain embodiments, the subject has not been previously diagnosed with acute kidney failure. In certain embodiments, the subject has not been previously diagnosed with HIV-related nephropathy. In certain embodiments, the subject has not been diagnosed with cancer. In certain embodiments, the subject has not been diagnosed with prostate cancer. In certain embodiments, the subject has not been diagnosed with lung cancer. In certain embodiments, the subject has not been previously diagnosed with any one of diabetic nephropathy, HIV/AIDS, and acute kidney failure. In certain embodiments, the subject has not been previously diagnosed with any one of diabetic nephropathy, HIV/AIDS, prostate cancer, and acute kidney failure. In certain embodiments, the subject has not been previously diagnosed with any one of diabetic nephropathy, HIV-related nephropathy, prostate cancer, and acute kidney failure. In certain embodiments, the subject has not been previously diagnosed with any one of diabetic nephropathy, HIV-related nephropathy, and acute kidney failure. In some embodiments of the methods, uses, or product for uses herein, the subject has not been previously diagnosed with diabetes. In some embodiments of the methods, uses, or product for uses herein, the subject has not been previously diagnosed with Type 2 diabetes. In certain of the foregoing embodiments, the subject has been determined to have controlled serum glucose levels as described anywhere herein.

[00237] In some embodiments, the subject does not have one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure. In some embodiments, the subject does not have one or more of diabetic nephropathy, HIV/AIDS, prostate cancer, or acute kidney failure. In some embodiments, the subject does not have one or more of diabetic nephropathy, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject does not

have one or more of diabetic nephropathy, HIV-related nephropathy, or acute kidney failure. In certain embodiments, the subject does not have diabetic nephropathy. In certain embodiments, the subject does not have HIV/AIDS. In certain embodiments, the subject does not have acute kidney failure. In certain embodiments, the subject does not have HIV-related nephropathy. In certain embodiments, the subject does not have prostate cancer. In certain embodiments, the subject does not have any one of diabetic nephropathy, HIV/AIDS, and acute kidney failure. In certain embodiments, the subject does not have any one of diabetic nephropathy, HIV/AIDS, prostate cancer, and acute kidney failure. In certain embodiments, the subject does not have any one of diabetic nephropathy, HIV-related nephropathy, prostate cancer, and acute kidney failure. In certain embodiments, the subject does not have any one of diabetic nephropathy, HIV-related nephropathy, and acute kidney failure. In some embodiments, the subject does not have diabetes. In some embodiments, the subject does not have Type 2 diabetes. In certain of the foregoing embodiments, the subject has been determined to have controlled serum glucose levels as described anywhere herein.

[00238] In some embodiments, the subject does not suffer from one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure. In some embodiments, the subject does not suffer from one or more of diabetic nephropathy, HIV/AIDS, prostate cancer, or acute kidney failure. In some embodiments, the subject does not suffer from one or more of diabetic nephropathy, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject does not suffer from one or more of diabetic nephropathy, HIV-related nephropathy, or acute kidney failure. In certain embodiments, the subject does not suffer from diabetic nephropathy. In certain embodiments, the subject does not suffer from HIV/AIDS. In certain embodiments, the subject does not suffer from acute kidney failure. In certain embodiments, the subject does not suffer from HIV-related nephropathy. In certain embodiments, the subject does not suffer from prostate cancer. In certain embodiments, the subject does not suffer from any one of diabetic nephropathy, HIV/AIDS, and acute kidney failure. In certain embodiments, the subject does not suffer from any one of diabetic nephropathy, HIV/AIDS, prostate cancer, and acute kidney failure. In certain embodiments, the subject does not suffer from any one of diabetic nephropathy, HIV-related nephropathy, prostate cancer, and acute kidney failure. In certain embodiments, the subject does not suffer from any one of diabetic nephropathy, HIV-related nephropathy, and acute kidney failure. In some embodiments, the subject does not

suffer from diabetes. In some embodiments, the subject does not suffer from Type 2 diabetes. In certain of the foregoing embodiments, the subject has been determined to have controlled serum glucose levels as described anywhere herein.

[00239] In some embodiments, the subject is not being treated for one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure. In some embodiments, the subject is not being treated for one or more of diabetic nephropathy, HIV/AIDS, prostate cancer, or acute kidney failure. In some embodiments, the subject is not being treated for one or more of diabetic nephropathy, HIV-related nephropathy, prostate cancer, or acute kidney failure. In some embodiments, the subject is not being treated for one or more of diabetic nephropathy, HIV-related nephropathy, or acute kidney failure. In certain embodiments, the subject is not being treated for diabetic nephropathy. In certain embodiments, the subject is not being treated for HIV/AIDS. In certain embodiments, the subject is not being treated for acute kidney failure. In certain embodiments, the subject is not being treated for HIV-related nephropathy. In certain embodiments, the subject is not being treated for prostate cancer. In certain embodiments, the subject is not being treated for any one of diabetic nephropathy, HIV/AIDS, and acute kidney failure. In certain embodiments, the subject is not being treated for any one of diabetic nephropathy, HIV/AIDS, prostate cancer, and acute kidney failure. In certain embodiments, the subject is not being treated for any one of diabetic nephropathy, HIV-related nephropathy, prostate cancer, and acute kidney failure. In certain embodiments, the subject is not being treated for any one of diabetic nephropathy, HIV-related nephropathy, and acute kidney failure. In some embodiments, the subject is not being treated for diabetes. In some embodiments, the subject is not being treated for Type 2 diabetes. In certain of the foregoing embodiments, the subject has been determined to have controlled serum glucose levels as described anywhere herein.

[00240] In some embodiments, the subject has been determined to have controlled serum glucose levels; or the subject has not been diagnosed with one or more of HIV-related nephropathy or acute kidney failure. In certain embodiments, the subject has been determined to have controlled serum glucose levels. For example, the subject has been determined to have a fasting serum glucose level of below about 130 mg/dL, about 125 mg/dL, about 120 mg/dL, about 115 mg/dL, about 110 mg/dL, about 105 mg/dL, about 100 mg/dL, about 95 mg/dL, about 90 mg/dL, about 85 mg/dL, about 80 mg/dL, or about 75 mg/dL, or any value in between. In certain embodiments, the subject has not been diagnosed with one or more of HIV-related nephropathy or

acute kidney failure. In certain embodiments, the subject has been determined to have controlled serum glucose levels as described anywhere herein; and the subject has not been diagnosed with one or more of HIV-related nephropathy or acute kidney failure.

[00241] In some embodiments, the subject has not been previously diagnosed with a chronic kidney disease that is other than FSGS. Non-limiting examples include a diabetic kidney disease, a hypertensive kidney disease, IgA nephropathy, or a primary glomerulopathy that is determined to not be associated with FSGS. In certain embodiments, the subject has not been previously diagnosed with a diabetic kidney disease. In certain embodiments, the subject has not been previously diagnosed with a hypertensive kidney disease. In certain embodiments, the subject has not been diagnosed with a primary glomerulopathy that is determined to not be associated with FSGS.

[00242] In some embodiments, the subject does not have a chronic kidney disease that is other than FSGS. Non-limiting examples include a diabetic kidney disease, a hypertensive kidney disease, or a primary glomerulopathy that is determined to not be associated with FSGS. In certain embodiments, the subject does not have a diabetic kidney disease. In certain embodiments, the subject does not have a hypertensive kidney disease. In certain embodiments, the subject does not have a primary glomerulopathy that is determined to not be associated with FSGS.

[00243] In some embodiments, the subject does not suffer from a chronic kidney disease that is other than FSGS. Non-limiting examples include a diabetic kidney disease, a hypertensive kidney disease, or a primary glomerulopathy that is determined to not be associated with FSGS. In certain embodiments, the subject does not suffer from a diabetic kidney disease. In certain embodiments, the subject does not suffer from a hypertensive kidney disease. In certain embodiments, the subject does not suffer from a primary glomerulopathy that is determined to not be associated with FSGS.

[00244] In some embodiments, the subject is not being treated for a chronic kidney disease that is other than FSGS. Non-limiting examples include a diabetic kidney disease, a hypertensive kidney disease, or a primary glomerulopathy that is determined to not be associated with FSGS. In certain embodiments, the subject is not being treated for a diabetic kidney disease. In certain embodiments, the subject is not being treated for a hypertensive kidney disease. In

certain embodiments, the subject is not being treated for a primary glomerulopathy that is determined to not be associated with FSGS.

IV. TREATMENT OUTCOME

[00245] In some embodiments of the methods, uses, or product for uses herein, renal inflammation is decreased after treatment with atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, renal inflammation in the subject is decreased by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In some embodiments, the renal inflammation in the subject is decreased by at least about 20%, about 30%, about 40%, about 50%, about 60% about 70% about 80%, about 90%, or about 95%, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00246] In some embodiments, renal fibrosis is decreased after treatment with atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, renal fibrosis in the subject is decreased by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the renal fibrosis in the subject is decreased by at least about 20%, about 30%, about 40%, about 50%, about 60% about 70% about 80%, about 90%, or about 95%, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00247] In some embodiments, renal fibrosis in the subject is decreased to less than about 50% of the cortical area after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, renal fibrosis in the subject is decreased to less than about 40% of the cortical area. For example, in some embodiments, renal fibrosis in the subject is decreased to less than about 35%, about 30%, about 25%, about 20%, about 15%, or about 10%, or any value in between, of the cortical area. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00248] In some embodiments, the rate of decrease in eGFR of the subject is reduced by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, 2 weeks, 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the rate of decrease in eGFR of the subject is reduced by at least about 20%. For example, in some embodiments, the rate of decrease in eGFR of the subject is reduced by at least about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95%, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 6 months and about 1 year.

[00249] In some embodiments, the rate of decrease in eGFR of the subject is reduced to below about 10 mL/min per year after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about

4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In some embodiments, the rate of decrease in eGFR of the subject is reduced to below about 9 mL/min per year. For example, in some embodiments, the rate of decrease in eGFR of the subject is reduced to below about 8 mL/min per year, about 7 mL/min per year, about 6 mL/min per year, about 5 mL/min per year, about 4 mL/min per year, about 3 mL/min per year, about 2 mL/min per year, or about 1 mL/min per year, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 6 months and about 1 year.

[00250] In some embodiments, the risk of the subject developing ESKD is reduced by about 20% to about 99% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). For example, the risk of the subject developing ESKD can be reduced by about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, or about 99%, or any value in between. In certain of the foregoing embodiments, the subject has been treated for between about 90 days to about 180 days. In certain embodiments, the risk of the subject developing ESKD is reduced by about 20% to about 99% after between about 90 and about 180 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 6 months and about 1 year.

[00251] In some embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below about 15 mL/min/1.73m². In certain embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below 15 mL/min/1.73m² by at least about 10%. For example, in some embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below about 15 mL/min/1.73m² by at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 100%, about 150%, about 200%, about 250%, about 300%, about 350%, about 400%, about 450%, or about 500%, or any value in between.

[00252] In some embodiments, the method increases the time between the diagnosis of FSGS in the subject and the time when eGFR of the subject falls below 15 mL/min/1.73m² by at least about 1 year. For example, the method can delay the time when eGFR of the subject falls below 15 mL/min/1.73m² by at least about 1.5 years, about 2 years, about 2.5 years, about 3 years, about 3.5 years, about 4 years, about 4.5 years, about 5 years, about 5.5 years, about 6 years, about 6.5 years, about 7 years, about 7.5 years, about 8 years, about 8.5 years, about 9 years, about 9.5 years, about 10 years, about 11 years, about 12 years, about 13 years, about 15 years, about 15 years, about 16 years, about 17 years, about 18 years, about 19 years, or about 20 years, or any value in between.

[00253] In some embodiments, the method reduces the average rate of decrease in eGFR by from about 0.75 mL/min/year to about 75 mL/min/year for at least about 3 months (e.g., at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months, at least about a year, at least about 1.5 years, or at least about 2 years) prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. For example, the method reduces the average rate of decrease in eGFR by about 0.75 mL/min/year, about 1 mL/min/year, about 1.5 mL/min/year, about 2 mL/min/year, about 2.5 mL/min/year, about 3 mL/min/year, about 3.5 mL/min/year, about 4 mL/min/year, about 4.5 mL/min/year, about 5 mL/min/year, about 5.5 mL/min/year, or about 6 mL/min/year. In some embodiments, the method reduces the average rate of decrease in eGFR by from about 4 mL/min/year to about 5 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the method reduces the average rate of decrease in

eGFR by from about 3 mL/min/year to about 6 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the method reduces the average rate of decrease in eGFR by from about 4 mL/min/year to about 5 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the decrease in eGFR in mL/min/year refers to units per 1.73m^2 .

[00254] In some embodiments, the method reduces the average rate of decrease in eGFR by from about 15% to about 70% (about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, or about 70%) after between about 6 months and about 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the average rate of decrease in eGFR may be reduced by about 15%, after about 6 months, 9, months, 12 months, 15 months, 18 months, 21 months, or 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the average rate of decrease in eGFR may be reduced by about 20%, after about 6 months, 9, months, 12 months, 15 months, 18 months, 21 months, or 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the average rate of decrease in eGFR may be reduced by about 25%, after about 6 months, 9, months, 12 months, 15 months, 18 months, 21 months, or 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the average rate of decrease in eGFR may be reduced by about 30%, after about 6 months, 9, months, 12 months, 15 months, 18 months, 21 months, or 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00255] In another aspect, provided herein is a method of decreasing proteinuria, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.

[00256] In some embodiments, the amount of protein (e.g., albumin) in the urine of the subject is reduced by at least about 10% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks,

about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In some embodiments, the amount of protein in the urine of the subject is reduced by at least about 15%. For example, in some embodiments, the amount of protein in the urine of the subject is reduced by at least about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, or about 95%, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 10 weeks to about 24 weeks. In some instances, the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 10 weeks (e.g., after about 10 weeks, about 11 weeks, about 12 weeks, about 13 weeks, about 14 weeks, about 15 weeks, about 16 weeks, about 17 weeks, about 18 weeks, about 19 weeks, about 20 weeks, about 21 weeks, about 22 weeks, about 23 weeks, about 24 weeks, about 25 weeks, about 26 weeks, about 27 weeks, about 28 weeks, about 29 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks) of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some instances, the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 12 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some instances, the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 12 weeks to about 24 weeks (and all ranges inclusive) of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some instances, the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00257] In certain embodiments, the amount of protein (e.g., albumin) in the urine of the subject is reduced by about 20% to about 80% after between about 15 day and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 25% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 30% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 35% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 40% to about 80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 45% to about

80%. In certain of these embodiments, the amount of protein in the urine of the subject is reduced by about 50% to about 80%.

[00258] In some embodiments, the amount of protein (e.g., albumin) in the urine of the subject is reduced by about 100 mg/dL to about 3,000 mg/dL after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 2,500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 2,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 1,500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 1,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 400 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 300 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 100 mg/dL to about 200 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 2,500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 2,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 1,500 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 1,000 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 900 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 500 mg/dL to about 800 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 600 mg/dL to about 900 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 700 mg/dL to

about 900 mg/dL. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 1,000 mg/dL to about 2,000 mg/dL. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00259] In certain embodiments, the amount of protein (e.g., albumin) in the urine of the subject is reduced by about 100 mg/dL to about 500 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 200 mg/dL to about 500 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 300 mg/dL to about 500 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00260] In certain embodiments, the amount of protein (e.g., albumin) in the urine of the subject is reduced by about 500 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 600 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In certain embodiments, the amount of protein in the urine of the subject is reduced by about 700 mg/dL to about 900 mg/dL after between about 15 days and about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00261] In some embodiments, the subject has a reduced level of protein (e.g., albumin) in the urine of below about 1.0 gram/day after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks). In some embodiments, the subject has a reduced level of protein in the urine of below about 0.9 gram/day. For example, in some embodiments, the subject has a reduced level of protein in the urine of below about 0.8 gram/day, about 0.7 gram/day, about 0.6 gram/day, 0.5 gram/day, about 0.4 gram/day, about 0.3

gram/day, or about 0.2 gram/day, or any value in between. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days.

[00262] In another aspect, provided herein is a method of decreasing fatigue, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof. Fatigue can be measured using methods known in the art. *See e.g.*, Machado. M., Int J Dermatol, 2021 Sep;60(9):1053-1069, which is incorporated by reference in its entirety.

[00263] In some embodiments, the subject is between about 15 and about 40 years old. In some embodiments, the subject is between about 15 to about 25 years old, about 20 to about 30 years old, about 25 to about 35 years old, about 30 to about 40 years old, or any age in between. In some embodiments, the subject is between about 20 to about 30 years old, or any age in between. In some embodiments, the subject is about 20 years old, about 21 years old, about 22 years old, about 23 years old, about 24 years old, about 25 years old, about 26 years old, about 27 years old, about 28 years old, about 29 years old, or about 30 years old.

[00264] In some embodiments, the level of fatigue of the patient is reduced following treatment with atrasentan or a pharmaceutically acceptable salt thereof. In some embodiments, the fatigue is reduced by about 5% to about 80% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In certain embodiments, the fatigue is reduced by about 10% to about 75%. In certain embodiments, the fatigue is reduced by about 10% to about 70%. In certain embodiments, the fatigue is reduced by about 10% to about 65%. In certain embodiments, the fatigue is reduced by about 10% to about 60%. In certain embodiments, the fatigue is reduced by about 10% to about 55%. In certain embodiments, the fatigue is reduced by about 10% to about 50%. In certain embodiments, the fatigue is reduced by about 10% to about 45%. In certain embodiments, the fatigue is reduced by about 10% to about 40%. In certain embodiments, the fatigue is reduced by about 10% to about

35%. In certain embodiments, the fatigue is reduced by about 10% to about 30%. In certain embodiments, the fatigue is reduced by about 10% to about 25%. In certain embodiments, the fatigue is reduced by about 10% to about 20%. In certain embodiments, the fatigue is reduced by about 10% to about 15%. In certain of the foregoing embodiments, the subject has been treated with atrasentan or a pharmaceutically acceptable salt thereof for between about 15 days and about 30 days. In certain embodiments, the decrease in fatigue comprises a decrease in the score on one or more of the Fatigue Severity Scale, the Chalder Fatigue Scale, the FACIT Fatigue Scale, the Brief Fatigue Inventory, the FACT-F Subscale, Global Vigor and Affect, the May and Kline Adjective Checklist, the Pearson-Byars Fatigue Feeling Checklist, the Rhoten Fatigue Scale, the Schedule of Fatigue and Anergia, or the Checklist Individual Strength.

[00265] Some embodiments provide a method of inhibiting mesangial cell activation in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject; wherein the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure.

[00266] Some embodiments provide a method of inhibiting PDGF signaling activity (e.g., decreasing the expression and/or activity of one or more of PIK3R1, PDGFRA, NFKBIA, PIK3CG, PLA2G4A, TIAM1, PDGFB, NFKB1, and MAP3K1) in a mesangial cell in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject; wherein the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure.

[00267] Some embodiments provide a method of inhibiting mesangial cell activation, comprising contacting a mesangial cell with an effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[00268] In some embodiments, the mesangial activation is induced by IgA immune complexes. In some embodiments, the mesangial activation is associated with the presence of IgA immune complexes. The presence and/or amount of IgA immune complexes can be detected by a variety of methods. For example, the complexes may be detected in serum or urine, and can also be detected in a kidney biopsy sample.

[00269] In some embodiments, the inhibiting of mesangial cell activation comprises reducing expression and/or activity of one or more biomarkers indicative of mesangial cell proliferation. In some embodiments, inhibiting of mesangial cell activation comprises reducing mesangial cell inflammation. In some embodiments, reducing mesangial cell inflammation comprises reducing expression and/or activity of one or more of IL6, MCP1, or other biomarkers indicative of mesangial cell inflammation. In some embodiments, reducing mesangial cell inflammation comprises reducing expression and/or activity of IL-6. In some embodiments, the expression and/or activity of one or more biomarkers indicative of mesangial cell inflammation is reduced by about 25% to about 99% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In some embodiments, the expression and/or activity of one or more biomarkers indicative of mesangial cell inflammation is reduced by about 25% to about 50%, about 40% to about 60%, about 50% to about 75%, about 60% to about 80%, about 75% to about 90%, about 85% to about 99%, or any value in between. For example, in some such embodiments, the one or more biomarkers can be IL-6.

[00270] In some embodiments, inhibiting of mesangial cell activation comprises reducing mesangial cell inflammation. In some embodiments, reducing mesangial cell inflammation comprises reducing IL-6 signaling (e.g., reducing the expression and/or activity in one or more protein involved in an IL-6 signaling pathway, e.g., a reduction in the expression and/or activity of one or more of Cntfr, Il1b, Csf1, Il2ra, Map3k8, and Il1r1). In some embodiments, reducing mesangial cell inflammation comprises reducing the expression and/or activity of one or more (e.g., 1, 2, 3, 4, or 5) of: Cntfr, Il1b, Csf1, Il2ra, Map3k8, Il1r1.

[00271] In some embodiments, the inhibiting of mesangial cell activation comprises reducing the pro-fibrotic response in the mesangial cells. In some embodiments, reducing the pro-fibrotic response in the mesangial cells comprises reducing expression and/or activity of one or more of NF- κ B, TGF, PDGF, CTGF, MMP, TIMPS, or other biomarkers indicative of mesangial cell fibrosis. In some embodiments, the expression and/or activity of one or more of NF- κ B, TGF,

PDGF, CTGF, MMP, and TIMPS, is reduced by about 25% to about 99% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between), relative to the expression and/or activity prior to administration of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the expression and/or activity of one or more of NF- κ B, TGF, PDGF, CTGF, MMP, and TIMPS is reduced by about 25% to about 50%, about 40% to about 60%, about 50% to about 75%, about 60% to about 80%, about 75% to about 90%, about 85% to about 99%, or any value in between.

[00272] In some embodiments, inhibiting of mesangial cell activation comprises reducing the pro-fibrotic response in the mesangial cells. In some embodiments, reducing the pro-fibrotic response comprises reducing NF- κ B signaling. In some embodiments, reducing the pro-fibrotic response comprises reducing the expression and/or activity of one or more (e.g., 1, 2, 3, 4, or 5) of: Pfkfb3, Nr4a1, Gem, Fosl2, Klf4, F3, Nfkb1a, Ifit2, Nr4a2, Klf2, Jag1, Dnajb4, Il1b, Spsb1, Btg2, Atf3, Csf1, Trib1, Zbtb10, Btg1, Rhob, Nfat5, Edn1, Rel, Nr4a3, Nfkb1, Serpine1, Ccl20, Per1, Cxcl2, Map3k8, Traf1, and/or increasing the expression and/or activity of one or more (e.g., 1, 2, 3, 4, or 5) of: Ehd1, Snn, Tnfaip8, Ackr3, Id2, Ccn1, Efna1, Ccnd1, Cdkn1a, Pnrc1 (in cases where the component inhibits NF- κ B signaling).

[00273] In some embodiments, reducing the pro-fibrotic response comprises reducing PDGF signaling. In some embodiments, reducing the pro-fibrotic response comprises reducing the expression and/or activity of one or more (e.g., 1, 2, 3, 4, or 5) of: Pik3r1, Pdgfra, Nfkb1a, Pik3cg, Pla2g4a, Tiam1, Pdgfb, Nfkb1, and/or increasing the expression and/or activity of one or more (e.g., 1, 2, 3, 4, or 5) of: Hras (in cases where the component inhibits PDGF signaling).

[00274] In some embodiments, the expression and/or activity of NF- κ B and/or PDGF expression and/or activity, is reduced by about 25% to about 99% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about

50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between), relative to the expression and/or activity prior to administration of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the expression and/or activity of NF- κ B and/or PDGF is reduced by about 25% to about 50%, about 40% to about 60%, about 50% to about 75%, about 60% to about 80%, about 75% to about 90%, about 85% to about 99%, or any value in between.

[00275] In some embodiments, reducing the pro-fibrotic response in the mesangial cells comprises reducing matrix secretion by mesangial cells. In some embodiments, reducing matrix secretion by mesangial cells comprises reducing expression and/or activity of one or more of excess matrix secretion by mesangial cells.

[00276] Some embodiments provide a method of reducing activation of a mesangial cell in contact with an IgA immune complex, comprising contacting a mesangial cell with an effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, reducing activation of a mesangial cell comprises reducing expression and/or activity of one or more biomarkers indicative of mesangial cell proliferation.

[00277] In some embodiments, reducing activation of a mesangial cell comprises reducing mesangial cell inflammation. In some embodiments, reducing mesangial cell inflammation comprises reducing expression and/or activity of one or more of IL6, MCP1, or other biomarkers indicative of mesangial cell inflammation.

[00278] In some embodiments, reducing activation of a mesangial cell comprises reducing the pro-fibrotic response in the mesangial cells. In some embodiments, reducing the pro-fibrotic response in the mesangial cells comprises reducing expression and/or activity of one or more of TGF, PDGF, CTGF, MMP, TIMPS, or other biomarkers indicative of mesangial cell fibrosis.

[00279] In some embodiments, reducing the pro-fibrotic response in the mesangial cells comprises reducing matrix secretion by mesangial cells. In some embodiments, reducing matrix secretion by mesangial cells comprises reducing expression and/or activity of one or more biomarkers indicative of excess matrix secretion by mesangial cells.

[00280] In some embodiments, the reducing activation of a mesangial cell comprises reducing undesired mesangial cell migration. In some embodiments, the reduction in undesired mesangial cell migration occurs after about 15 days to about 30 days after treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the reduction in undesired mesangial cell migration occurs after about 3 months to about 6 months after treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00281] In some embodiments, the reducing activation of a mesangial cell comprises reducing undesired mesangial cell proliferation. In some embodiments, the reduction in undesired mesangial cell proliferation occurs after about 15 days to about 30 days after treatment with atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the reduction in undesired mesangial cell proliferation occurs after about 3 months to about 6 months after treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

[00282] In some embodiments, the undesired mesangial cell proliferation is reduced by about 25% to about 99% after treatment with atrasentan or a pharmaceutically acceptable salt thereof (e.g., after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between). In some embodiments, the undesired mesangial cell proliferation is reduced by about 25% to about 50%, about 40% to about 60%, about 50% to about 75%, about 60% to about 80%, about 75% to about 90%, about 85% to about 99%, or any value in between.

[00283] In some embodiments, mesangial cell activation can be assessed by one or more of serum analysis, urinalysis, and microscopy of a kidney biopsy sample (e.g., light microscopy and/or immunofluorescence microscopy).

[00284] In some embodiments, the contacting occurs *in vitro*. In some embodiments, the contacting occurs *in vivo*.

[00285] Some embodiments provide a method of treating FSGS in a subject in need thereof, comprising: a) determining that the subject has elevated serum Gd-IgA1 levels; and b) administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable

salt thereof, to the subject. In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with HIV-related nephropathy. In some embodiments, the subject has not been previously diagnosed with cancer. In some embodiments, the cancer is lung cancer or prostate cancer.

[00286] Some embodiments provide a method of treating FSGS in a subject in need thereof, comprising: a) determining that the subject has elevated levels of mesangial activation; and b) administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject.

[00287] In some embodiments, determining of elevated levels of mesangial activation comprises obtaining a sample from the subject and assessing the level of mesangial activation in the same. In some embodiments, the sample is a kidney biopsy sample. In some embodiments, the sample is selected from a blood sample, a urine sample, a kidney biopsy sample, or a combination of two or three of the foregoing.

[00288] In some embodiments, the sample exhibits elevated levels of one or more of: matrix secretion by the mesangial cells, IgA-immune complex deposition, mesangial cell proliferation, and endocapillary cell proliferation. In some embodiments, the sample exhibits elevated levels of IgA-immune complex deposition.

[00289] Some embodiments provide a method of treating FSGS in a subject in need thereof, comprising: a) determining that the subject does not have one or more of an acute kidney injury, diabetic nephropathy, IgA nephropathy, sickle cell nephropathy, HIV/AIDS, or acute kidney failure; b) determining that the subject has elevated serum Gd-IgA1 levels; and c) administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject.

[00290] Some embodiments provide a method of treating FSGS in a subject in need thereof, comprising: a) determining that the subject does not have one or more of diabetic nephropathy, IgA nephropathy, sickle cell nephropathy, HIV/AIDS, or acute kidney failure; b) determining that the subject has elevated serum Gd-IgA1 levels; and c) administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject.

[00291] Some embodiments provide a method of treating FSGS in a subject in need thereof, comprising: a) determining that the subject does not have one or more of an acute kidney injury, diabetic nephropathy, IgA nephropathy, sickle cell nephropathy, HIV/AIDS, or acute kidney failure; b) determining that the subject has elevated levels of mesangial activation; and c) administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject.

[00292] Some embodiments provide a method of treating FSGS in a subject in need thereof, comprising: a) determining that the subject does not have one or more of diabetic nephropathy, IgA nephropathy, sickle cell nephropathy, HIV/AIDS, or acute kidney failure; b) determining that the subject has elevated levels of mesangial activation; and c) administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject.

[00293] In some embodiments, the subject has been determined to have proteinuria of at least about 1 g/day in at least two of three consecutive readings over the year prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has been determined to have proteinuria of about 1 g/day to about 15 g/day in at least two of three consecutive readings over the year prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. For example, about 1 g/day, about 1.2 g/day, about 1.4 g/day, about 1.6 g/day, about 1.8 g/day, or 2 g/day, about 2.5 g/day, about 3 g/day, about 3.5 g/day, about 4 g/day, about 4.5 g/day, about 5 g/day, about 6 g/day, about 7 g/day, about 8 g/day, about 9 g/day, about 10 g/day, about 11 g/day, about 12 g/day, about 13 g/day, about 14 g/day, or about 15 g/day.

[00294] In some embodiments, the subject has been administered a maximally tolerated stable dose of a RAS inhibitor for at least 12 weeks prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is concurrently administered a maximally tolerated stable dose of a RAS inhibitor and a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the RAS inhibitor is an angiotensin-converting enzyme inhibitor. In some embodiments, the RAS inhibitor is an angiotensin receptor blocker (ARB).

[00295] In some embodiments, the subject has been determined to have an eGFR of at least 30 mL/min/1.73 m² prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has been determined to have an eGFR of about 30 mL/min/1.73 m² to about 60 mL/min/1.73 m² prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[00296] In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with HIV-related nephropathy. In some embodiments, the subject has not been previously diagnosed with cancer. In some embodiments, the cancer is lung cancer or prostate cancer.

[00297] Some embodiments provide a method of treating FSGS in a subject in need thereof, comprising: a) determining that the subject has elevated levels of IgA-immune complexes in the kidney; and b) administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to the subject.

[00298] In some embodiments, determining of elevated levels of IgA-immune complexes in the kidney comprises obtaining a sample from the subject and assessing the level of IgA-immune complexes in the same. In some embodiments, the sample is a kidney biopsy sample. In some embodiments, the sample is selected from a blood sample, a urine sample, a kidney biopsy sample, or a combination of two or three of the foregoing. In some embodiments, the IgA-immune complexes are deposited in the mesangium.

[00299] In some embodiments, the levels of IgA-immune complexes can be assessed by one or more of serum analysis, urinalysis, and microscopy of a kidney biopsy sample (e.g., light microscopy and/or immunofluorescence microscopy).

[00300] In some embodiments, the sample exhibits elevated levels of one or more of: matrix secretion by the mesangial cells, IgA-immune complex deposition in the mesangium, mesangial cell activation, mesangial cell proliferation, and endocapillary cell proliferation.

[00301] In some embodiments, the subject has been determined to have proteinuria of at least about 1 g/day in at least two of three consecutive readings over the year prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has been determined to have proteinuria

of about 1 g/day to about 15 g/day in at least two of three consecutive readings over the year prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. For example, about 1 g/day, about 1.2 g/day, about 1.4 g/day, about 1.6 g/day, about 1.8 g/day, about 2 g/day, about 2.5 g/day, about 3 g/day, about 3.5 g/day, about 4 g/day, about 4.5 g/day, about 5 g/day, about 6 g/day, about 7 g/day, about 8 g/day, about 9 g/day, about 10 g/day, about 11 g/day, about 12 g/day, about 13 g/day, about 14 g/day, or about 15 g/day.

[00302] In some embodiments, the subject has been administered a maximally tolerated stable dose of a RAS inhibitor for at least 12 weeks prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject is concurrently administered a maximally tolerated stable dose of a RAS inhibitor and a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the RAS inhibitor is an angiotensin-converting enzyme inhibitor. In some embodiments, the RAS inhibitor is an angiotensin receptor blocker (ARB).

[00303] In some embodiments, the subject has been determined to have an eGFR of at least 30 mL/min/1.73 m² prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the subject has been determined to have an eGFR of about 30 mL/min/1.73 m² to about 60 mL/min/1.73 m² prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[00304] In some embodiments, the subject has not been previously diagnosed with one or more of diabetic nephropathy, HIV/AIDS, or acute kidney failure. In some embodiments, the subject has not been previously diagnosed with HIV-related nephropathy. In some embodiments, the subject has not been previously diagnosed with cancer. In some embodiments, the cancer is lung cancer or prostate cancer.

[00305] In some embodiments, the methods include determining, in the subject, expression and/or activity of one or more of ET1, TGF, PDGF, CTGF, MMP, TIMPS, IGF1, DPEP1, ASL, AMN, ALPL, SLC6A19, IL-6, and NF-kB. In some embodiments, expression and/or activity are determined prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, expression and/or

activity are determined after administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[00306] In some embodiments, the determining the expression and/or activity is performed prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the determining the expression and/or activity is performed after administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, for example, after treatment for about 1 week, about 2 weeks, about 3 weeks, about 4 weeks, about 5 weeks, about 6 weeks, about 7 weeks, about 8 weeks, about 9 weeks, about 10 weeks, about 20 weeks, about 30 weeks, about 40 weeks, about 50 weeks, about 60 weeks, about 70 weeks, about 80 weeks, about 90 weeks, about 100 weeks, about 110 weeks, about 120 weeks, about 130 weeks, about 140 weeks, about 150 weeks, about 160 weeks, about 170 weeks, about 180 weeks, about 190 weeks, or about 200 weeks, or any value in between.

[00307] In some embodiments, the subject has been determined to have elevated expression and/or activity of one or more of ET1, TGF, PDGF, CTGF, MMP, TIMPS, IGF1, DPEP1, ASL, AMN, ALPL, SLC6A19, IL-6, NF-kB, PKC, PI3K, Src, Ras, ERK1/2, Rho, Rac, Akt, mTOR, NADPH oxidase, MAPK, cPLA₂, TNF- α , IL-1, CAM, COX-2, iNOS, JAK, STAT3, PI3K, Akt/PKB, IKKs, IkBs, NF-kB, MAPK, Ras, Raf, MEK, ERK, MCP1, Cntfr, Il1b, Csf1, Il2ra, Map3k8, Il1r1, Pfkfb3, Nr4a1, Gem, Fosl2, Klf4, F3, Nfkb1a, Ifit2, Nr4a2, Klf2, Jag1, Dnajb4, Il1b, Spsb1, Btg2, Atf3, Csf1, Trib1, Zbtb10, Btg1, Rhob, Nfat5, Edn1, Rel, Nr4a3, Nfkb1, Serpine1, Ccl20, Per1, Cxcl2, Map3k8, Traf1, Pik3r1, Pdgfra, Nfkb1a, Pik3cg, Pla2g4a, Tiam1, and Pdgfb. In some embodiments, the subject has been determined to have elevated expression and/or activity of one or more of ET1, TGF, PDGF, CTGF, MMP, TIMPS, IGF1, DPEP1, ASL, AMN, ALPL, SLC6A19, IL-6, NF-kB, PKC, PI3K, Src, Ras, ERK1/2, Rho, Rac, Akt, mTOR, NADPH oxidase, MAPK, cPLA₂, TNF- α , IL-1, CAM, COX-2, iNOS, JAK, STAT3, PI3K, Akt/PKB, IKKs, IkBs, NF-kB, MAPK, Ras, Raf, MEK, ERK, and MCP1. In some embodiments, the subject has been determined to have elevated expression and/or activity of one or more of Cntfr, Il1b, Csf1, Il2ra, Map3k8, Il1r1, Pfkfb3, Nr4a1, Gem, Fosl2, Klf4, F3, Nfkb1a, Ifit2, Nr4a2, Klf2, Jag1, Dnajb4, Il1b, Spsb1, Btg2, Atf3, Csf1, Trib1, Zbtb10, Btg1, Rhob, Nfat5, Edn1, Rel, Nr4a3, Nfkb1, Serpine1, Ccl20, Per1, Cxcl2, Map3k8, Traf1, Pik3r1, Pdgfra, Nfkb1a, Pik3cg, Pla2g4a, Tiam1, and Pdgfb. In some embodiments, the subject has been determined to

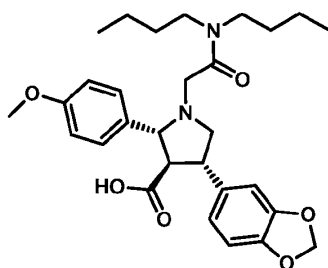
have elevated expression and/or activity of one or more of ET1, TGF, PDGF, CTGF, MMP, TIMPS, IGF1, DPEP1, ASL, AMN, ALPL, SLC6A19, IL-6, and NF-kB. In some embodiments, the subject has been determined to have elevated expression and/or activity of one or more of ET1, TGF, PDGF, CTGF, MMP, TIMPS, IGF1, DPEP1, ASL, AMN, ALPL, and SLC6A19.

[00308] Some embodiments provide a method of treating FSGS in a subject, comprising: (a) determining that the subject has elevated expression and/or activity of one or more of ET1, TGF, PDGF, CTGF, MMP, TIMPS, IGF1, DPEP1, ASL, AMN, ALPL, SLC6A19, IL-6, NF-kB, PKC, PI3K, Src, Ras, ERK1/2, Rho, Rac, Akt, mTOR, NAPDH oxidase, MAPK, cPLA₂, TNF- α , IL-1, CAM, COX-2, iNOS, JAK, STAT3, PI3K, Akt/PKB, IKKs, IkBs, NF-kB, MAPK, Ras, Raf, MEK, ERK, MCP1, Cntfr, Il1b, Csf1, Il2ra, Map3k8, Il1r1, Pfkfb3, Nr4a1, Gem, Fosl2, Klf4, F3, Nfkb1a, Ifit2, Nr4a2, Klf2, Jag1, Dnajb4, Il1b, Spsb1, Btg2, Atf3, Csf1, Trib1, Zbtb10, Btg1, Rhob, Nfat5, Edn1, Rel, Nr4a3, Nfkb1, Serpine1, Ccl20, Per1, Cxcl2, Map3k8, Traf1, Pik3r1, Pdgfra, Nfkb1a, Pik3cg, Pla2g4a, Tiam1, and Pdgfb; and (b) administering to the subject a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

[00309] Some embodiments provide a method of treating FSGS in a subject determined to have elevated expression and/or activity of one or more of ET1, TGF, PDGF, CTGF, MMP, TIMPS, IGF1, DPEP1, ASL, AMN, ALPL, SLC6A19, IL-6, NF-kB, PKC, PI3K, Src, Ras, ERK1/2, Rho, Rac, Akt, mTOR, NAPDH oxidase, MAPK, cPLA₂, TNF- α , IL-1, CAM, COX-2, iNOS, JAK, STAT3, PI3K, Akt/PKB, IKKs, IkBs, NF-kB, MAPK, Ras, Raf, MEK, ERK, MCP1, Cntfr, Il1b, Csf1, Il2ra, Map3k8, Il1r1, Pfkfb3, Nr4a1, Gem, Fosl2, Klf4, F3, Nfkb1a, Ifit2, Nr4a2, Klf2, Jag1, Dnajb4, Il1b, Spsb1, Btg2, Atf3, Csf1, Trib1, Zbtb10, Btg1, Rhob, Nfat5, Edn1, Rel, Nr4a3, Nfkb1, Serpine1, Ccl20, Per1, Cxcl2, Map3k8, Traf1, Pik3r1, Pdgfra, Nfkb1a, Pik3cg, Pla2g4a, Tiam1, and Pdgfb, comprising administering to the subject a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

V. ATRASENTAN

[00310] Atrasentan, also known as (2*R*,3*R*,4*S*)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid, ABT-627, A-147627, or A-127722, is a small molecule of the following chemical structure:



Molecular Weight: 510.62

[00311] Atrasentan and methods of preparation thereof are described in U.S. Patent No. 7,208,517 and International Patent Application Publication No. WO 1997/030045 (see e.g., Example 501), each of which is incorporated herein by reference in its entirety.

[00312] In some embodiments, atrasentan is administered as a free base. In some other embodiments, atrasentan is administered as a pharmaceutically acceptable salt as described anywhere herein.

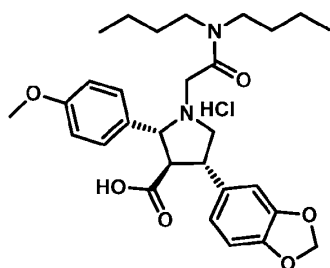
[00313] Atrasentan is an ET_A inhibitor which is about 1,860 times more selective for ET_A relative to ET_B. As used herein "ET_A" is the abbreviation for endothelin receptor A; and "ET_B" is the abbreviation of endothelin receptor B. *See, e.g.*, Ann Rheum Dis., 66(11), pp. 1467–1472 (2007); Eur. Resp. J., 37, pp. 475-476 (2011); Plos One, 9, e87548 (2014); J. Clin. Oncol., 10, 31(14), pp. 1740-7 (2013); Pharmacol. Rev., 68 (2) pp. 357-418 (2016); and Nephrol. Dial. Transplant., 29, pp. i69–i73 (2014).

Salts

[00314] In some embodiments, atrasentan is in the form of a pharmaceutically acceptable salt. The phrase "pharmaceutically acceptable salt" as used herein, refers to pharmaceutically acceptable organic or inorganic salts of a compound of the disclosure (e.g., atrasentan). Exemplary salts include acid addition salts formed by the reaction between atrasentan and an acid (e.g., organic acid or inorganic acid). Non-limiting examples include: sulfate, citrate, acetate, oxalate, chloride, bromide, iodide, nitrate, bisulfate, phosphate, acid phosphate, isonicotinate, lactate, salicylate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, mandelate (e.g., (*S*)-mandelate or (*R*)-mandelate), gentisinate, fumarate, gluconate, glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate "mesylate", ethanesulfonate, benzenesulfonate, and p-toluenesulfonate, pamoate (i.e., 4,4'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Exemplary salts also include base addition salts formed by the reaction between atrasentan and a base. Non-limiting examples include: alkali metal

(*e.g.*, sodium and potassium) salts, alkaline earth metal (*e.g.*, magnesium) salts, and ammonium salts. A pharmaceutically acceptable salt may involve the inclusion of another molecule such as an acetate ion, a succinate ion or other counter ion. The counter ion may be any organic or inorganic moiety that stabilizes the charge on the parent compound. Furthermore, a pharmaceutically acceptable salt may have more than one charged atom in its structure. Instances where multiple charged atoms are part of the pharmaceutically acceptable salt can have multiple counter ions. Hence, a pharmaceutically acceptable salt can have one or more charged atoms and/or one or more counter ion. When referring to atrasentan, the term “salt” or “salts” is understood to be a salt of atrasentan that can be present alone or in a mixture with free atrasentan.

[00315] In some embodiments, atrasentan is in the form of a hydrochloride salt. The hydrochloride salt of atrasentan, also known as atrasentan hydrochloride (CAS Number: 195733-43-8); atrasentan hydrogen chloride; atrasentan hydrochloride salt; atrasentan chloride salt; atrasentan HCl; atrasentan monohydrochloride; (2*R*,3*R*,4*S*)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl) pyrrolidine-3-carboxylic acid, monohydrochloride; 3-pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)-, hydrochloride (1:1), (2*R*, 3*R*, 4*S*)-; (2*R*, 3*R*, 4*S*)-1-[(dibutylcarbonyl)methyl]-2-(*p*-methoxyphenyl)-4-[3,4-(methylenedioxy)phenyl]-3-pyrrolidinecarboxylic acid, monohydrochloride; 3-pyrrolidinecarboxylic acid, 4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)-, monohydrochloride, [2*R*-(2*α*, 3*β*, 4*α*)]; ABT-627; A-147627.1; Abbott-147627.1, has the following structure:



Molecular Weight: 547.08

wherein the molar ratio of atrasentan to chloride is 1:1. Atrasentan hydrochloride and methods of preparation thereof are further described in U.S. Patent No. 7,208,517 and International Patent Application Publication No. WO 1997/030045 (see *e.g.*, Example 501), each of which is incorporated herein by reference in its entirety.

[00316] In some embodiments, atrasentan is in the form of a mandelate salt. In certain embodiments, atrasentan is in the form of a (*S*)-mandelate salt. In certain embodiments, atrasentan is in the form of a (*R*)-mandelate salt. In certain embodiments, in the atrasentan mandelate salt, atrasentan and mandelate has a molar ratio of 1:1. In certain embodiments, in the atrasentan mandelate salt, atrasentan and mandelate has a molar ratio of 2:1. Atrasentan mandelate salt and methods of preparation thereof are further described in US. Patent Nos. 8,962,675 and 9,637,476, each of which is incorporated herein by reference in its entirety.

[00317] In some embodiments, atrasentan is in the form of a hemisulfate salt. Hemisulfate salt and methods of preparation thereof are further described in US. Patent Nos. 8,962,675 and 9,637,476, each of which is incorporated herein by reference in its entirety.

[00318] In some embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is in the form of an anhydrate. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is in the form of a hydrate. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is in the form of a solvate.

Stereochemistry

[00319] Atrasentan possesses three asymmetric centers and can be produced as individual stereoisomers (*e.g.*, enantiomers or diastereomers) or as mixtures thereof as described in U.S. Patent No. 7,208,517 and International Patent Application Publication No. WO 1997/030045. In some embodiments, atrasentan as described herein comprises the (2*R*,3*R*,4*S*)-stereoisomer, that is (2*R*,3*R*,4*S*)-4-(1,3-benzodioxol-5-yl)-1-[2-(dibutylamino)-2-oxoethyl]-2-(4-methoxyphenyl)pyrrolidine-3-carboxylic acid. In certain embodiments, atrasentan is the (2*R*,3*R*,4*S*)-stereoisomer that is substantially free of the other stereoisomers (*e.g.*, contains <10%, <5%, <2%, <1%, <0.5%, <0.1%, or <0.05% of other stereoisomers).

Polymorphs

[00320] Atrasentan or a pharmaceutically acceptable salt thereof, as described herein, can be in one or more polymorphic forms. In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof is substantially amorphous (*e.g.*, >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% amorphous). In some embodiments, atrasentan or a

pharmaceutically acceptable salt thereof is substantially crystalline (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% crystalline).

[00321] In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof comprises Atrasentan Hydrochloride Crystalline Form 1. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is substantially Atrasentan Hydrochloride Crystalline Form 1 (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% Form 1). Atrasentan Hydrochloride Crystalline Form 1 and methods of making the same are described in International Patent Application Publication No. WO 2006/034094, which is incorporated by reference herein in its entirety.

[00322] In some embodiments, Atrasentan Hydrochloride Crystalline Form 1 is characterized, when measured at about 25°C with Cu-K α radiation, by an X-ray powder diffraction pattern with at least three peaks (e.g., 3, 4, 5, 6, or 7) having respective 2 θ values of about 8.3°, 9.7°, 10.0°, 13.0°, 15.6°, 17.2° or 19.5°. In certain embodiments, Atrasentan Hydrochloride Crystalline Form 1 is characterized, when measured at about 25 °C with Cu-K α radiation, by an X-ray powder diffraction pattern with at least three peaks having respective 2 θ values of about 8.3°, 9.7°, 10.0°, 13.0°, 15.6°, 17.2° or 19.5°, and essentially without peaks having 2 θ values below about 6.2° and/or between about 6.6° and 8.0°.

[00323] In some embodiments, Atrasentan Hydrochloride Crystalline Form 1 is characterized in the orthorhombic crystal system and P2₁2₁2₁ space group, when measured at about 25°C with Cu-K α radiation, by lattice parameters a, b and c of 17.663 Å $\pm$ 0.005 Å, 21.24 Å $\pm$ 0.01 Å and 8.005 Å $\pm$ 0.002 Å, respectively.

[00324] In some embodiments, Atrasentan Hydrochloride Crystalline Form 1 has substantial crystalline purity. In some embodiments, Atrasentan Hydrochloride Crystalline Form 1 has substantial chemical purity. In some embodiments, Atrasentan Hydrochloride Crystalline Form 1 has substantial diastereomeric purity.

[00325] Representative characteristic peak positions in the X-ray powder diffraction pattern of Atrasentan Hydrochloride Crystalline Form I, expressed as degrees relative to 2 θ , are, when measured at about 25°C with Cu-K α radiation, about 8.3°((020), 77.35%); 9.7°((120), 76.37%); 10.0°((200), 14.53%); 13.2°((220), 28.03%); 13.6°((130), 16.71%); 14.9°((121), 38.93%); 15.8°((310), 13.11%); 16.2°((230), 18.09%); 17.4°((320), 15.87%); 17.5°((131), 37.80%); 19.6°((240), 28.77%); 20.8°((141), 46.26%); 23.3°((112), 100.0%); 24.3°((151),

52.6%); 25.3°((341), 13.08%); and 25.9°((132), 33.98%). Each peak position is shown with its accompanying Miller index (hkl) values and its integrated intensity (peak height). It is meant to be understood that peak heights may vary and will be dependent on variables such as the temperature, size of crystal size or morphology, sample preparation, or sample height in the analysis well of the Scintag×2 Diffraction Pattern System. It is also meant to be understood that peak positions may vary when measured with different radiation sources. For example, Cu-Kα1, Mo-Kα, Co-Kα and Fe-Kα radiation, having wavelengths of 1.54060 Å, 0.7107 Å, 1.7902 Å and 1.9373 Å, respectively, may provide peak positions that differ from those measured with Cu-Kα radiation.

[00326] In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof comprises Atrasentan Hydrochloride Crystalline Form 2. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is substantially Atrasentan Hydrochloride Crystalline Form 2 (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% Form 2). Atrasentan Hydrochloride Crystalline Form 2 and methods of making the same are described in International Patent Application Publication No. WO 2006/034084, which is incorporated by reference herein in its entirety.

[00327] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 2 is characterized, when measured at about 25 °C with Cu-Kα radiation, by an X-ray powder diffraction pattern with peaks having respective 2θ values of about 6.7° and 22.05° and at least one peak having a respective 2θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00328] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 2 has substantial crystalline purity and is characterized, when measured at about 25°C with Cu-Kα radiation, by an X-ray powder diffraction pattern with peaks having respective 2θ values of about 6.7° and 22.05° and at least one peak having a respective 2θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00329] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 2 has substantial crystalline purity and substantial chemical purity; and said Atrasentan Hydrochloride Crystalline Form 2 is characterized, when measured at about 25°C with Cu-Kα radiation, by an X-ray powder diffraction pattern with peaks having respective 2θ values of about 6.7° and 22.05° and at least one peak having a respective 2θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00330] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 2 has substantial crystalline purity, substantial chemical purity, and substantial diastereomeric purity; and said Atrasentan Hydrochloride Crystalline Form 2 is characterized, when measured at about 25 °C with Cu-K α radiation, by an X-ray powder diffraction pattern with peaks having respective 2 θ values of about 6.7° and 22.05° and at least one peak having a respective 2 θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00331] In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof comprises Atrasentan Hydrochloride Crystalline Form 3. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is substantially Atrasentan Hydrochloride Crystalline Form 3 (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% Form 3). Atrasentan Hydrochloride Crystalline Form 3 and methods of making the same are described in International Patent Application Publication No. WO 2006/034234 and U.S. Patent No. 9,051,301, each of which is incorporated by reference herein in its entirety.

[00332] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 3 is characterized, when measured at about 25°C with Cu-K α radiation, by an X-ray powder diffraction pattern with peaks having respective 2 θ values of about 6.7° and 21.95° and at least one peak having a respective 2 θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00333] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 3 has substantial crystalline purity and is characterized, when measured at about 25 °C with Cu-K α radiation, by an X-ray powder diffraction pattern with peaks having respective 2 θ values of about 6.7° and 21.95° and at least one peak having a respective 2 θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00334] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 3 has substantial crystalline purity and substantial chemical purity; and said Atrasentan Hydrochloride Crystalline Form 3 is characterized, when measured at about 25°C with Cu-K α radiation, by an X-ray powder diffraction pattern with peaks having respective 2 θ values of about 6.7° and 21.95° and at least one peak having a respective 2 θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00335] In certain embodiments, Atrasentan Hydrochloride Crystalline Form 3 has substantial crystalline purity, substantial chemical purity, and substantial diastereomeric purity; and said Atrasentan Hydrochloride Crystalline Form 3 is characterized, when measured at about 25 °C with Cu-K α radiation, by an X-ray powder diffraction pattern with peaks having respective

2 θ values of about 6.7° and 21.95° and at least one peak having a respective 2 θ value of about 8.4°, 15.6°, 18.0°, 18.5°, 19.8° or 20.6°.

[00336] In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof comprises amorphous atrasentan hydrochloride. In certain embodiments, atrasentan hydrochloride is substantially amorphous (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% amorphous). Amorphous atrasentan hydrochloride and methods of making the same are described in International Patent Application Publication No. WO 2006/034085, which is incorporated by reference herein in its entirety.

[00337] In certain embodiments, the amorphous atrasentan hydrochloride has substantial chemical purity. In certain embodiments, the amorphous atrasentan hydrochloride has substantial diastereomeric purity.

[00338] In some embodiments, the atrasentan or a pharmaceutically acceptable salt thereof comprises a crystalline atrasentan mandelate salt. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is substantially a crystalline atrasentan mandelate salt (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% crystalline atrasentan mandelate salt).

[00339] In certain embodiments, the crystalline atrasentan mandelate salt is a crystalline atrasentan (*S*)-mandelate salt. In certain embodiments, the atrasentan (*S*)-mandelate salt is an anhydrous salt. In certain embodiments, the atrasentan (*S*)-mandelate salt is a solvated salt. In certain embodiments, the atrasentan (*S*)-mandelate salt is a solvated salt selected from the group consisting of an acetonitrile solvate, an ethanol solvate, and a pyridine solvate. In certain embodiments, the atrasentan (*S*)-mandelate salt is a hydrated salt.

(a) (S)-Mandelate Salt (1:1 Stoichiometry)

[00340] In certain embodiments, the crystalline atrasentan (*S*)-mandelate salt is a crystalline atrasentan (*S*)-mandelate salt wherein the molar ratio of atrasentan to (*S*)-mandelate is about 1:1. In certain embodiments, the atrasentan (*S*)-mandelate salt is an anhydrous salt. In certain embodiments, the atrasentan (*S*)-mandelate salt is a solvated salt. In certain embodiments, the atrasentan (*S*)-mandelate salt is a solvated salt selected from the group consisting of an acetonitrile solvate, an ethanol solvate, and a pyridine solvate. In certain embodiments, the atrasentan (*S*)-mandelate salt is a hydrated salt. In certain embodiments, the atrasentan or a

pharmaceutically acceptable salt thereof is substantially (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5%) a crystalline atrasentan (*S*)-mandelate salt wherein the molar ratio of atrasentan to (*S*)-mandelate is about 1:1.

[00341] In certain embodiments, the crystalline (*S*)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 5.5 ± 0.2 , 9.7 ± 0.2 , and 19.4 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic $K\alpha_1$ radiation. In certain embodiments, the crystalline (*S*)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 5.5 ± 0.2 , 9.7 ± 0.2 , 12.1 ± 0.2 , and 19.4 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic $K\alpha_1$ radiation. In certain embodiments, the crystalline (*S*)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 5.5 ± 0.2 , 9.7 ± 0.2 , 12.1 ± 0.2 , 18.0 ± 0.2 , 18.4 ± 0.2 , and 19.4 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic $K\alpha_1$ radiation. In certain embodiments, the experimental error associated with the X-ray powder diffraction peak values recited in the various embodiments above is ± 0.1 degrees 2θ . In certain embodiments, the crystalline (*S*)-mandelate salt is an anhydrous salt. In certain embodiments, the molar ratio of atrasentan to (*S*)-mandelate is about 1:1.

[00342] In certain embodiments, the crystalline (*S*)-mandelate salt has an orthorhombic lattice type. In certain embodiments, the crystalline (*S*)-mandelate salt has a $P2_12_12_1$ space group. In certain embodiments, the crystalline (*S*)-mandelate salt has unit cell *a*, *b* and *c* values of about 9.954 Å, about 11.049 Å, and about 30.861 Å, respectively. In certain embodiments, the crystalline (*S*)-mandelate salt has unit cell α , β and γ values of about 90°, about 90°, and about 90°, respectively. In certain embodiments, the crystalline (*S*)-mandelate salt has at least three or more of the following properties: (a) an orthorhombic lattice type, (b) a $P2_12_12_1$ space group, (c) unit cell *a*, *b* and *c* values of about 9.954 Å, about 11.049 Å, and about 30.861 Å, respectively, and/or (d) unit cell α , β and γ values of about 90°, about 90°, and about 90°, respectively. In certain embodiments, the crystalline (*S*)-mandelate salt has: (a) an orthorhombic lattice type, (b) a $P2_12_12_1$ space group, (c) unit cell *a*, *b* and *c* values of about 9.954 Å, about 11.049 Å, and about 30.861 Å, respectively, and (d) unit cell α , β and γ values of about 90°, about 90°, and about 90°, respectively. In certain embodiments, the crystalline (*S*)-mandelate salt is an anhydrous salt. In certain embodiments, the molar ratio of atrasentan to (*S*)-mandelate is about 1:1.

(b) (S)-Mandelate Salt (2:1 Stoichiometry)

[00343] In certain embodiments, the crystalline (S)-mandelate salt is a crystalline atrasentan (S)-mandelate salt wherein the molar ratio of atrasentan to (S)-mandelate is about 2:1. In certain embodiments, the crystalline atrasentan (S)-mandelate salt is an anhydrous salt. In certain embodiments, the crystalline atrasentan (S)-mandelate salt is a solvated salt. In certain embodiments, the crystalline atrasentan (S)-mandelate salt is a hydrated salt. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is substantially (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5%) a crystalline atrasentan (S)-mandelate salt wherein the molar ratio of atrasentan to (S)-mandelate is about 2:1.

[00344] In certain embodiments, the crystalline (S)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 4.5 ± 0.2 , 8.6 ± 0.2 , and 18.1 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic K α 1 radiation. In certain embodiments, the crystalline (S)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 4.5 ± 0.2 , 8.6 ± 0.2 , 18.1 ± 0.2 , and 18.7 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic K α 1 radiation. In certain embodiments, the crystalline (S)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 4.5 ± 0.2 , 8.6 ± 0.2 , 9.1 ± 0.2 , 18.1 ± 0.2 , and 18.7 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic K α 1 radiation. In certain embodiments, the experimental error associated with the X-ray powder diffraction peak values recited in the various embodiments above is ± 0.1 degrees 2θ . In certain embodiments, the crystalline (S)-mandelate salt is an anhydrous salt. In certain embodiments, the crystalline (S)-mandelate salt is a hydrated salt.

[00345] In certain embodiments, the crystalline atrasentan mandelate salt is a crystalline atrasentan (R)-mandelate salt. In certain embodiments, the crystalline atrasentan (R)-mandelate salt is an anhydrous salt. In certain embodiments, the crystalline atrasentan (R)-mandelate salt is a solvated salt. In certain embodiments, the crystalline atrasentan (R)-mandelate salt is a hydrated salt.

(c) (R)-Mandelate Salt (1:1 Stoichiometry)

[00346] In certain embodiments, the crystalline atrasentan (R)-mandelate salt is a crystalline atrasentan (R)-mandelate salt wherein the molar ratio of atrasentan to (R)-mandelate is about 1:1. In certain embodiments, the crystalline atrasentan (R)-mandelate salt is an anhydrous

salt. In certain embodiments, the crystalline atrasentan (*R*)-mandelate salt is a solvated salt. In certain embodiments, the crystalline atrasentan (*R*)-mandelate salt is a hydrated salt. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is substantially (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5%) a crystalline atrasentan (*R*)-mandelate salt wherein the molar ratio of atrasentan to (*R*)-mandelate is about 1:1.

[00347] In certain embodiments, the crystalline atrasentan (*R*)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 5.7 ± 0.2 , 11.8 ± 0.2 , and 20.9 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic K α 1 radiation. In certain embodiments, the crystalline atrasentan (*R*)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 5.7 ± 0.2 , 8.2 ± 0.2 , 11.8 ± 0.2 , and 20.9 ± 0.2 degrees 2θ when measured at about 25 °C with monochromatic K α 1 radiation. In certain embodiments, the crystalline atrasentan (*R*)-mandelate salt has an X-ray powder diffraction pattern comprising peaks at 5.7 ± 0.2 , 8.2 ± 0.2 , 8.6 ± 0.2 , 11.8 ± 0.2 , and 20.9 ± 0.2 degrees 2θ when measured at about 25°C with monochromatic K α 1 radiation. In certain embodiments, the experimental error associated with the X-ray powder diffraction peak values recited in the various embodiments above is ± 0.1 degrees 2θ . In certain embodiments, the crystalline atrasentan (*R*)-mandelate salt is an anhydrous salt.

[00348] In some embodiments, the atrasentan or a pharmaceutically acceptable salt thereof comprises an amorphous atrasentan mandelate salt. In certain embodiments, the atrasentan or a pharmaceutically acceptable salt thereof is substantially an amorphous atrasentan mandelate salt (e.g., >75%, >80%, >85%, >90%, >95%, >98%, >99%, or >99.5% amorphous atrasentan mandelate salt).

[00349] In certain embodiments, the amorphous atrasentan mandelate salt is amorphous atrasentan (*S*)-mandelate salt. In certain embodiments, the amorphous atrasentan (*S*)-mandelate salt is an anhydrous salt. In certain embodiments, the amorphous atrasentan (*S*)-mandelate salt is a solvated salt. In certain embodiments, the amorphous atrasentan (*S*)-mandelate salt is a solvated salt selected from the group consisting of an acetonitrile solvate, an ethanol solvate, and a pyridine solvate. In certain embodiments, the amorphous atrasentan (*S*)-mandelate salt is a hydrated salt. In certain embodiments, in the amorphous atrasentan (*S*)-mandelate salt, the molar ratio of atrasentan and (*S*)-mandelate is about 1:1. In certain embodiments, in the amorphous atrasentan (*S*)-mandelate salt, the molar ratio of atrasentan and (*S*)-mandelate is about 2:1.

[00350] In certain embodiments, the amorphous atrasentan mandelate salt is amorphous atrasentan (*R*)-mandelate salt. In certain embodiments, the amorphous atrasentan (*R*)-mandelate salt is an anhydrous salt. In certain embodiments, the amorphous atrasentan (*R*)-mandelate salt is a solvated salt. In certain embodiments, the amorphous atrasentan (*R*)-mandelate salt is a solvated salt selected from the group consisting of an acetonitrile solvate, an ethanol solvate, and a pyridine solvate. In certain embodiments, the amorphous atrasentan (*R*)-mandelate salt is a hydrated salt. In certain embodiments, in the amorphous atrasentan (*R*)-mandelate salt, the molar ratio of atrasentan and (*R*)-mandelate is about 1:1. In certain embodiments, in the amorphous atrasentan (*R*)-mandelate salt, the molar ratio of atrasentan and (*R*)-mandelate is about 2:1.

[00351] Crystalline and amorphous atrasentan mandelate salts are further described in U.S. Patent Nos. 8,962,675 and 9,637,476, each of which is incorporated herein by reference in its entirety.

VI. FORMULATION

[00352] The term “pharmaceutical composition” as used herein is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present disclosure encompass any composition made by admixing a compound of the present disclosure, or a pharmaceutically acceptable salt, or solvate or solvate of the salt thereof, and a pharmaceutically acceptable carrier.

[00353] The amount administered depends on the compound formulation, route of administration, etc. and is generally empirically determined, and variations will necessarily occur depending on the target, the host, and the route of administration, etc. Generally, the quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 milligram (mg) to about 10 mg or from about 0.5 mg to about 2 mg, according to the particular application. For convenience, the total daily dosage may be divided and administered in portions during the day.

[00354] Pharmaceutical compositions of the present disclosure for injection comprise pharmaceutically acceptable sterile aqueous or non-aqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and non-aqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

[00355] These pharmaceutical compositions may also contain adjuvants such as preservative, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of micro-organisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents that delay absorption such as aluminum monostearate and gelatin. The compounds can be incorporated into slow release or targeted delivery systems such as polymer matrices, liposomes, and microspheres. Such formulations may provide more effective distribution of the compounds.

[00356] The pharmaceutical compositions that are injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid pharmaceutical compositions that can be dissolved or dispersed in sterile water or other sterile injectable medium prior to use.

[00357] Solid dosage forms of the instant pharmaceutical compositions for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting

agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

[00358] Solid pharmaceutical compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugar as well as high molecular weight polyethylene glycols and the like.

[00359] The solid dosage forms of the instant pharmaceutical compositions of tablets, dragées, capsules, pills, and granules can be prepared with coatings and shells such as enteric coatings and other pharmaceutical coatings. They may optionally contain opacifying agents and can also be of a formulation that they release the active ingredient(s) only, or preferentially, in a certain part of the intestinal tract, optionally, in a delayed manner. Examples of embedding pharmaceutical compositions which can be used include polymeric substances and waxes.

[00360] The active compounds can also be in microencapsulated form, if appropriate, with one or more of the above-mentioned excipients.

[00361] Liquid dosage forms of the instant pharmaceutical compositions for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

[00362] Besides inert diluents, the oral pharmaceutical compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, and perfuming agents.

[00363] Suspensions of the instant compounds, in addition to the active compounds, may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, and tragacanth, and mixtures thereof.

[00364] The compounds and compositions described herein can, for example, be administered orally or parenterally, with a dosage ranging from about 0.01 milligrams per kilogram (mg/kg) to about 0.05 mg/kg, every 4 to 120 hours, or according to the requirements of the particular drug, dosage form, and/or route of administration. The interrelationship of dosages for animals and humans (based on milligrams per meter squared of body surface) is described by Freireich *et al.*, Cancer Chemother. Rep. 50, 219-244 (1966). Body surface area may be approximately determined from height and weight of the patient. *See, e.g.*, Scientific Tables, Geigy Pharmaceuticals, Ardsley, N.Y., 537 (1970). In certain embodiments, the compositions are administered by oral administration or by injection. The methods herein contemplate administration of an effective amount of compound or compound composition to achieve a desired or stated effect. Typically, the pharmaceutical compositions of the present disclosure will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy.

[00365] Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the patient's disposition to the disease, and the judgment of the treating physician.

[00366] Dosage forms include from about 0.01 mg to about 10 mg (including, from about 0.1 mg to about 5 mg, from about 0.2 mg to about 4 mg, from about 0.3 mg to about 3 mg, from about 0.4 mg to about 2 mg, from about 0.5 mg to about 1.5 mg, from about 0.6 mg to about 1 mg, or from about 1.25 mg to about 1.75 mg) of a compound of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the dosage form include about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.65, about 0.7 mg, about 0.75, about 0.8 mg, about 0.85, about 0.9 mg, about 0.95 mg, about 1 mg, about 1.05 mg, about 1.1 mg, about 1.15 mg, about 1.2 mg, about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, about 1.75 mg, about 1.8 mg, about 1.85 mg, about 1.9 mg, about 1.95 mg, about 2 mg, or any value in between, of atrasentan, or a pharmaceutically acceptable salt thereof. In some embodiments, the dosage form includes about 0.75 mg of atrasentan, or a pharmaceutically acceptable salt thereof. In some

embodiments, the dosage form includes about 1.5 mg of atrasentan, or a pharmaceutically acceptable salt thereof.

[00367] The dosage forms can further include a pharmaceutically acceptable carrier and/or an additional therapeutic agent.

[00368] Appropriate dosage levels may be determined by any suitable method. Preferably, the active substance is administered at a frequency of 1 to 4 times per day for topical administration, or less often if a drug delivery system is used. Nevertheless, actual dosage levels and time course of administration of the active ingredients in the pharmaceutical compositions of the present disclosure may be varied so as to obtain an amount of the active ingredient which is effective to achieve a desired therapeutic response for a particular patient, composition and mode of administration, without being intolerably toxic to the patient. In certain cases, dosages may deviate from the stated amounts, in particular as a function of age, gender, body weight, diet and general health status of the patient, route of administration, individual response to the active ingredient, nature of the preparation, and time or interval over which administration takes place. Thus, it may be satisfactory in some cases to manage with less than the aforementioned minimum amount, whereas in other cases the stated upper limit may be exceeded. It may in the event of administration of larger amounts be advisable to divide these into multiple individual doses spread over the day.

Exemplary Dosage Forms of Atrasentan

[00369] In some embodiments, provided herein a stable solid pharmaceutical dosage form comprising: (a) about 0.25 mg to about 1.25 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof; wherein the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.05 weight percent to about 2.0 weight percent on an atrasentan free base equivalent weight basis; and (b) a pharmaceutically acceptable diluent.

[00370] In some embodiments, provided herein a stable solid pharmaceutical dosage form comprising: (a) about 0.25 mg to about 1.25 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof; wherein the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.05 weight percent to about 2.0 weight percent on an atrasentan free base equivalent weight basis; (b) a pharmaceutically

acceptable anti-oxidant; wherein the molar ratio of the anti-oxidant to atrasentan, or pharmaceutically acceptable salt thereof, is from about 10:1 to about 1:10; and (c) a pharmaceutically acceptable diluent.

[00371] In some embodiments, provided herein a stable solid pharmaceutical dosage form comprising: (a) about 0.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof; wherein the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.05 weight percent to about 2.0 weight percent on an atrasentan free base equivalent weight basis; and (b) a pharmaceutically acceptable diluent.

[00372] In some embodiments, provided herein a stable solid pharmaceutical dosage form comprising: (a) about 1.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof; wherein the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.05 weight percent to about 2.0 weight percent on an atrasentan free base equivalent weight basis; (b) a pharmaceutically acceptable anti-oxidant; wherein the molar ratio of the anti-oxidant to atrasentan, or pharmaceutically acceptable salt thereof, is from about 10:1 to about 1:10; and (c) a pharmaceutically acceptable diluent.

[00373] In certain of these embodiments, degradation of atrasentan in the dosage form is less than degradation of atrasentan in an otherwise identical dosage form lacking the anti-oxidant when the dosage forms are stored for a storage period of six months at about 40° C. and about 75% relative humidity.

[00374] In some embodiments, the dosage form is stored during the storage period in a semi-permeable container or a substantially impermeable container. In some embodiments, the dosage form is stored during the storage period in a sealed HDPE bottle or a blister package. In some embodiments, the dosage form is stored during the storage period in a sealed HDPE bottle. In some embodiments, the dosage form is stored during the storage period in a blister package.

(i) Atrasentan

[00375] The dosage form can comprise a free base of atrasentan, a pharmaceutically acceptable salt of atrasentan, or a combination thereof. In some embodiments, the dosage form comprises a free base of atrasentan. In some embodiments, the dosage form comprises a pharmaceutically acceptable salt of atrasentan. In some embodiments, the dosage form comprises

atrasentan hydrochloride. In some embodiments, the dosage form comprises atrasentan hydrochloride having a polymorph form selected from the group consisting of amorphous atrasentan hydrochloride, Atrasentan Hydrochloride Crystalline Form 1, Atrasentan Hydrochloride Crystalline Form 2, and Atrasentan Hydrochloride Crystalline Form 3. In some embodiments, the dosage form comprises amorphous atrasentan hydrochloride. In some embodiments, the dosage form comprises Atrasentan Hydrochloride Crystalline Form 1. In some embodiments, the dosage form comprises Atrasentan Hydrochloride Crystalline form 2. In some embodiments, the dosage form comprises atrasentan hydrochloride crystalline form 3. In some embodiments, the dosage form comprises atrasentan mandelate. In certain embodiments, the dosage form comprises a crystalline atrasentan mandelate (e.g., a crystalline atrasentan (*S*)-mandelate and/or a crystalline atrasentan (*R*)-mandelate). In certain embodiments, the dosage form comprises an amorphous atrasentan mandelate (e.g., an amorphous atrasentan (*S*)-mandelate and/or an amorphous atrasentan (*R*)-mandelate). In certain of the foregoing embodiments (when the dosage form comprises a crystalline and/or amorphous atrasentan (*S*)- and/or (*R*)-mandelate), the molar ratio of atrasentan and mandelate is 1:1. In certain other embodiments, the molar ratio of atrasentan and mandelate is 2:1.

[00376] In certain embodiments, the dosage form comprises amorphous atrasentan hydrochloride; and it is substantially free (e.g., contains <10%, <5%, <1%, <0.5%, <0.1%, <0.05%) of other forms (e.g., other salts and/or other polymorphs) of atrasentan. In certain embodiments, the dosage form comprises Atrasentan Hydrochloride Crystalline Form 1; and it is substantially free of (e.g., contains <10%, <5%, <1%, <0.5%, <0.1%, <0.05%) other forms (e.g., other salts and/or other polymorphs) of atrasentan. In certain embodiments, the dosage form comprises Atrasentan Hydrochloride Crystalline form 2; and it is substantially free of other forms (e.g., other salts and/or other polymorphs) of atrasentan. In certain embodiments, the dosage form comprises atrasentan hydrochloride crystalline form 3; and it is substantially free (e.g., contains <10%, <5%, <1%, <0.5%, <0.1%, <0.05%) of other forms (e.g., other salts and/or other polymorphs) of atrasentan. In certain embodiments, the dosage form comprises crystalline atrasentan (*S*)-mandelate; and it is substantially free (e.g., contains <10%, <5%, <1%, <0.5%, <0.1%, <0.05%) of other forms (e.g., other salts and/or other polymorphs) of atrasentan. In certain embodiments, the dosage form comprises crystalline atrasentan (*R*)-mandelate; and it is substantially free (e.g., contains <10%, <5%, <1%, <0.5%, <0.1%, <0.05%) of other forms (e.g.,

other salts and/or other polymorphs) of atrasentan. In certain embodiments, the dosage form comprises amorphous atrasentan (*S*)-mandelate; and it is substantially free (e.g., contains <10%, <5%, <1%, <0.5%, <0.1%, <0.05%) of other forms (e.g., other salts and/or other polymorphs) of atrasentan. In certain embodiments, the dosage form comprises amorphous atrasentan (*R*)-mandelate; and it is substantially free (e.g., contains <10%, <5%, <1%, <0.5%, <0.1%, <0.05%) of other forms (e.g., other salts and/or other polymorphs) of atrasentan.

[00377] In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.1 weight percent to about 2.0 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.2 weight percent to about 1.0 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.3 weight percent to about 0.8 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.40 weight percent to about 0.45 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 0.60 weight percent to about 0.65 weight percent on an atrasentan free base equivalent weight basis.

[00378] In some embodiments, the dosage form comprises from about 0.40 mg to about 1.00 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, the dosage form comprises from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, the dosage form comprises about 0.50 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, the dosage form comprises about 0.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, the dosage form comprises from about 1.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, the dosage form comprises about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

(ii) Diluent

[00379] Suitable diluents for use in the disclosed dosage forms include, but are not limited to, lactose (such as lactose monohydrate, lactose anhydrous, and PHARMATOSE® DCL21), sucrose, glucose, mannitol, sorbitol, isomalt, microcrystalline cellulose (such as AVICEL® PH101 and AVICEL® PH102), silicified microcrystalline cellulose (such as PROSOLV® SMCC 50 and SMCC 90), dicalcium phosphate, starches, and combinations thereof. In some embodiments, the diluent is selected from the group consisting of lactose, mannitol, isomalt, microcrystalline cellulose, dicalcium phosphate, and combinations thereof. In some embodiments, the diluent is lactose.

[00380] In some embodiments, the weight percent of the diluent in the dosage form is from about 70 weight percent to about 99 weight percent. In some embodiments, the weight percent of the diluent in the dosage form is from about 80 weight percent to about 99 weight percent. In some embodiments, the weight percent of the diluent in the dosage form is from about 85 weight percent to about 99 weight percent. In certain of the foregoing embodiments, the diluent is selected from the group consisting of lactose, mannitol, isomalt, and combinations thereof. As a non-limiting example, the diluent can be lactose.

(iii) Binder

[00381] In some embodiments, the dosage form further comprises a pharmaceutically acceptable binder (e.g., polymeric binder). Suitable binders for use in the disclosed dosage forms include, but are not limited to, celluloses, such as hydroxypropyl methylcellulose (e.g., Hypromellose E5 (Premium LV)), hydroxypropyl ethylcellulose, and hydroxypropyl cellulose, and other pharmaceutically acceptable substances with cohesive properties. In some embodiments, the binder is selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose. In some embodiments, the binder is hydroxypropyl methylcellulose. In some embodiments, the binder is hydroxypropylcellulose. In some embodiments, the binder is hydroxyethylpropylcellulose.

[00382] In some embodiments, the dosage form further comprises a pharmaceutically acceptable binder; and the weight percent of the binder in the dosage form is from about 1.0 weight percent to about 10.0 weight percent. In some embodiments, the weight

percent of the binder in the dosage form is from about 1.0 weight percent to about 8.0 weight percent. In some embodiments, the weight percent of the binder in the dosage form is from about 1.0 weight percent to about 5.0 weight percent. In certain of the foregoing embodiments, the binder is a polymeric binder selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose

[00383] In some embodiments, the dosage form further comprises a pharmaceutically acceptable binder; and the weight to weight ratio of the binder to atrasentan, or pharmaceutically acceptable salt thereof, is from about 2:1 to about 25:1 on an atrasentan free base equivalent weight basis. In some embodiments, the weight to weight ratio of the binder to the atrasentan, or pharmaceutically acceptable salt thereof, is from about 1:1 to about 20:1 on an atrasentan free base equivalent weight basis. In some embodiments, the weight to weight ratio of the binder to the atrasentan, or pharmaceutically acceptable salt thereof, is from about 1:1 to about 15:1 on an atrasentan free base equivalent weight basis. In certain embodiments, the binder is a polymeric binder selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose;

(iv) Disintegrant

[00384] In some embodiments, the dosage form optionally comprises a pharmaceutically acceptable disintegrant. Suitable disintegrants for use in the disclosed dosage forms include, but are not limited to, cross-linked polyvinyl pyrrolidone (such as POLYPLASDONE™ XL), corn starch, potato starch, maize starch and modified starches (including sodium starch glycolate), agar-agar, alginic acids, microcrystalline cellulose, sodium croscarmellose, and combinations thereof. In some embodiments, the disintegrant is selected from the group consisting of crospovidone, sodium starch glycolate, and sodium croscarmellose. In some embodiments, the disintegrant is a cross-linked polyvinyl pyrrolidone. In some embodiments, the disintegrant is crospovidone.

[00385] In some embodiments, the dosage form further comprises a pharmaceutically acceptable disintegrant. In certain embodiments, the weight percent of the disintegrant in the dosage form is from about 1.0 weight percent to about 10.0 weight percent. In some embodiments, the weight percent of the disintegrant in the dosage form is from about 1.0 weight percent to about 6.0 weight percent. In some embodiments, the weight percent of the

disintegrant in the dosage form is from about 1.0 weight percent to about 4.0 weight percent. In certain of the foregoing embodiments, the disintegrant is crospovidone.

[00386] In some embodiments, the dosage form further comprises a pharmaceutically acceptable disintegrant and the weight to weight ratio of the disintegrant to the anti-oxidant (e.g., L-cysteine), or pharmaceutically acceptable salt or ester thereof, is from about 60:1 to about 3:1. In some embodiments, the weight to weight ratio of the disintegrant to the anti-oxidant (e.g., L-cysteine), or pharmaceutically acceptable salt or ester thereof, is from about 50:1 to about 4:1. In some embodiments, the weight to weight ratio of the disintegrant to the anti-oxidant (e.g., L-cysteine), or pharmaceutically acceptable salt or ester thereof, is from about 35:1 to about 5:1.

(v) Additional Excipients

[00387] In further embodiments, the dosage form optionally comprises a pharmaceutically acceptable lubricant and/or glidant. Suitable lubricants and glidants for use in the disclosed dosage forms include, but are not limited to, silicon dioxide (such as SYLOID® 244FP and AEROSIL® 200), glyceryl behenate (such as COMPRITOL®), talc, stearic acid, solid polyethylene glycols, silica gel and mixtures thereof and other substances with lubricating or gliding properties. In certain embodiments, the lubricant is glyceryl behenate (such as COMPRITOL®). In certain embodiments, the glidant is silicon dioxide (such as SYLOID® 244FP). In certain embodiments, the lubricant is glyceryl behenate and the glidant is silicon dioxide.

[00388] In some embodiments, the dosage form further comprises a pharmaceutically acceptable glidant. In another aspect, the weight percent of the glidant in the dosage form is from about 0.1 weight percent to about 1.5 weight percent. In some embodiments, the weight percent of the glidant in the dosage form is from about 0.1 weight percent to about 1.0 weight percent. In some embodiments, the weight percent of the glidant in the dosage form is from about 0.1 weight percent to about 0.8 weight percent. In some embodiments, the glidant is silicon dioxide.

[00389] In some embodiments, the dosage form further comprises a pharmaceutically acceptable lubricant. In some embodiments, the dosage form further comprises a pharmaceutically acceptable, hydrophobic lubricant. In some embodiments, the weight percent

of the lubricant in the dosage form is from about 0.05 weight percent to about 5.0 weight percent. In some embodiments, the weight percent of the lubricant in the dosage form is from about 0.2 weight percent to about 3.0 weight percent. In some embodiments, the weight percent of the lubricant in the dosage form is from about 0.5 weight percent to about 2.0 weight percent. In certain embodiments, the lubricant is glyceryl behenate.

[00390] In some embodiments, the dosage form further comprises a disintegrant, a glidant, and a lubricant.

(vi) Anti-Oxidant

[00391] Suitable anti-oxidants for use in the disclosed dosage forms include anti-oxidants that function as reducing agents and are oxidized to pharmaceutically acceptable reduced products in the dosage form. In some embodiments, the anti-oxidant has an oxidation reduction potential less than the oxidation reduction potential of atrasentan (i.e., an oxidation reduction potential less than about 900 mV) and greater than about 550 mV. In some embodiments, the anti-oxidant has an oxidation reduction potential less than about 550 mV. In some embodiments, the anti-oxidant has an oxidation reduction potential from about 1 mV to about 550 mV. In some embodiments, the solubility of the anti-oxidant in water at about 25°C is greater than about 24 mg/mL. In some embodiments, the anti-oxidant is an amino acid, or a pharmaceutically acceptable salt or ester thereof. In some embodiments, the anti-oxidant is cysteine. In some embodiments, the anti-oxidant is L-cysteine, or a pharmaceutically acceptable salt or ester thereof. In some embodiments, the anti-oxidant is selected from the group consisting of L-cysteine hydrochloride monohydrate, L-cysteine hydrochloride anhydrate, and L-cysteine ethyl ester. In some embodiments, the dosage form comprises L-cysteine hydrochloride monohydrate.

[00392] In some embodiments, the weight percent of the anti-oxidant in the dosage form is from about 0.05 weight percent to about 1.0 weight percent. In some embodiments, the weight percent of the anti-oxidant in the dosage form is from about 0.07 weight percent to about 0.7 weight percent. In some embodiments, the weight percent of the anti-oxidant in the dosage form is from about 0.09 weight percent to about 0.5 weight percent.

[00393] In some embodiments, the molar ratio of the anti-oxidant to atrasentan, or pharmaceutically acceptable salt thereof, is from about 10:1 to about 1:10. In some embodiments, the molar ratio of the anti-oxidant to atrasentan, or pharmaceutically acceptable salt thereof, in the

dosage form is from about 5:1 to about 1:5. In some embodiments, the molar ratio of the anti-oxidant to atrasentan, or pharmaceutically acceptable salt thereof, is from about 2:1 to about 1:2. In some embodiments, the molar ratio of the anti-oxidant to atrasentan, or pharmaceutically acceptable salt thereof, is about 1:1.

[00394] In some embodiments, the anti-oxidant is L-cysteine, or a pharmaceutically acceptable salt thereof. In certain embodiments, the weight percent of the L-cysteine, or pharmaceutically acceptable salt or ester thereof, in the dosage form is from about 0.05 weight percent to about 1.0 weight percent. In certain embodiments, the weight percent of the L-cysteine, or pharmaceutically acceptable salt or ester thereof, in the dosage form is from about 0.07 weight percent to about 0.7 weight percent. In certain embodiments, the weight percent of the L-cysteine, or pharmaceutically acceptable salt or ester thereof, in the dosage form is from about 0.09 weight percent to about 0.5 weight percent.

[00395] In certain embodiments, the molar ratio of the L-cysteine, or pharmaceutically acceptable salt or ester thereof, to atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 10:1 to about 1:10. In certain embodiments, the molar ratio of the L-cysteine, or pharmaceutically acceptable salt or ester thereof, to atrasentan, or pharmaceutically acceptable salt thereof, in the dosage form is from about 5:1 to about 1:5. In certain embodiments, the molar ratio of the L-cysteine, or pharmaceutically acceptable salt or ester thereof, to atrasentan, or pharmaceutically acceptable salt thereof, is from about 2:1 to about 1:2. In certain embodiments, the molar ratio of the L-cysteine, or pharmaceutically acceptable salt or ester thereof, to atrasentan, or pharmaceutically acceptable salt thereof, is about 1:1.

[00396] In certain embodiments, the anti-oxidant is selected from the group consisting of L-cysteine hydrochloride monohydrate, L-cysteine hydrochloride anhydrate, and L-cysteine ethyl ester. In some embodiments, the dosage form comprises L-cysteine hydrochloride monohydrate.

(vii) Additional Embodiments

[00397] In some embodiments, the dosage form comprises atrasentan or a pharmaceutically acceptable salt thereof and an anti-oxidant. In certain of these embodiments, the anti-oxidant is L-cysteine, or pharmaceutically acceptable salt or ester thereof. In some embodiments, the molar ratio of the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable

salt or ester thereof) is from about 5:1 to about 1:5. In certain of the foregoing embodiments, the dosage form further comprises a pharmaceutically acceptable polymeric binder selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose; the molar ratio of the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable salt or ester thereof) to atrasentan, or pharmaceutically acceptable salt thereof, is from about 5:1 to about 1:5; and the weight to weight ratio of the binder to atrasentan, or pharmaceutically acceptable salt thereof, is from about 1:1 to about 20:1 on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form further comprises a disintegrant and the weight to weight ratio of the disintegrant to the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable salt or ester thereof) is from about 60:1 to about 3:1. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in this dosage form is from about 0.2 weight percent to about 1.0 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form comprises from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00398] In some embodiments, the dosage form comprises a pharmaceutically acceptable polymeric binder selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose; the molar ratio of the anti-oxidant (e.g., L-cysteine, or a pharmaceutically acceptable salt or ester thereof), to atrasentan, or pharmaceutically acceptable salt thereof, is from about 2:1 to about 1:2; and the weight to weight ratio of the binder to atrasentan, or pharmaceutically acceptable salt thereof, is from about 1:1 to about 15:1 on an atrasentan free base equivalent weight basis. In some embodiments, the dosage form further comprises a disintegrant and the weight to weight ratio of the disintegrant to the anti-oxidant (e.g., L-cysteine, or a pharmaceutically acceptable salt or ester thereof), is from about 50:1 to about 4:1. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in this dosage form is from about 0.2 weight percent to about 1.0 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form comprises from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00399] In some embodiments, the dosage form comprises a pharmaceutically acceptable polymeric binder selected from the group consisting of hydroxymethylpropylcellulose,

hydroxyethylpropylcellulose, and hydroxypropylcellulose; the molar ratio of the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable salt or ester thereof), to atrasentan, or pharmaceutically acceptable salt thereof, is about 1:1; and the weight to weight ratio of the binder to atrasentan, or pharmaceutically acceptable salt thereof, is from about 1:1 to about 15:1 on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form further comprises a disintegrant and the weight to weight ratio of the disintegrant to the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable salt or ester thereof), is from about 35:1 to about 5:1. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in this dosage form is from about 0.3 weight percent to about 0.8 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form comprises from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, this dosage form comprises from about 1.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00400] In some embodiments, the dosage form comprises a pharmaceutically acceptable polymeric binder selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose; the dosage form comprises from about 0.05 weight percent to about 1.0 weight percent of the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable salt or ester thereof); and the dosage form comprises from about 1.0 weight percent to about 10.0 weight percent of the binder. In some embodiments, this dosage form further comprises a disintegrant and the weight percent of the disintegrant in the dosage form is from about 1.0 weight percent to about 10.0 weight percent. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in this dosage form is from about 0.1 weight percent to about 2.0 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form comprises from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, this dosage form comprises from about 1.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00401] In some embodiments, the dosage form comprises a pharmaceutically acceptable polymeric binder selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose; the dosage form comprises from about 0.07 weight percent to about 0.70 weight percent of the anti-oxidant (e.g., L-cysteine, or

pharmaceutically acceptable salt or ester thereof); and the dosage form comprises from about 1.0 weight percent to about 8.0 weight percent of the binder. In some embodiments, this dosage form further comprises a disintegrant and the weight percent of the disintegrant in the dosage form is from about 1.0 weight percent to about 6.0 weight percent. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in this dosage form is from about 0.2 weight percent to about 1.0 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form comprises from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, this dosage form comprises from about 1.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00402] In some embodiments, the dosage form comprises a pharmaceutically acceptable polymeric binder selected from the group consisting of hydroxymethylpropylcellulose, hydroxyethylpropylcellulose, and hydroxypropylcellulose; the dosage form comprises from about 0.09 weight percent to about 0.80 weight percent of the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable salt or ester thereof) and the dosage form comprises from about 1.0 weight percent to about 5.0 weight percent of the binder. In some embodiments, this dosage form further comprises a disintegrant and the weight percent of the disintegrant in the dosage form is from about 1.0 weight percent to about 4.0 weight percent. In some embodiments, the weight percent of atrasentan, or pharmaceutically acceptable salt thereof, in this dosage form is from about 0.3 weight percent to about 0.8 weight percent on an atrasentan free base equivalent weight basis. In some embodiments, this dosage form comprises from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, this dosage form comprises from about 1.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00403] In some embodiments, the dosage form comprises:

- (a) about 0.1 weight percent to about 2.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
- (b) about 0.05 weight percent to about 1.0 weight percent of the anti-oxidant (e.g., L-cysteine, or pharmaceutically acceptable salt or ester thereof);
- (c) about 75 weight percent to about 99 weight percent of the diluent;
- (d) about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable binder;

- (e) optionally, about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable disintegrant;
 - (f) optionally, about 0 weight percent to about 1.5 weight percent of a pharmaceutically acceptable glidant; and
 - (g) optionally, about 0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable lubricant;
- wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00404] In some embodiments, the dosage form comprises:

- (a) about 0.1 weight percent to about 2.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
- (b) about 0.05 weight percent to about 1.0 weight percent of the anti-oxidant (L-cysteine, or pharmaceutically acceptable salt or ester thereof);
- (c) about 75 weight percent to about 99 weight percent of the diluent;
- (d) about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable binder;
- (e) about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable disintegrant;
- (f) optionally, about 0 weight percent to about 1.5 weight percent of a pharmaceutically acceptable glidant; and
- (g) optionally, about 0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00405] In some embodiments, the dosage form comprises:

- (a) about 0.2 weight percent to about 1.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
- (b) about 0.07 weight percent to about 0.7 weight percent of the anti-oxidant (L-cysteine, or pharmaceutically acceptable salt or ester thereof);
- (c) about 82 weight percent to about 99 weight percent of the diluent;
- (d) about 1.0 weight percent to about 8.0 weight percent of a pharmaceutically acceptable binder;
- (e) optionally, about 1.0 weight percent to about 6.0 weight percent of a pharmaceutically acceptable disintegrant;

(f) optionally, about 0 weight percent to about 1.0 weight percent of a pharmaceutically acceptable glidant; and
(g) optionally, about 0 weight percent to about 3.0 weight percent of a pharmaceutically acceptable lubricant;
wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00406] In some embodiments, the dosage form comprises:

(a) about 0.2 weight percent to about 1.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
(b) about 0.07 weight percent to about 0.70 weight percent of L-cysteine, or pharmaceutically acceptable salt or ester thereof;
(c) about 82 weight percent to about 99 weight percent of the diluent;
(d) about 1.0 weight percent to about 8.0 weight percent of a pharmaceutically acceptable binder;
(e) about 1.0 weight percent to about 6.0 weight percent of a pharmaceutically acceptable disintegrant;
(f) optionally, about 0 weight percent to about 1.0 weight percent of a pharmaceutically acceptable glidant; and
(g) optionally, about 0 weight percent to about 3.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00407] In some embodiments, the dosage form comprises:

(a) about 0.3 weight percent to about 0.8 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
(b) about 0.09 weight percent to about 0.50 weight percent of L-cysteine, or pharmaceutically acceptable salt or ester thereof;
(c) about 87 weight percent to about 99 weight percent of a pharmaceutically acceptable diluent;
(d) about 1.0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable binder;
(e) optionally, about 1.0 weight percent to about 4.0 weight percent of a pharmaceutically acceptable disintegrant;
(f) optionally, about 0 weight percent to about 0.75 weight percent of a pharmaceutically acceptable glidant; and

(g) optionally, about 0 weight percent to about 2.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00408] In some embodiments, the dosage form comprises:

(a) about 0.3 weight percent to about 0.8 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;

(b) about 0.09 weight percent to about 0.50 weight percent of L-cysteine, or pharmaceutically acceptable salt or ester thereof;

(c) about 87 weight percent to about 99 weight percent of a pharmaceutically acceptable diluent;

(d) about 1.0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable binder;

(e) about 1.0 weight percent to about 4.0 weight percent of a pharmaceutically acceptable disintegrant;

(f) optionally, about 0 weight percent to about 0.75 weight percent of a pharmaceutically acceptable glidant; and

(g) optionally, about 0 weight percent to about 2.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00409] In some embodiments, the dosage form comprises:

(a) about 0.1 weight percent to about 2.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;

(b) about 75 weight percent to about 99 weight percent of the diluent;

(c) about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable binder;

(d) optionally, about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable disintegrant;

(e) optionally, about 0 weight percent to about 1.5 weight percent of a pharmaceutically acceptable glidant; and

(f) optionally, about 0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00410] In some embodiments, the dosage form comprises:

- (a) about 0.1 weight percent to about 2.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
- (b) about 75 weight percent to about 99 weight percent of the diluent;
- (c) about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable binder;
- (d) about 1.0 weight percent to about 10.0 weight percent of a pharmaceutically acceptable disintegrant;
- (e) optionally, about 0 weight percent to about 1.5 weight percent of a pharmaceutically acceptable glidant; and
- (f) optionally, about 0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00411] In some embodiments, the dosage form comprises:

- (a) about 0.2 weight percent to about 1.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
- (b) about 82 weight percent to about 99 weight percent of the diluent;
- (c) about 1.0 weight percent to about 8.0 weight percent of a pharmaceutically acceptable binder;
- (d) optionally, about 1.0 weight percent to about 6.0 weight percent of a pharmaceutically acceptable disintegrant;
- (e) optionally, about 0 weight percent to about 1.0 weight percent of a pharmaceutically acceptable glidant; and
- (f) optionally, about 0 weight percent to about 3.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00412] In some embodiments, the dosage form comprises:

- (a) about 0.2 weight percent to about 1.0 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;
- (b) about 82 weight percent to about 99 weight percent of the diluent;
- (c) about 1.0 weight percent to about 8.0 weight percent of a pharmaceutically acceptable binder;
- (d) about 1.0 weight percent to about 6.0 weight percent of a pharmaceutically acceptable disintegrant;

(e) optionally, about 0 weight percent to about 1.0 weight percent of a pharmaceutically acceptable glidant; and

(f) optionally, about 0 weight percent to about 3.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00413] In some embodiments, the dosage form comprises:

(a) about 0.3 weight percent to about 0.8 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;

(b) about 87 weight percent to about 99 weight percent of a pharmaceutically acceptable diluent;

(c) about 1.0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable binder;

(d) optionally, about 1.0 weight percent to about 4.0 weight percent of a pharmaceutically acceptable disintegrant;

(e) optionally, about 0 weight percent to about 0.75 weight percent of a pharmaceutically acceptable glidant; and

(f) optionally, about 0 weight percent to about 2.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00414] In some embodiments, the dosage form comprises:

(a) about 0.3 weight percent to about 0.8 weight percent of atrasentan, or pharmaceutically acceptable salt thereof, on an atrasentan free base equivalent weight basis;

(b) about 87 weight percent to about 99 weight percent of a pharmaceutically acceptable diluent;

(c) about 1.0 weight percent to about 5.0 weight percent of a pharmaceutically acceptable binder;

(d) about 1.0 weight percent to about 4.0 weight percent of a pharmaceutically acceptable disintegrant;

(e) optionally, about 0 weight percent to about 0.75 weight percent of a pharmaceutically acceptable glidant; and

(f) optionally, about 0 weight percent to about 2.0 weight percent of a pharmaceutically acceptable lubricant;

wherein the cumulative weight percent for all components of the dosage form equals 100 percent.

[00415] In some embodiments, the dosage form satisfies one or more of the following conditions:

- (a) the diluent is lactose;
- (b) the dosage form comprises a pharmaceutically acceptable binder and the binder is hydroxypropyl methylcellulose;
- (c) the dosage form comprises a pharmaceutically acceptable disintegrant and the disintegrant is crospovidone;
- (d) the dosage form comprises a pharmaceutically acceptable glidant and the glidant is silicon dioxide;
- (e) the dosage form comprises a pharmaceutically acceptable lubricant and the lubricant is glyceryl behenate.

[00416] In some embodiments, the dosage form is a solid pharmaceutical dosage form comprising from about 0.25 mg to about 1.25 mg of the atrasentan or a pharmaceutically acceptable salt thereof (e.g., atrasentan hydrochloride) on an atrasentan parent equivalent weight basis. In some embodiments, the pharmaceutical composition comprises from about 0.40 mg to about 1.00 mg of atrasentan or a pharmaceutically acceptable salt thereof (e.g., atrasentan hydrochloride) on an atrasentan parent equivalent weight basis. In some embodiments, the pharmaceutical composition comprises from about 0.40 mg to about 0.85 mg of atrasentan or a pharmaceutically acceptable salt thereof (e.g., atrasentan hydrochloride) on an atrasentan parent equivalent weight basis. In some embodiments, the pharmaceutical composition comprises from about 0.50 mg of atrasentan or a pharmaceutically acceptable salt thereof (e.g., atrasentan hydrochloride) on an atrasentan parent equivalent weight basis. In some embodiments, the pharmaceutical composition comprises from about 0.75 mg of atrasentan or a pharmaceutically acceptable salt thereof (e.g., atrasentan hydrochloride) on an atrasentan parent equivalent weight basis. In some embodiments, the dosage form is a solid pharmaceutical dosage form comprising from about 1.25 mg to about 1.75 mg of the atrasentan or a pharmaceutically acceptable salt thereof (e.g., atrasentan hydrochloride) on an atrasentan parent equivalent weight basis. In some embodiments, the pharmaceutical composition comprises from about 1.5 mg of atrasentan or a pharmaceutically acceptable salt thereof (e.g., atrasentan hydrochloride) on an atrasentan parent equivalent weight basis. In certain of the foregoing embodiments, the dosage form is a tablet.

[00417] In some embodiments, the dosage form is a tablet. In some embodiments, the tablet has a weight from about 37.5 mg to about 1500 mg. In some embodiments, the tablet has a weight from about 50 mg to about 750 mg. In some embodiments, the tablet has a weight

from about 50 mg to about 250 mg. In some embodiments, the tablet has a weight from about 75 mg to about 500 mg. In some embodiments, the tablet has a weight from about 75 mg to about 150 mg. In some embodiments, the tablet has a weight from about 100 mg to about 250 mg. In some embodiments, the tablet has a weight from about 100 mg to about 230 mg. In some embodiments, the tablet has a water content is below about 10%. In certain embodiments, the tablet has a water content of about 4%-6% (e.g., about 4%-5%).

[00418] In general, the tablet optionally can be surrounded or coated with at least one non-rate-controlling layer. The non-rate-controlling layer can be formed as a single layer, coating or membrane or a plurality of single layers, coatings or membranes. The functions of the non-rate-controlling layer can include, for example, providing further stability for the atrasentan, serving as a process aid and/or as a cosmetic enhancement for the formulation, and/or acting as a masking agent to reduce any undesired odor associated with the formulation (such as the odor commonly associated with L-cysteine).

[00419] When the dosage form comprises a non-rate-controlling layer, the non-rate-controlling layer can be made of one or more polymers, as well as, other ingredients known in the art, such as, but not limited to, plasticizers, pigments/opacifiers, waxes, etc. Examples of polymers that can be used include, but are not limited to, hydroxypropyl methylcellulose, hydroxypropyl cellulose, methylcellulose, polyvinyl alcohol and polyethylene glycol. Examples of plasticizers that can be used include, but are not limited to, polyethylene glycol(s), glycerin, triacetin, triethyl citrate, diethyl phthalate, L-cysteine, and mineral oils. Examples of pigments/opacifiers that can be used include, but are not limited to, water soluble dyes (for example, sunset yellow, quinoline yellow, erythrosine, and tartrazine), pigments (for example, aluminum lakes, titanium oxides, iron oxides and talc), and natural products (for example, riboflavin, carotenoids, chlorophyll, anthocyanins, and carmine). An example of a wax that can be used includes, but is not limited to, a paraffin wax.

[00420] In some embodiments, the dosage form is a tablet coated with a pharmaceutically acceptable polymer.

[00421] In some embodiments, the dosage form is a capsule.

[00422] In some embodiments, the dosage form is packaged in a semi-permeable container. In some embodiments, the semi-permeable container is a blister pack.

[00423] In some embodiments, the dosage form is packaged in a substantially impermeable container.

[00424] In some embodiments, the dosage form is an immediate release dosage form. In some embodiments, the dosage form is an immediate release tablet and releases at least about 85% of the atrasentan, or pharmaceutically acceptable salt thereof, within about 45 minutes as determined in an in vitro dissolution test conducted using a USP Dissolution Apparatus 2 (Paddle Apparatus), a 0.01N hydrochloric acid dissolution medium, and a paddle rotation of 50 RPM. In some embodiments, the dosage form is an immediate release tablet and releases at least about 75% of the atrasentan, or pharmaceutically acceptable salt thereof, within about 30 minutes.

[00425] In some embodiments, the dosage form comprises less than about 1.0 weight percent of total impurities resulting from degradation of the atrasentan, or pharmaceutically acceptable salt thereof, after a storage period of six months at about 40° C. and about 75% relative humidity. In some embodiments, degradation of the atrasentan, or pharmaceutically acceptable salt thereof, is analyzed using high-performance liquid chromatography.

[00426] In some embodiments, the dosage form comprises less than about 0.6 weight percent of any single impurity resulting from degradation of the atrasentan, or pharmaceutically acceptable salt thereof, after a storage period of six months at about 40° C and about 75% relative humidity. In some embodiments, degradation of the atrasentan, or pharmaceutically acceptable salt thereof, is analyzed using high-performance liquid chromatography.

[00427] In some embodiments, the dosage form comprises less than about 1.0 weight percent of total impurities and less than about 0.6 weight percent of any single impurity resulting from degradation of the atrasentan, or pharmaceutically acceptable salt thereof, after a storage period of six months at about 40° C and about 75% relative humidity. In some embodiments, degradation of the atrasentan, or pharmaceutically acceptable salt thereof, is analyzed using high-performance liquid chromatography.

[00428] In certain embodiments, the dosage form is selected from the group consisting of:

Tablet Core Composition		
Ingredient	Weight/Weight%	mg/Tablet
Atrasentan Monohydrochloride	0.31	0.37 ^a
Lactose Monohydrate (Regular)	91.19	109.4
Hypromellose E5 (Premium IV)	3.00	3.6
Crospovidone (Polyplasdone™ XL)	3.50	4.2
Silicon Dioxide (SYLOID®)	0.50	0.6
Glyceryl Behenate (COMPRITOL®)	1.50	1.8
Purified Water ^b	n/a	n/a
Total	100%	120 mg
Film Coated Table Composition		
Ingredient	Weight/Weight% ^c	mg/Tablet ^d
PEG1450	3	0.1
Hypromellose E3 (Premium IV)	97	3.5
Purified Water	n/a	n/a

^aAtrasentan monohydrochloride salt factor = 1.07 (i.e., 0.35 mg free base × 1.07 = 0.37 mg salt).

^bGranulation suspension medium. Less than 2% in final product.

^cBased on aqueous solution of 10% solids.

^dBased on a 120 mg tablet weight with a coating weight gain of 3%.

Tablet Core Composition		
Ingredient	Weight/Weight%	mg/Tablet
Atrasentan Monohydrochloride	0.4460	0.5350 ^a
Lactose Monohydrate (Regular)	91.05	109.3
Hypromellose E5 (Premium IV)	3.000	3.600
Crospovidone (Polyplasdone™ XL)	3.500	4.200
Silicon Dioxide (SYLOID® 244FP)	0.500	0.600
Glyceryl Behenate (COMPRITOL®)	1.500	1.80
Purified Water ^b	n/a	n/a
Total	100%	120 mg
Film Coated Table Composition		

Ingredient	Weight/Weight% ^c	mg/Tablet ^d
PEG1450	3	0.1080
Hypromellose E3 (Premium IV)	97	3.492
Purified Water	n/a	n/a
Total	100%	123.6 mg

^aAtrasentan monohydrochloride salt factor = 1.07 (i.e., 0.50 mg free base $\times$ 1.07 = 0.5350 mg salt).

^bGranulation suspension medium. Less than 2% in final product.

^cBased on aqueous solution of 10% solids.

^dBased on a 120 mg tablet weight with a coating weight gain of 3%.

Tablet Core Composition		
Ingredient	Weight/Weight%	mg/Tablet
Atrasentan Monohydrochloride	0.6690	0.8025 ^a
Lactose Monohydrate (Regular)	90.83	109.0
Hypromellose E5 (Premium IV)	3.000	3.600
Crospovidone (Polyplasdone™ XL)	3.500	4.200
Silicon Dioxide (SYLOID® 244FP)	0.500	0.600
Glyceryl Behenate (COMPRITOL®)	1.500	1.80
Purified Water ^b	n/a	n/a
Total	100%	120 mg
Film Coated Table Composition		
Ingredient	Weight/Weight% ^c	mg/Tablet ^d
PEG1450	3	0.1080
Hypromellose E3 (Premium IV)	97	3.492
Purified Water	n/a	n/a
Total	100%	123.6 mg

^aAtrasentan monohydrochloride salt factor = 1.07 (i.e., 0.75 mg free base $\times$ 1.07 = 0.8025 mg salt).

^bGranulation suspension medium. Less than 2% in final product.

^cBased on aqueous solution of 10% solids.

^dBased on a 120 mg tablet weight with a coating weight gain of 3%.

[00429] In certain embodiments, the dosage form is selected from the group consisting of:

Tablet Core Composition		
Ingredient	Weight/Weight%	mg/Tablet

Atrasentan Monohydrochloride	0.4460	0.5350 ^a
Lactose Monohydrate (Regular)	90.91	109.1
L-Cysteine Hydrochloride Monohydrate	0.1440	0.1728
Hypromellose E5 (Premium IV)	3.000	3.600
Crospovidone (Polyplasdone™ XL)	3.500	4.200
Silicon Dioxide (SYLOID® 244FP)	0.500	0.600
Glyceryl Behenate (COMPRITOL®)	1.500	1.800
Purified Water ^b	n/a	n/a
Total	100%	120 mg

Film Coated Table Composition

Ingredient	Weight/Weight% ^c	mg/Tablet ^d
PEG1450	3	0.1
Hypromellose E3 (Premium IV)	97	3.5
Purified Water	n/a	n/a
Total	100%	123.6 mg

^aAtrasentan monohydrochloride salt factor = 1.07 (i.e., 0.5 mg free base × 1.07 = 0.5350 mg salt).

^bGranulation suspension medium. Less than 2% in final product.

^cBased on aqueous solution of 10% solids.

^dBased on a 120 mg tablet weight with a coating weight gain of 3%.

Tablet Core Composition		
Ingredient	Weight/Weight%	mg/Tablet
Atrasentan Monohydrochloride	0.6690	0.8025 ^a
Lactose Monohydrate (Regular)	90.61	108.7
L-Cysteine Hydrochloride Monohydrate	0.216	0.2592
Hypromellose E5 (Premium IV)	3.000	3.600
Crospovidone (Polyplasdone™ XL)	3.500	4.200
Silicon Dioxide (SYLOID® 244FP)	0.500	0.600

Glyceryl Behenate (COMPRITOL®)	1.500	1.800
Purified Water ^b	n/a	n/a
Total	100%	120 mg
Film Coated Table Composition		
Ingredient	Weight/Weight%^c	mg/Tablet^d
PEG1450	3	0.1080
Hypromellose E3 (Premium IV)	97	3.492
Purified Water	n/a	n/a
Total	100%	123.6 mg

^aAtrasentan monohydrochloride salt factor = 1.07 (i.e., 0.75 mg free base × 1.07 = 0.8025 mg salt).

^bGranulation suspension medium. Less than 2% in final product.

^cBased on aqueous solution of 10% solids.

^dBased on a 120 mg tablet weight with a coating weight gain of 3%.

Tablet Core Composition		
Ingredient	Weight/Weight%	mg/Tablet
Atrasentan Monohydrochloride	0.31	0.372 ^a
Lactose Monohydrate (Regular)	91.09	109.3
L-Cysteine Hydrochloride Monohydrate	0.0999	0.120
Hypromellose E5 (Premium IV)	3.00	3.6
Crospovidone (Polyplasdone™ XL)	3.50	4.2
Silicon Dioxide (SYLOID® 244FP)	0.50	0.60
Glyceryl Behenate (COMPRITOL®)	1.50	1.8
Purified Water ^b	n/a	n/a
Total	100%	120 mg
Film Coated Table Composition		
Ingredient	Weight/Weight%^c	mg/Tablet^d
PEG1450	3	0.1
Hypromellose E3 (Premium IV)	97	3.5
Purified Water	n/a	n/a
Total	100%	123.6 mg

^aAtrasentan monohydrochloride salt factor = 1.07 (i.e., 0.35 mg free base × 1.07 = 0.37 mg salt).

^bGranulation suspension medium. Less than 2% in final product.

^cBased on aqueous solution of 10% solids.

^dBased on a 120 mg tablet weight with a coating weight gain of 3%.

[00430] The formulations of atrasentan or a pharmaceutically acceptable salt thereof and methods of making the same are further described in U.S. Patent No. 9,364,458 and U.S. Patent No. 10,016,393, each of which is incorporated herein by reference in its entirety.

VII. DOSAGE AND ADMINISTRATION

[00431] In some embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is between about 0.001 mg and 0.1 mg per kg of the subject's body weight (*e.g.*, about 0.001, about 0.002, about 0.003, about 0.004, about 0.005, about 0.006, about 0.007, about 0.008, about 0.009, about 0.01, about 0.015, about 0.02, about 0.025, about 0.03, about 0.035, about 0.04, about 0.045, about 0.05, about 0.055, about 0.06, about 0.065, about 0.07, about 0.075, about 0.08, about 0.085, about 0.09, about 0.095, or about 0.10 mg per kg, or any value in between, of the subject's body weight) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00432] In some embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is between about 0.1 mg and 10 mg (*e.g.* about 0.1, about 0.2, about 0.3, about 0.4, about 0.5, about 0.6, about 0.7, about 0.75, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 1.6, about 1.7, about 1.8, about 1.9, about 2.0, about 2.5, about 3.0, about 3.5, about 4.0, about 4.5, about 5.0, about 5.5, about 6.0, about 6.5, about 7.0, about 7.5, about 8.0, about 8.5, about 9.0, about 9.5, or about 10.0 mg, or any value in between) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is about 0.75 mg (*e.g.*, when administered once per day) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is about 0.25 mg (*e.g.*, when administered once per day) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is about 0.35 mg (*e.g.*, when administered once per day) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is about 1.0 mg (*e.g.*, when administered once per day) of atrasentan or an

equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is about 1.25 mg (*e.g.*, when administered once per day) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is about 1.5 mg (*e.g.*, when administered once per day) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is about 1.75 mg (*e.g.*, when administered once per day) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain of these embodiments, a dose of atrasentan or a pharmaceutically acceptable salt thereof is 0.75 mg (*e.g.*, 1×0.75 mg tablets; or 1.5×0.50 mg tablets) of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof, administered once per day.

[00433] In some embodiments, a dose of atrasentan, or salt or solvate thereof, contains a therapeutically effective amount of atrasentan, or salt or solvate thereof. In other embodiments, a dose of atrasentan, or salt or solvate thereof, contains less than a therapeutically effective amount of atrasentan, or salt or solvate thereof, (*e.g.*, when multiple doses are given in order to achieve the desired clinical or therapeutic effect).

[00434] In some embodiments, the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.20 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. For example, the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof can be about 0.20 mg, about 0.30 mg, about 0.40 mg, about 0.50 mg, about 0.60 mg, about 0.70 mg, about 0.80 mg, about 0.90 mg, about 1.0 mg, about 1.1 mg, about 1.2 mg, about 1.3 mg, about 1.4 mg, or about 1.5 mg of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.25 mg to about 1.25 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. In certain embodiments, the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.40 mg to about 0.85 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. For example, the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof can be about 0.5 mg, about 0.55 mg, about 0.6 mg, about 0.65 mg, about 0.7 mg, about 0.75 mg, about 0.8 mg, or about 0.85 mg of atrasentan or an

equivalent amount of a pharmaceutically acceptable salt thereof. In some embodiments, the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 1.25 mg to about 1.75 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof. For example, the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof can be about 1.25 mg, about 1.3 mg, about 1.35 mg, about 1.4 mg, about 1.45 mg, about 1.5 mg, about 1.55 mg, about 1.6 mg, about 1.65 mg, about 1.7 mg, or about 1.75 mg of atrasentan or an equivalent amount of a pharmaceutically acceptable salt thereof. As a non-limiting example, the therapeutically effective amount of atrasentan or pharmaceutically acceptable salt thereof can be about 0.75 mg of atrasentan or about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

[00435] Atrasentan, or salt or solvate thereof, can be administered by any suitable route and mode. Suitable routes of administering antibodies and/or antibody-drug conjugate of the present disclosure are well known in the art and may be selected by those of ordinary skill in the art. In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof administered parenterally. Parenteral administration refers to modes of administration other than enteral and topical administration, usually by injection, and include epidermal, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, intratendinous, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intracranial, intrathoracic, epidural and intrasternal injection and infusion. In some embodiments, the route of administration of atrasentan is intravenous injection or infusion. In some embodiments, the route of administration of atrasentan is intravenous infusion. In some embodiments, the route of administration of atrasentan is intravenous injection or infusion. In some embodiments, the atrasentan is intravenous infusion. In some embodiments, the route of administration of atrasentan is oral.

[00436] In one embodiment of the methods or uses or product for uses provided herein, atrasentan is administered to the subject daily, twice daily, three times daily or four times daily. In some embodiments, atrasentan is administered to the subject every other day, once about every week or once about every three weeks. In some embodiments, atrasentan is administered to the subject once per day. In some embodiments, atrasentan is administered to the subject twice per day. In some embodiments, atrasentan is administered to the subject at a dose of about 0.75 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of 0.75

mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of about 0.25 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of 0.25 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of about 0.35 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of 0.35 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of about 0.5 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of 0.5 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of about 1.0 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of 1.0 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of about 1.5 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of 1.5 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of about 1.75 mg once per day. In some embodiments, atrasentan is administered to the subject at a dose of 1.75 mg once per day.

VIII. COMBINATION THERAPY

[00437] The methods of the present disclosure also contemplate treatments comprising administering atrasentan or a pharmaceutically acceptable salt thereof, as described in any of the embodiments of the disclosure, in combination with one or more additional therapeutic agents (such as an inhibitor of one or more elements of the renin-angiotensin-aldosterone system). Accordingly, atrasentan or a pharmaceutically acceptable salt thereof as described anywhere herein can be administered alone or in combination with one or more additional therapeutic agents. When administered in combination with one or more additional therapeutic agents, separate dosage forms can be administered to the subject or a single dosage form comprising both atrasentan, or a pharmaceutically acceptable salt thereof, and the additional therapeutic agent(s) can be administered to the subject. If administered as a separate dosage form, the additional therapeutic agent may be administered simultaneously with the atrasentan dosage form of the present disclosure or sequentially (in either order) with the atrasentan dosage form of the present disclosure. Administration of two or more agents in combination can also be referred to herein as “co-administration.”

[00438] Representative additional therapeutic agents include, for example, diuretics, antihypertensive agents, therapeutic agents for diabetes or diabetic complications, and therapeutic agents for hyperlipidemia.

[00439] In some instances, one or more additional agents is administered at a dosage that is stable for at least 12 weeks prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof

[00440] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more diuretics such as hydrochlorothiazide (such as MICROZIDE™ or ORETIC™), hydroflumethiazide (such as SALURON™), bumetanide (such as BUMEX™), torsemide (such as DEMADEx™), metolazone (such as ZAROXOLYN™), chlorothiazide (such as DIURIL™, ESIDRIX™ or HYDRODIURIL™) triamterene (such as DYRENIUM™), ethacrynic acid (such as EDECRIN™), chlorthalidone (such as HYGROTON™), furosemide (such as LASIX™), indapamide (such as LOZOL™) or amiloride (such as MIDAMOR™ or MODURETIC™).

[00441] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more thiazide diuretics, such as chlorothiazide, chlorthalidone, hydrochlorothiazide, trichlormethiazide, indapamide, or metolazone.

[00442] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more loop diuretics, such as bumetanide, ethacrynic acid, furosemide, or torsemide.

[00443] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more potassium-sparing diuretics, such as amiloride, eplerenone, spironolactone, and triamterene.

[00444] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more angiotensin converting enzyme (ACE) inhibitors such as quinapril (such as ACCUPRIL™), fosinopril, perindopril (such as ACEON™), captopril (such as CAPOTEN™), enalapril (such as VASOTEC™), ENALAPRILAT™, ramipril (such as ALTACE™), cilazapril, delapril, fosinopril (such as MONOPRIL™), zofenopril, indolapril, benazepril (such as LOTENSIN™), lisinopril (such as PRINIVIL™ or ZESTRIL™), spirapril,trandolapril (such as MAVIK™), perindopril, pentopril, moexipril (such as UNIVASC™), pivopril, temocapril, omapatrilat, imidapril, rescinamine, benazeprilat, fosinoprilat, ramiprilat,

perindoprilat, quinaprilat, trandolaprilat, moexiprilat, Quinoline Yellow WS, or cilazaprilat. In certain embodiments, the ACE inhibitor is selected from: quinapril, fosinopril perindopril, captopril, enalapril, enalaprilat, ramipril, cilazapril, delapril, fosinopril, zofenopril, indolapril, benazepril, lisinopril, spirapril, trandolapril, perindep, pentopril, moexipril, rescinamine, and pivopril.

[00445] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more angiotensin II receptor blockers (ARB) such as candesartan (such as ATACAND™), candesartan cilexetil, eprosartan (such as TEVETEN™), irbesartan (such as AVEPRO™) losartan (such as COZAAR™), olmesartan, olmesartan medoxomil (such as BENICAR™) tasosartan, telmisartan (such as MICARDIS™), valsartan (such as DIOVAN™), zolasartan, azilsartan medoxomil, F1-6828K, RNH-6270, UR-7198, Way-126227, KRH-594, TAK-536, BRA-657, or TA-606. In certain embodiments, the ARB is selected from: candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan, olmesartan medoxomil, telmisartan, valsartan, azilsartan medoxomil, and BRA-657.

[00446] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more calcium channel blockers such as nifedipine (such as ADALAT™, ADALAT CC™, or PROCARDIA™), verapamil (such as GALAN™, COVERA-HS™, ISOPTIN SR™, or VERELAN™), diltiazem (such as CARDIZEM™, CARDIZEM CD™, CARDIZEM LA™, CARDIZEM SR™, DILACOR™, TIAMATE™, or TIAZAC™), isradipine (such as DYNACIRC™ or DYNACIRC CR™), amlodipine (such as NORVASC™), felodipine (such as PLENDIL™), nisoldipine (such as SULAR™), bepridil (such as VASCOR™), vatanidipine, clevidipine, lercanidipine, or dilitiazem.

[00447] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more renin inhibitors such as aliskiren (such as TEKTURNAT™).

[00448] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more aldosterone receptor antagonists such as eplerenone (such as INSpra™) or spironolactone (such as ALDACTONE™).

[00449] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more alpha blockers such as doxazosin (such as

CARDURA™) phenoxybenzamine (such as DIBENZYLINE™), terazosin (such as HYTRIN™), CDR1-93/478, or CR-2991.

[00450] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more beta blockers such as timolol (such as BLOCARDENT™) carteolol (such as CARTROL™), carvedilol (such as COREG™), nadolol (such as CORGARD™), propranolol (such as INNOPRAN XL™), betaxolol (such as KERLONE™) penbutolol (such as LEVATOL™), metoprolol (such as LOPRESSOR™ or TOPROL-XL™), atenolol (such as TENORMIN™), pindolol (such as VISKEN™), or bisoprolol.

[00451] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more alpha-beta blockers such as labetalol (such as NORMODYNE™ or TRANDATE™).

[00452] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more central antiadrenergics such as methyl dopa (such as ALDOMET™), clonidine (such as CATAPRES™ or CATAPRES-TTS™), guanfacine (such as TENEX™), or guanabenz (such as WYTENSIN™).

[00453] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more glycosides/inotropic agents such as digoxin (such as LANOXIN™).

[00454] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more alpha glucosidase inhibitors, such as miglitol (such as GLYSET™) or acarbose (such as PRECOSE™).

[00455] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more biguanides, such as roseiglitazone (such as AVANDAMET™) or metformin (such as GLUCOPHAGE™ or GLUCOPHAGE XR™).

[00456] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more insulins, such as HUMALOG™, HUMALOG 50/50™, HUMALOG 75/25™, HUMULIN 50/50™, HUMALIN 75/25™, HUMALIN L™, HUMALIN N™, HUMALIN R™, HUMALIN R U-500™, HUMALIN U™, ILETIN II LENTE™, ILETIN II NPH™, ILETIN II REGULAR™, LANTUS™, NOVOLIN 70/30™, NOVILIN N™, NOVILIN R™, NOVOLOG™, or VELOSULIN BR™, and EXUBERA™.

[00457] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more meglitinides, such as repaglinide (such as PRANDINTM) or nateglinide (such as STARLIXTM).

[00458] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more sulfonylureas, such as glimepiride (such as AMARYLTM), glyburide (such as DIABETATM, GLYNASE PRESTABTM or MICRONASETM), or glipizide (such as GLUCOTROLTM, or GLUCOTROL XLTM).

[00459] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more thiazolidinediones, such as pioglitazone (such as ACTOSTM) or rosiglitazone (such as AVANDIATM).

[00460] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with niacin or one or more nicotinic acid derivatives, such as NIACORTM, NIASPANTM, NICOLARTM, or SLO-NIACINTM.

[00461] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more fabric acid derivatives, such as clofibrate (such as ATROMID-STM), gemfibrozil (such as LOPIDTM), or fenofibrate (such as TRICORTM).

[00462] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more bile acid sequestrants, such as colestipol (such as COLESTIDTM), cholestyramine (such as LOCHOLESTTM, PREVALITETM, QUESTRANTM, or QUESTRAN LIGHTTM), or colesevelam (such as WELCHOLTM).

[00463] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more cholesterol absorption inhibitors, such as ezetimibe (such as ZETIATM).

[00464] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) such as fluvastatin (such as LESCOLTM), atorvastatin (such as LIPITORTM), lovastatin (such as ALTOCORTM or MEVACORTM), pravastatin (such as PRAVACHOLTM), rosuvastatin (such as CRESTORTM), simvastatin (such as ZOCORTM), or pitavastatin.

[00465] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more additional agents. In some embodiments, the

one or more additional agents is an immunosuppressant. In some embodiments, the one or more additional agents are selected from aminopterin, azathioprine, cyclosporin A, D-penicillamine, gold salts, hydroxychloroquine, leflunomide, methotrexate, minocycline, rapamycin, sulfasalazine, tacrolimus (FK506), and pharmaceutically acceptable salts thereof. As a non-limiting example, the one or more additional agents can be hydroxychloroquine.

[00466] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof may be co-administered with one or more additional therapeutic agents selected group the group consisting of SGLT-2 inhibitor (such as canagliflozin), GR-immunosuppressant (such as budesonide), MASP-2 antibodies (such as OMS721), dual ET1A/ARB inhibitors (such as sparsentan), B cell modulators (e.g., APRIL modulators such as atacicept, APL-2, and VIS649), SYK inhibitor (such as fosamatinib), complement factor 3 convertase inhibitor (such as LNP023), NRF2 activator (such as Bardoxolone), and RNAi therapeutic targeting the C5 component of the complement pathway (e.g., cemdisiram).

[00467] In some embodiments, the one or more additional agents are SGLT-2 inhibitors. In some embodiments, the one or more additional agents is a SGLT-2 inhibitor selected from dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, bexagliflozin, licogliflozin, janagliflozin (XZP-5695), tofogliflozin, ertugliflozin, henagliflozin (SHR-3824), enavogliflozin (DWP-16001), TA-1887 (3-(4-cyclopropylbenzyl)-4-fluoro-1-(β -D-glucopyranosyl)-1H-indole), indole-N-glycoside 18 (3-(4-ethylbenzyl)-1-(β -D-glucopyranosyl)-1H-indole), sotagliflozin, luseogliflozin, sergliflozin etabonate, remogliflozin, remogliflozin etabonate, and T-1095 (((2R,3S,4S,5R,6S)-6-(2-(3-(benzofuran-5-yl)propanoyl)-3-hydroxy-5-methylphenoxy)-3,4,5-trihydroxytetrahydro-2H-pyran-2-yl) etabonate). In some embodiments, the one or more additional agents is a SGLT-2 inhibitor selected from bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, licogliflozin, sotagliflozin, and tofogliflozin. In some embodiments, the one or more additional agents is bexagliflozin. In some embodiments, the one or more additional agents is canagliflozin. In some embodiments, the one or more additional agents is dapagliflozin. In some embodiments, the one or more additional agents is empagliflozin. In some embodiments, the one or more additional agents is ertugliflozin. In some embodiments, the one or more additional agents is ipragliflozin. In some embodiments, the one or more additional agents is luseogliflozin. In some embodiments, the one or more additional agents is remogliflozin. In some embodiments, the one or more

additional agents is sergliflozin. In some embodiments, the one or more additional agents is licogliflozin. In some embodiments, the one or more additional agents is sotagliflozin. In some embodiments, the one or more additional agents is tofogliflozin. In some embodiments, the SGLT-2 inhibitor is dapagliflozin propylene glycol hydrate. In some embodiments, the SGLT-2 inhibitor is canagliflozin hemihydrate.

[00468] In some embodiments, the amount of the SGLT-2 inhibitor is from about 1 mg to about 350 mg. For example, about 1 mg to about 175 mg, about 175 mg to about 350 mg, or about 90 mg to about 260 mg. In some embodiments, the amount of the SGLT-2 inhibitor is from about 85 mg to about 325 mg. In some embodiments, the amount of the SGLT-2 inhibitor is from about 1 mg to about 50 mg, about 20 mg to about 70 mg, about 50 mg to about 100 mg, about 70 mg to about 120 mg, about 90 mg to about 140 mg, about 110 mg to about 160 mg, about 130 mg to about 180 mg, about 150 mg to about 200 mg, about 170 mg to about 220 mg, about 190 mg to about 240 mg, about 210 mg to about 260 mg, about 230 mg to about 280 mg, about 250 mg to about 300 mg, about 270 mg to about 320 mg, or about 290 mg to about 350 mg. For example, about 100 mg or about 300 mg. In some embodiments, the amount of the SGLT-2 inhibitor is from about 1 to about 15 mg. For example, about 1 to about 10 mg or about 5 to about 15 mg. In some embodiments, the amount of the SGLT-2 inhibitor is from 1 mg to about 3 mg, about 2 mg to about 4 mg, about 3 mg to about 5 mg, about 4 mg to about 6 mg, about 5 mg to about 7 mg, about 6 mg to about 8 mg, about 7 mg to about 9 mg, about 8 mg to about 10 mg, about 9 mg to about 11 mg, about 10 mg to about 12 mg, about 11 mg to about 13 mg, about 12 mg to about 14 mg, or about 13 mg to about 15 mg.

[00469] In some embodiments, the SGLT-2 inhibitor is canagliflozin. In some embodiments, 100 mg or 300 mg of canagliflozin is administered. In some embodiments, 100 mg or 300 mg of canagliflozin hemihydrate is administered. In some embodiments, the SGLT-2 inhibitor is dapagliflozin. In some embodiments, the SGLT-2 inhibitor is dapagliflozin propylene glycol hydrate. In some embodiments, 5 mg or 10 mg of dapagliflozin is administered. In some embodiments, 5 mg or 10 mg of dapagliflozin propylene glycol hydrate is administered. In some embodiments, the SGLT-2 inhibitor is empagliflozin. In some embodiments, 10 mg or 25 mg of empagliflozin is administered. In some embodiments, the SGLT-2 inhibitor is ertugliflozin. In some embodiments, 5 mg or 15 mg of ertugliflozin is administered. In some embodiments, the SGLT-2 inhibitor is ipragliflozin. In some embodiments, 25 mg or 50 mg of ipragliflozin is

administered. In some embodiments, the SGLT-2 inhibitor is bexagliflozin. In some embodiments, 20 mg of bexagliflozin is administered. In some embodiments, the SGLT-2 inhibitor is sotagliflozin. In some embodiments, 200 mg or 400 mg of sotagliflozin is administered. In some embodiments, the SGLT-2 inhibitor is licogliflozin. In some embodiments, 15 mg, 50 mg, 75 mg or 150 mg of licogliflozin is administered.

[00470] In any of the embodiments described herein, various combinations of atrasentan, or a pharmaceutically acceptable salt thereof, and a SGLT-2 inhibitor, producing an effect, are contemplated. In some embodiments, the effect, for example, any of the beneficial or desired results as described herein, is greater than the sum of the effect observed when the same amount of atrasentan, or a pharmaceutically acceptable salt thereof, when co-administered, and the same amount of the SGLT-2 inhibitor when co-administered, are administered as a monotherapy. In some embodiments, the co-administration of atrasentan, or a pharmaceutically acceptable salt thereof, and a SGLT-2 inhibitor, produce an effect, for example, a therapeutic effect using a smaller dose of either, or both, of the compounds as a monotherapy. For example, producing a therapeutic effect using a smaller dose of atrasentan, or a pharmaceutically acceptable salt thereof, and/or the SGLT-2 inhibitor compared to the amount used in monotherapy. For example, in some embodiments, the dose of atrasentan, or a pharmaceutically acceptable salt thereof, administered in combination with a SGLT-2 inhibitor may be about 50% to about 90% of the dose of atrasentan, or a pharmaceutically acceptable salt thereof, administered as a monotherapy to produce the same therapeutic effect, e.g., any of the beneficial or desired results including described herein. In some embodiments, the dose of the SGLT-2 inhibitor, administered in combination with atrasentan, or a pharmaceutically acceptable salt thereof, may be about 50% to about 90% of the dose of the SGLT-2 inhibitor, administered as a monotherapy to produce the same therapeutic effect, e.g., any of the beneficial or desired results including described herein. For example, treating FSGS, decreasing renal inflammation and/or fibrosis, decreasing proteinuria, decreasing fatigue, reducing the rate of decline in eGFR, delaying the onset of ESKD, decreasing fatigue, and reducing activation of a mesangial cell.

[00471] In some embodiments, the present disclosure relates to the use of atrasentan or a pharmaceutically acceptable salt thereof in combination with a second therapeutic for treating a condition as described in the various embodiments of the disclosure.

[00472] In some embodiments, the present disclosure relates to the use of atrasentan or a pharmaceutically acceptable salt thereof, for treating a condition as described in the various embodiments of the disclosure, wherein the use comprises one or more additional therapeutic agent.

[00473] In some embodiments, the present disclosure relates to a pharmaceutical composition comprising atrasentan or a pharmaceutically acceptable salt thereof, and further comprising one or more additional therapeutic agent.

[00474] In some embodiments, the one or more additional therapeutic agent inhibits one or more elements of the renin-angiotensin-aldosterone system. In some embodiments, the one or more additional therapeutic agent is selected from the group consisting of diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor (ARB) blockers, calcium channel blockers, renin inhibitors, and aldosterone antagonists. In certain particular embodiments, the one or more additional therapeutic agent is selected from the group consisting of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs). In certain embodiments, the one or more additional therapeutic agent is selected from one or more angiotensin converting enzyme inhibitors. In certain embodiments, the one or more additional therapeutic agent is selected from one or more angiotensin II receptor blockers. In certain embodiments, the one or more additional therapeutic agent comprises one or more ACE inhibitors and one or more ARBs. For example, the one or more inhibitors of the renin-angiotensin system can be ACE inhibitor, ARB, or a combination thereof. For example, the ACE inhibitor can be selected from: quinapril, fosinopril perindopril, captopril, enalapril, enalaprilat, ramipril, cilazapril, delapril, fosinopril, zofenopril, indolapril, benazepril, lisinopril, spirapril,trandolapril, perindep, pentopril, moexipril, rescinnamine, and pivopril. For example, the ARB can be selected from: candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan, olmesartan medoxomil, telmisartan, valsartan, azilsartan medoxomil, and BRA-657.

[00475] In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof, may be co-administered with a SGLT-2 inhibitor and one or more ACE inhibitors and/or one or more ARBs. In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof, may be co-administered with a SGLT-2 inhibitor and one or more ACE inhibitors. In some embodiments, atrasentan or a pharmaceutically acceptable salt thereof, may be co-administered with a SGLT-2 inhibitor and one or more ARBs. In some embodiments, atrasentan

or a pharmaceutically acceptable salt thereof, may be co-administered with a SGLT-2 inhibitor, an ACE inhibitor, and an ARB.

[00476] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, patent applications, and sequence accession numbers cited herein are hereby incorporated by reference in their entirety for all purposes.

[00477] The disclosure will be more fully understood by reference to the following examples. They should not, however, be construed as limiting the scope of the disclosure. It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

EXAMPLES

Example 1: A Phase 2, Open-Label, Basket Study of Atrasentan in Patients with Proteinuric Glomerular Diseases

Background

[00478] Atrasentan has a well characterized safety profile in over 5,000 subjects with diabetic kidney disease (DKD). The benefit of atrasentan was demonstrated in DKD in reducing albuminuria and improving clinical outcomes. The present study evaluates efficacy and safety of 1.5 mg oral atrasentan daily (QD) (based on tolerability) in FSGS subjects who received and tolerated 0.75 mg atrasentan QD for 6 weeks (Cohort 5) or at least 12 weeks (Cohort 2b).

[00479] The most common adverse events associated with treatment (fluid retention, hemodilution, and vasodilation) were consistent with its on-target pharmacologic mechanism of action.

[00480] Through dose-range finding studies and exposure-response analyses, an optimal daily dose of atrasentan of 0.75 mg was identified that led to marked reduction in UACR with only modest fluid retention. This dose was then used in a large Phase 3 randomized placebo-controlled study in DKD subjects already optimized on RAS inhibitors to evaluate the effect of

atrasentan on delaying time to ESKD or doubling of serum creatinine. While this study was halted prematurely as a result of longer than expected timelines to completion due to a lower accrual of kidney events and despite the smaller number of primary endpoint events, subjects who tolerated atrasentan and demonstrated an early reduction of UACR showed a benefit on delaying renal outcomes. The risks of fluid retention were shown to be mitigated by careful monitoring and use of diuretics. Additional potential risks include decreased sperm concentrations, teratogenicity, and those related to atrasentan's vasodilatory effects including hypotension. In the present study, preliminary pharmacokinetic (PK) analysis available up to Week 24 in the FSGS cohort (Cohort 2) demonstrated lower than expected drug exposures (steady state 24h trough concentrations) in this cohort that were approximately half the drug exposures observed in the other cohorts (Cohort 1, 3 and 4) at 0.75 mg QD dosing. The mean steady state 24h-trough atrasentan plasma concentrations in the FSGS cohort (Cohort 2), are below the target range anticipated to produce a proteinuria lowering effect based on the exposure-response analysis in DKD population at the 0.75 mg/day dose level. Fluid retention in patients treated with atrasentan is based on an exposure to the drug rather than the dose, thus increasing the dose to 1.5 mg QD to achieve the target exposure range is not expected to increase adverse effects in this cohort.

[00481] In addition, patients with FSGS are dose titrated to 1.5 mg atrasentan if they demonstrate clinical safety and tolerability to 0.75 mg atrasentan.

[00482] The proposed dose of 0.75 mg daily atrasentan has been extensively studied clinically in over 5,000 subjects with DKD and has demonstrated significant reductions in albuminuria and the relative risk of the primary composite renal endpoint and has also shown an acceptable safety profile in this high-risk patient population. The 0.75 mg dose was selected from multiple dose range-finding Phase 2 studies in subjects with DKD. In the RADAR Phase 2b study, the 0.75 mg dose produced a near maximal (35%) proteinuria reduction with only minimal evidence for fluid retention based on assessment of body weight, edema incidence and treatment discontinuations (de Zeeuw, 2014). The higher 1.25 mg dose only incrementally further reduced proteinuria (38%) but was associated with greater fluid retention related adverse events including treatment discontinuation. Separate Phase 2 studies have shown that lower 0.25 mg and 0.5 mg doses of atrasentan, failed to significantly reduce proteinuria relative to placebo. A detailed PK-pharmacodynamic (PD) exposure-response (ER) model in DKD confirmed the 0.75 mg dose provides a C_{trough} range (1.2-2.2 ng/mL) that results in the most favorable benefit/risk with respect

to maximizing proteinuria reduction while minimizing the potential for fluid retention (Koomen, 2018; Heerspink et al, 2017). Atrasentan exposures below this therapeutic range were associated with insufficient proteinuria reduction for clinical benefit. Based on preliminary pharmacokinetic analyses available up to Week 24 in subjects with FSGS, lower than expected exposures (steady state 24-hour trough concentrations) were observed that were approximately half the exposures observed in subjects with other proteinuric glomerular diseases at 0.75 mg QD dosing and below the therapeutic exposure range established previously for proteinuria lowering in DKD. Therefore, subjects with FSGS will be dose titrated to a maximum of 1.5 mg daily of atrasentan if the 0.75 mg dose has been tolerated in an attempt to produce atrasentan C_{trough} exposures similar to the 0.75 mg dose in the other proteinuric glomerular diseases.

Table 1. Objectives and Endpoints:

Objectives	Endpoints	Cohort				
		1 IgAN	2 FSGS	3 Alport Syndrome	4 DKD	5 and 2b FSGS
Primary						
To evaluate the effect of atrasentan on proteinuria/albuminuria levels in subjects at risk of progressive loss of kidney function	Change from baseline at Week 12 in UPCR (based on 24-hour urine collection)	X	X	X		
	Change from baseline at Week 12 in UACR, based on first morning void (FMV) urine collection				X	
To evaluate the effect of atrasentan on proteinuria/albuminuria levels in subjects at risk of progressive loss of kidney function	- Change from baseline at Week 24 in UPCR (based on 24-hour urine collection) in Cohort 2b - Change from baseline at Week 30 in UPCR (based on 24-hour urine collection) for Cohort 5					X

Objectives	Endpoints	Cohort				
		1 IgAN	2 FSGS	3 Alport Syndrome	4 DKD	5 and 2b FSGS
Pharmacokinetics						
To evaluate the pharmacokinetics (PK) of atrasentan	Atrasentan plasma concentration over time	X	X	X	X	X
Safety						
To characterize the safety and tolerability of atrasentan in subjects at risk of progressive loss of kidney function	- Type, incidence, severity, seriousness, and relatedness of adverse events (AEs) - Incidence, severity, seriousness, and relatedness of adverse events of special interest (AESI) including events of fluid overload and anemia - Clinically significant changes in physical exam, vital signs, electrocardiogram (ECG), and safety laboratory tests, including urinalysis	X	X	X	X	X
Exploratory						
Additional efficacy objectives	Percent of subjects achieving proteinuria reduction to less than 0.3 g/day	X				
	Percent of subjects achieving UPCR <1.5 g/g and > 40% reduction from baseline		X			X
	Change from baseline to Week 52 in UPCR or UACR, based on FMV urine collection	X	X	X	X	X

Objectives	Endpoints	Cohort				
		1 IgAN	2 FSGS	3 Alport Syndrome	4 DKD	5 and 2b FSGS
	Change from baseline in estimated glomerular filtration rate (eGFR) at Week 52	X	X	X	X	X
	Change from baseline in audiometry assessments (pure-tone audiometry, word recognition score, otoacoustic emission and Tinnitus Handicap Inventory)			X		
Evaluate the long-term safety and tolerability of atrasentan in the Treatment Extension	Type, incidence, severity, seriousness, and relatedness of AEs	X	X	X	X	X
Evaluate the long-term efficacy of atrasentan in the Treatment Extension	Change from baseline in UPCR (cohorts 1-3 and 5)	X	X	X		X
Evaluate the long-term efficacy of atrasentan in the Treatment Extension	Change from baseline in UACR (Cohort 4)				X	

Study Design

[00483] This Phase 2, open-label, basket-design study will evaluate the efficacy and safety of atrasentan in subjects with proteinuric glomerular disease at risk of progressive loss of kidney function. Study schema is provided in **Figure 1**. Subjects will be enrolled in disease specific cohorts as follows:

- Cohort 1: IgAN (with UPCR 0.5 to <1.0 g/g)
- Cohort 2: FSGS

- Cohort 2b: FSGS (dose escalation)
- Cohort 3: Alport syndrome
- Cohort 4: DKD
- Cohort 5: FSGS (higher dose cohort)

[00484] Approximately 20 subjects will be enrolled into each cohort (~100 subjects total). The Sponsor, in consultation with the safety committee, has the option to expand enrollment into any cohort up to 40 subjects (maximum 200 subjects total). The study will be comprised of a pre-screening period (as shown in **Figure 1**), screening, treatment, treatment extension (optional), and follow-up periods.

[00485] The optional pre-screening period (up to 6 months prior to Day 1/Baseline) is intended for subjects who do not have recent documented eGFR, UPCR, or UACR values to assess initial eligibility. After subjects sign a short pre-screening informed consent form (ICF), a blood and/or urine sample may be collected to measure eGFR, proteinuria (UPCR) and/or albuminuria (urine albumin to creatinine ration (UACR)) at a local laboratory.

[00486] After signing an informed consent form, subjects will undergo screening assessments to determine eligibility to 1 of the 5 cohorts within 6 weeks (i.e., up to 6 weeks or 42 days). On Day 1, eligible subjects will initiate treatment with oral atrasentan QD over 52 weeks. Subjects will be followed for 28 days following the last dose of study drug administration. Pregnancy testing for women of childbearing potential (WOCBP) and counselling for all fertile men and WOCBP regarding study requirements for contraception use will also occur throughout the study (refer below for more details). Subjects will be required to closely monitor their weight. All subjects will return for a follow-up visit 28 days after the last dose of study drug. Assessments will be done.

[00487] Subjects who prematurely discontinue study drug before Week 52 will have an End of Treatment (EoT) visit and return in 28 days to complete end of study (EoS) procedures.

Inclusion Criteria for Subjects

[00488] Subjects in Cohort 1 (IgAN) include the following characteristics:

- Biopsy-proven IgAN that, in the opinion of the Investigator, is not due to secondary causes. The biopsy could have occurred at any point in time prior to study. A diagnostic report must be available for review by the Sponsor or designee.

- Receiving a maximally tolerated and optimized dose of a RAS inhibitor that has been stable for at least 12 weeks prior to screening.
- $\text{UPCR} \geq 0.5$ and < 1.0 g/g (≥ 500 mg/g and < 1000 mg/g; ≥ 56.5 mg/mmol and < 113 mg/mmol) based on a central laboratory assessment of first morning void urine collected at screening (either a single assessment or the average of available assessments) OR a central laboratory assessment from another Chinook clinical trial completed within 28 days of the screening visit with the Sponsor's Medical Monitor (or designee) approval.
- $\text{eGFR} \geq 30$ mL/min/1.73 m².

[00489] Subjects in Cohorts 2 and 5 (FSGS) include the following characteristics:

- Biopsy-confirmed FSGS or documentation of a genetic mutation in a podocyte protein associated with FSGS. This includes secondary causes of FSGS if it does not violate other inclusion and exclusion criteria.
- $\text{UPCR} > 1$ g/g (> 1000 mg/g; 113 mg/mmol) based on a central laboratory assessment of first morning void urine collected at screening
- $\text{eGFR} \geq 30$ mL/min/1.73 m².
- Receiving a maximally tolerated and optimized dose of a RAS inhibitor that has been stable for at least 12 weeks prior to screening.
- If receiving systemic corticosteroids or other immunosuppressants, dose must be stable for 12 weeks prior to start of study drug and anticipated to remain on a stable dose at least through week 12. For tacrolimus, dose may be variable if serum drug levels are within target range for 12 weeks prior to start of study drug.
- Body mass index (BMI) ≤ 40 kg/m².

[00490] Subjects in Cohort 2b (FSGS Subjects with at Least 12 Weeks of Treatment in Cohort 2) include the following characteristics:

- Subjects in Cohort 2 who have completed treatment with 0.75 mg atrasentan for at least 12 weeks.
- Subjects have tolerated treatment with 0.75 mg atrasentan and meet criteria for dose escalation.

- Subjects who have completed an EoS visit in cohort 2 may be eligible to enroll in Cohort 2b if less than 90 days have elapsed since the EoS visit and if they meet all entry criteria except UPCR.

[00491] Subjects in Cohort 3 (Alport syndrome) include the following characteristics:

- Diagnosis of Alport syndrome by genetic testing (documented mutation in a gene associated with Alport syndrome, including COL4A3, COL4A4, or X-linked COL4A5 in the subject or a family member). Or subjects that, in the opinion of the Investigator, have strong clinical evidence of Alport syndrome (biopsy, familial genetics, family history & familial biopsy, microscopic hematuria, hearing loss pattern, fleck retinopathy).
- UPCR > 0.5 g/g (>500 mg/g; >56.5 mg/mmol) based on central laboratory assessment of first morning void urine at screening.
- Receiving a maximally tolerated and optimized dose of a RAS inhibitor that has been stable for at least 12 weeks prior to screening visit.
- eGFR ≥ 30 mL/min/1.73 m².

[00492] Subjects in Cohort 4 (DKD) include the following characteristics:

- Clinical diagnosis of Type 2 diabetes mellitus (T2DM) as per guidelines.
- Diagnosis of DKD, including the presence of the following criteria:
 - UACR ≥ 0.5 g/g (500 mg/g; 56.6 mg/mmol) based on central laboratory assessment of first morning void urine at screening
 - eGFR ≥ 45 mL/min/1.73 m²
- Receiving a maximally tolerated and optimized dose of a RAS inhibitor that has been stable for at least 12 weeks prior to the screening visit and stable dose of SGLT2 inhibitor for at least 12 weeks prior to screening.

[00493] For Cohorts 1-3 and 5 (IgAN, FSGS, Alport syndrome, respectively): age 18 years and older at the time of signing ICF. For Cohort 4 (DKD): age between 18 to 70 years old, inclusive, at the time of signing ICF. Further, all fertile men and WOCBP must be willing to abide with highly effective forms of contraception, as specified in the protocol, throughout the

study and for 1 month afterward. In WOCBP, use of hormonal contraceptive agents must have been started at least 1 month prior to baseline.

Exclusion Criteria

[00494] Subjects are excluded from the study if any of the following criteria apply:

Medical Conditions

1. Concurrent diagnosis of another cause of CKD or another primary glomerulopathy. Note: hypertensive nephrosclerosis is not exclusionary.
2. Clinical suspicion of rapidly progressive glomerulonephritis (RPGN) based on KDIGO guidelines or clinical suspicion of IgA vasculitis (Henoch-Schonlein Purpura).
3. History of organ transplantation (subjects with history of corneal transplant are not excluded).
4. Known history of congestive heart failure, diastolic dysfunction, or prior hospital admissions for conditions relating to fluid overload such as pulmonary edema, uncontrolled peripheral edema, pleural effusion, or ascites that in the opinion of the Investigator or Sponsor's Medical Monitor (or designee), might confound the results of the study or pose additional risk to the subject by their participation in the study.
5. Known history of clinically significant liver disease or transaminase or bilirubin values >2 times the upper limit of normal (ULN) for Cohorts 1-3; for Cohort 4 (DKD), alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 3 × ULN (subjects with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis will be allowed).
6. Active infection which may warrant systemic treatment.
7. Known history of human immunodeficiency virus (HIV) infection (HIV 1/2 antibodies).
8. Known active Hepatitis B (defined as hepatitis B surface antigen [HBsAg] reactive); Subjects with successfully treated hepatitis C can be considered for inclusion into the study upon consultation with the Sponsor's Medical Monitor (or designee).

9. History of malignancy unless cancer free for at least 5 years or non-melanoma skin cancer not requiring ongoing treatment. A subject with curatively treated cervical carcinoma in situ is eligible for this study.
10. Any history within 3 months of screening of clinically significant, unstable, or uncontrolled cardiovascular (including myocardial infarction, unstable angina, cardiovascular revascularization procedure, cerebrovascular accident, or transient ischemic attack), pulmonary, hepatic, renal, gastrointestinal, genitourinary, hematological, coagulation, immunological, endocrine/metabolic, or other medical disorder that, in the opinion of the Investigator or Sponsor's Medical Monitor (or designee), might confound the results of the study or pose additional risk to the subject by their participation in the study.

Diagnostic assessments

11. Brain natriuretic peptide (BNP) value of > 200 pg/mL (200 ng/L) at screening.
12. Platelet count $< 80,000$ per μL ($80 \times 10^9/\text{L}$) at screening.
13. Hemoglobin below 9 g/dL (90 g/L) at screening or prior history of blood transfusion for anemia within 3 months of screening.
14. Confirmed blood pressure > 150 mmHg systolic or > 95 mmHg diastolic based on a mean of 3 measurements obtained at screening.
15. Current diagnosis of nephrotic syndrome.
16. HbA1c $> 9.5\%$ in Cohort 4 (DKD), HbA1c $> 7.0\%$ in Cohorts 1-3.

Prior/Concomitant Medications

17. Except for Cohorts 2 and 5 (FSGS), use of systemic immunosuppressant medications including systemic steroids (prednisone~ or equivalent > 10 mg/day for more than 2 weeks within 3 months prior to screening), mycophenolate, azathioprine, tacrolimus, etc. for more than 2 weeks within the past 3 months prior to screening.
18. Use of rituximab within the past 6 months prior to screening.
19. Use of cyclosporine within the past 1 week prior to screening.
20. With the exception of DKD (Cohort 4), use of an SGLT2 inhibitor within the past 30 days.

Prior/Concurrent Clinical Study Experience

21. Have received any investigational agent within 1 month (or 5 half-lives of the agent, whichever is longer) prior to screening. If the investigational agent is a cytotoxic or immunosuppressive agent, then this washout period is 6 months.

Other Exclusions

22. History of an alcohol or illicit drug-related disorder within the past 3 years.
23. Pregnancy, breast feeding, or intent to become pregnant during the study period and at least 1 month afterward for females.
24. Intent to father a child or donate sperm during the study period and at least 1 month afterward for males.

Renin-Angiotensin System Inhibitors

[00495] All subjects should be on a stable and maximally tolerated dose of a RAS inhibitor (physician-choice) for at least 12 weeks prior to screening with plans to remain on stable dose throughout the study.

[00496] All efforts should be made to avoid dose modification or discontinuation of RAS inhibitor therapy. Sponsor's Medical Monitor (or designee) should be notified of any modification or discontinuation of background therapy.

[00497] If medically necessary, for example in the setting of an acute illness, dehydration, or similar event, temporary interruption of the RAS inhibitor will be allowed. Other reasons in which the RAS inhibitor may be reduced or halted during the study include hyperkalemia deemed clinically important and refractory to other interventions such as diuretics, potassium lowering agents, or dietary changes. Conversions from one RAS inhibitor to another should be avoided, but if required, then efforts should be made to use equivalent doses. The use of more than one RAS inhibitor concomitantly is prohibited.

[00498] Subjects with diabetic kidney disease should be on a stable label approved dose of SGLT2 inhibitor (Investigator's choice) for at least 12 weeks prior to screening and plan to remain on the same dose through at least Week 12.

Prohibited and Restricted Medications

[00499] The following medications are excluded for use during the study:

- Investigational or approved products for the treatment of their underlying kidney disease according to cohort of enrollment except for RAS inhibitors in all cohorts and SGLT2 in Cohort 4 (see below for restricted use of SGLT2 inhibitors (SGLT2i) in other cohorts). Immunosuppressants for FSGS are allowed per inclusion criteria.
- Organic anion transporting polypeptide (OATP) inhibitors (all cohorts)
- Potent inhibitors and inducers of CYP3A4, with the exception of short-term antiviral treatment as described below:
- Short-term use of anti-viral medications containing CYP3A4 inhibitors such as ritonavir, may be used with caution if medically needed and in consultation with the Sponsor's Medical Monitor (or designee) as a temporary interruption of atrasentan dosing may be required.
- Administration of Paxlovid (nirmatrelvir/ritonavir) for the treatment of COVID is allowed this clinical trial; however, atrasentan treatment should be discontinued for the 5-day treatment course of Paxlovid. Atrasentan treatment can be resumed 3-days following completion of the Paxlovid treatment course to allow CYP3A4 regeneration. (all cohorts)
- Atrasentan exposure may be affected by use of concomitant medications that are OATP1B1 or OATP1B3 inhibitors (e.g., protease inhibitors, cyclosporin, and clarithromycin, among others) as well as by those which are potent inhibitors or inducers of CYP3A4. Given the risk of potential drug interactions, Investigators should review all medications that a subject is taking throughout the study. Concomitant OATP1B1 and OATP1B3 inhibitors and potent CYP3A4 inhibitors and inducers are prohibited.

[00500] Restricted medications during the study are defined as medications which should be avoided, if possible, however, they are not necessarily prohibited. Restricted medications may be needed during the course of the study if the primary Investigator determines that the subject has clinical progression of kidney disease where it would be unacceptable to withhold rescue medications. This determination should consist of a comprehensive clinical evaluation of the subject including assessment of rate of increase of proteinuria and/or decrease in eGFR where it is not thought to be due to secondary causes that are expected to improve (e.g., acute illness causing acute kidney injury [AKI]). Unless it is considered a medical emergency,

this determination should be discussed with the Sponsor's Medical Monitor (or designee) prior to starting therapy with a restricted medication. Any determination of requirement of restricted medication will be documented in the subject's medical record and the medication will be recorded in the case report form (CRF).

[00501] In addition, in circumstances in which subjects receive restricted medications for other medical reasons than progression of kidney disease (e.g., systemic steroids for treatment of an exacerbation of asthma), this will not be considered a "restricted medication" unless given for a significant amount of time that may impact the integrity of clinical study data. The restricted medications, including timing and duration of treatment are described below.

[00502] Of note, administration of sensitive P-gp substrates (digoxin, dabigatran etexilate, and fexofenadine) must be delayed at least 4 hours after administration of atrasentan in all cohorts. In addition, the following medications are restricted in certain cohorts:

Cohort 1

- Systemic steroids (at doses greater than 20 mg/day of oral prednisone or equivalent including nefecon) or other immunosuppressive therapy including but not limited to mycophenolate, azathioprine, rituximab, cyclosporine, and tacrolimus
- Herbs with immunosuppressive qualities such as Wilfordii Hook F, Caulis sinomenii and Sinomenium acutum
- Acute use of NSAIDS (except prophylactic use of NSAIDs for cardiovascular prevention) within 1 week prior to any 24-hour urine collection
- SGLT2 inhibitors.

Cohort 2, 2b, 5

- Change in immunosuppression regimen from baseline
- Herbs with immunosuppressive qualities such as Wilfordii Hook F, Caulis sinomenii and Sinomenium acutum
- Acute use of NSAIDS (except prophylactic use of aspirin) within 1 week prior to any 24-hour urine collection
- SGLT2 inhibitors.

Cohort 3

- Systemic steroids (at doses greater than 20 mg/day of oral prednisone or equivalent) or other immunosuppressive therapy including but not limited to mycophenolate, azathioprine, rituximab, cyclosporine, and tacrolimus
- Herbs with immunosuppressive qualities such as Wilfordii Hook F, Caulis sinomenii and Sinomenium acutum
- Acute use of NSAIDS (except prophylactic use of aspirin) within 1 week prior to any 24-hour urine collection
- SGLT2 inhibitors.

Cohort 4 (DKD)

- Systemic steroids (at doses greater than 20 mg/day of oral prednisone or equivalent) or other immunosuppressive therapy including but not limited to mycophenolate, azathioprine, rituximab, cyclosporine, and tacrolimus
- Herbs with immunosuppressive qualities such as Wilfordii Hook F, Caulis sinomenii and Sinomenium acutum
- Acute use of NSAIDS (except prophylactic use of aspirin) within 1 week prior to any 24-hour urine collection
- Investigational or approved products for the treatment of DKD except for RAS inhibitors and SGLT2 inhibitors.
- Finerenone

Atrasentan used in study

[00503] Atrasentan is administered in accordance with the information in Table 2.

Table 2. Atrasentan

Investigational product name	Atrasentan (Active)
Dose formulation	Film-coated round tablets
Unit dose strength	0.75 mg per tablet
Dose regimen	1 or 2 tablets QD based on Cohort

Investigational product name	Atrasentan (Active)
Route of administration and administration instructions	Oral with or without food at approximately the same time each day. Subjects should not take more than the prescribed number of tablets each day. Subjects will be instructed that the bottle containing the study drug contains a desiccant canister, which should be returned to the bottle directly after each tablet removal.
Sourcing	Study drug will be provided to the site by the Sponsor or designated representative.
Packaging	Atrasentan tablets will be packaged in bottles (20 tablets per bottle).
Labeling	Label text will at a minimum include the protocol number, lot number, storage conditions, and Sponsor (or designee) name and address. Labels will comply with local regulatory requirements for study drug.

[00504] Atrasentan should be stored between 15° to 25°C (59° to 77°F), protected from moisture, in the supplied bottle which contains a desiccant canister (that should be returned to the bottle directly after each tablet removal). If the storage temperature falls outside the allowed range, the excursion must be reported immediately. In the event of a temperature excursion, affected study drug should be quarantined and should not be dispensed until notification of the final assessment and cleared by the Sponsor.

[00505] For Cohorts 1, 2, 3 and 4, no study drug dose reductions are permitted during the study. For Cohorts 2b and 5, based on tolerability assessments at the discretion of the Investigator, subjects can be dose reduced back to 0.75 mg QD.

Dose Escalation and Monitoring in Cohorts 2b and 5

[00506] Subjects with FSGS in Cohort 2 will have an option to dose escalate their study drug dose to 1.5 mg QD (from 0.75 mg) at or after Week 12 during scheduled visits. Subjects who dose escalate will be transitioned into cohort 2b and will be monitored in the Cohort 2b period for up to 52 weeks. Subjects will complete their scheduled visit per Cohort 2 on the day of dose escalation (in lieu of baseline visit for Cohort 2b) and will thereafter follow Cohort 2b.

[00507] In addition, subjects who have completed an EoS visit in Cohort 2 may be enrolled in Cohort 2b in consultation with the Sponsor's Medical Monitor (or designee). Baseline

assessments in Cohort 2b are only required if the days between the EoT visit in the Treatment Period and the enrollment visit in Cohort 2b is > 28 days.

[00508] Subjects in Cohort 5 will dose escalate study drug to 1.5 mg QD (from 0.75 mg) at Week 6, based on tolerability.

[00509] The decision to dose escalate for Cohorts 2 and 5 will be dependent on the subject's tolerability to the lower dose of atrasentan and based on Investigator's clinical discretion in consultation with the Sponsor's Medical Monitor (or designee). Subjects in both cohorts meeting any of the following criteria at the time of dose escalation will not be able to dose escalate:

- Any severe AESIs
- Any related SAE
- Clinical laboratory parameters on most recent central laboratory test results (Week 2 for Cohort 5 and previous scheduled visit prior to dose escalation in Cohort 2):
 - Drop in eGFR of < 30 mL/min/1.73 m² and more than 25% from baseline
 - Albumin < 3 g/dL and drop of more than 25% from baseline
 - Hemoglobin < 9 g/dL

[00510] All subjects with FSGS who dose escalated will undergo more frequent monitoring at 1-, 2- and 6-weeks post dose escalation. At the discretion of the Investigator in consultation with the Sponsor's Medical Monitor (or designee), subjects with FSGS who are unable to tolerate atrasentan at 1.5 mg QD may be dose down titrated to 0.75 mg QD, as shown in **Figure 2**.

Treatment Extension Period

[00511] Subjects in all cohorts at the discretion of the Investigator and in consultation with the Sponsor's Medical Monitor (or designee), will be allowed to continue into the Treatment Extension and receive treatment with oral atrasentan QD for up to 84 weeks. Subjects who consent to participate in this Treatment Extension period will commence with the enrollment visit, which should occur on the same day as the scheduled EoT visit in the Treatment period; the EoT visit will serve as the enrollment visit for these subjects and these subjects will not complete the EoS visit in the Treatment period. Subjects who complete an EoS visit in the Treatment period may be enrolled in the Treatment Extension if it has been less than 90 days since the EoS visit in consultation with the Sponsor's Medical Monitor (or designee); these subjects must

undergo the extension enrollment visit assessments if the days between the EoT visit in the Treatment period and the Extension enrollment visit is > 28 days.

[00512] Subjects who prematurely discontinue study drug before Extension Week 84 will have an Extension EoT visit within 7 days of last dose of the drug. All subjects will return for a EOT visit 28 days after the last dose of study drug.

[00513] In some instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study drug. For instance, subjects will be required to discontinue study drug for the following reasons:

- Evidence of pregnancy or noncompliance with protocol-specified contraception or pregnancy monitoring
- Initiation of maintenance dialysis or kidney transplantation
- Other study drug stopping criteria may be based on Investigator and subject discretion that may include fluid overload syndromes uncontrolled with diuretics and medical management, and any suspected study drug-related adverse event that represents unacceptable toxicity.

Study Assessments and Procedures

[00514] A full schedule of study assessments and procedures for the screening, treatment and follow up periods is provided.

[00515] The pre-screening period is for subjects who do not have recent documented eGFR, UPCr, or UACr values. Subjects who sign a pre-screening ICF may have a blood and/or urine sample collected to measure eGFR, UPCr, and/or UACr.

[00516] Pre-screening may be conducted within 6 months prior to beginning study drug and in advance of full study consent:

- Obtain and document pre-screening informed consent
- Obtain an FMV sample for UPCr, UACr, and/or serum for evaluation in eGFR (analysis to be done by a local laboratory) (Section [00521]).

[00517] The following procedures will be conducted within 42 days prior to a subject beginning study drug:

- Obtain and document informed consent
- Review medical history and obtain demographics

- Evaluate eligibility
- Perform a physical examination
- Record weight and height
- Record vital signs (temperature, heart rate, blood pressure)
- Perform a single 12-lead ECG
- Obtain blood for hematology, complete chemistry, BNP, and glycated hemoglobin (HbA1c) for central laboratory analysis.
- Obtain blood from WOCBP for a serum pregnancy test
- Counsel all fertile men and WOCBP on study contraception requirements
- Obtain FMV urine sample via central laboratory for UPCR, UACR, and urinalysis (Section)
- Record concomitant medications and SAEs
- Cohorts 1-3 and 5: During the Screening visit, ensure that the subject is in receipt of two urine collection containers for 24-hour urine collection and provide reminders for when samples are due. The two 24-hour urine collections should be completed within 14 days of each other, with the second one to be delivered at the Day1/Baseline visit. See Section **Error! Reference source not found.**
- During the Screening visit, ensure subject is in receipt of a FMV urine collection container and reminder for when to bring the sample back to the clinic. (Section [00521])
- Educate subjects to refrain from high protein meals and to avoid heavy/strenuous activity for 24 hours prior to scheduled laboratory assessments.

[00518] At the end of Treatment (Week 52 $\pm$ 7 days or within 7 days after study drug discontinuation), one or more of the following procedure will be conducted:

- Subjects transitioning to Treatment Extension, will undergo EoT visit as part of the Treatment period
- Perform a physical examination
- Perform a single 12-lead ECG
- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Obtain blood for hematology, and complete chemistry
- Obtain blood for HbA1c (Cohort 4 only)
- Obtain blood for PK pre-dose
- Obtain blood and urine samples for exploratory PD biomarkers

- Cohorts 1-3 and 5: Obtain FMV urine sample for UPCR, UACR, and urinalysis
- Cohorts 4 (DKD): Obtain FMV urine sample for UPCR, UACR, and urinalysis
- Obtain urine for pregnancy testing in WOCBP
- Counsel all fertile men and WOCBP on study contraception requirements through EoS (or at least 28 days post last study drug dose)
- Cohort 3 (Alport Syndrome): Audiometry exam
- Cohort 3 (Alport Syndrome): THI questionnaire
- Record concomitant medications and AEs
- Review drug diary, subject study drug compliance and perform study drug accountability
- Cohorts 2, 2b, 4 and 5 (FSGS and DKD): Review weight diary and discuss subject weight
- Remind subjects to refrain from high protein meals and to avoid heavy physical/strenuous activity for 24 hours prior to scheduled laboratory assessment.
- Cohorts 1-3 and 5 only: Obtain a single 24-hour urine collection
- Subjects should wait to take the study drug until the PK sample has been collected.

[00519] A the end of the **Study Visit** (+28 days from last dose of study drug) (± 7 days), one or more of the following procedure will be conducted:

- Record vital signs (temperature, heart rate, blood pressure)
- Record weight
- Obtain blood for hematology, and complete chemistry
- Obtain blood for serum pregnancy test in WOCBP
- Obtain FMV urine sample for UPCR, UACR, and urinalysis (Section [00521])
- Record concomitant medications and AEs
- Review and discuss subject weight

Efficacy Assessments

[00520] In order to assess efficacy of treatment, the following information will be collected.

[00521] Urine Protein to Creatinine Ratio (UPCR) will be assessed. Assessment of proteinuria plays an important role in the diagnosis of kidney disease and in monitoring disease

activity (Zhao, 2016). UPCR is widely used for proteinuria evaluation in clinical practice. UPCR will be measured using FMV urine sample and a 24-hour urine collection at timepoints.

[00522] First Morning Void (FMV) Urine Collection will be determined. FMV is defined as the collection of the first urine void after the individual awakes from sleep. The subject will be provided with urine collection containers prior to each visit where a FMV sample is required. The central laboratory will provide specific instructions for collection and storage of the specimens.

[00523] Urine Albumin to Creatinine Ratio (UACR) will be determined. UACR is used for diagnosis and monitoring of DKD (Persson, 2018). UACR will be measured based on FMV urine collection at timepoints.

[00524] Estimated Glomerular Filtration Rate (eGFR) will be assessed. eGFR will be calculated based on serum creatinine using the CKD-EPI equation.

[00525] Audiometry will be conducted at the timepoints for Cohort 3. Tests will be performed by audiologists and conducted in a sound attenuated booth/room with doors closed, using standard earphones or earphone inserts. If a subject is unable to perform audiometry, the site should contact the Sponsor's Medical Monitor (or designee) to discuss. This assessment could be made optional. Pure-tone audiometry (PTA) is a behavioral test used to measure hearing sensitivity. Tones of different frequencies are presented to find the hearing threshold, which is defined as the lowest level of sound that can be heard 50% of the time.

[00526] Audiometry is complemented by speech discrimination (Word Recognition Score (WRS) and an otoacoustic emissions (OAEs) test. WRS test is comprised of a list of country/language-specific words (typically list of 40 to 50 words) and usually presented at 60 dB to each ear separately. The score is recorded as a percentage of the words repeated correctly. OAEs are low-intensity sounds that are produced by functioning outer ear cells of the cochlea. OAEs test the presence or absence of cochlear function.

[00527] Tinnitus Handicap Inventory also will be assessed in Cohort 3. The THI is a self-reported, 25-item questionnaire to assess tinnitus impairment and effect on daily living (Newman, 1996). The 25 items are grouped into functional, emotional, and catastrophic subscales. This questionnaire was shown to be valid and with high test-retest reliability/repeatability (Newman, 1998).

Clinical Laboratory Tests**Table 3. Protocol-Required Laboratory Assessments to be performed by a central laboratory**

Hematology	Complete Chemistry	Urine Tests
Hematocrit	Albumin	Analysis of first morning void urine:
Hemoglobin	Alkaline phosphatase (ALP)	Urinary concentration of protein and creatinine for UPCR; urinary concentration of albumin and creatinine for UACR reporting; and urinalysis (per test specification below)
Red Blood Cells (RBC)	Alanine aminotransferase (ALT) (SGPT)	
White Blood Cells (WBC)	Aspartate aminotransferase (AST) (SGOT)	
Neutrophils	Bicarbonate	
Lymphocytes	Blood urea nitrogen (BUN)	
Monocytes	Calcium	
Basophils	Potassium	Analysis of 24-hour urine (Cohort 1-3):
Eosinophils	Chloride	• Albumin • Creatinine • Sodium • Protein • Potassium • Chloride • UPCR • UACR
Platelet count	Cholesterol**	
	Creatinine*	
	Direct bilirubin	
	Glucose**	
	Phosphorus	
	Sodium	
	Total bilirubin	
	Total protein	
	Uric acid	
	HDL**	Urinalysis of FMV or spot urine#
	Insulin (HOMA-IR)**	• Blood • Glucose • Ketones • pH • Protein • Albumin • Creatinine • Specific gravity • Leukocyte esterase
	LDH	
	Lipoprotein A**	
	LDL**	
	Triglycerides**	
	VLDL**	
	* eGFR will be calculated based on serum creatinine using the CKD-EPI equation	
	**Non-fasting	
		# Reflexive microscopic analysis may be requested for certain samples
		Urine Biomarker Collection
		Urine pregnancy test
	Additional Blood Collection	Additional Blood Tests
	Pharmacokinetic measurement	BNP
	Blood collection for exploratory biomarkers	HbA1c
	Optional blood collection for Pharmacogenetics	Serum hCG (pregnancy)

Abbreviations: BNP = brain natriuretic peptide; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; hCG = human chorionic gonadotropin; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; UACR = urinary albumin:creatinine ratio; UPCR = urine protein:creatinine Ratio; VLDL = very-low-density lipoprotein

Example 2: A Phase 2, Open-Label, Basket Study of Atrasentan in Patients with Proteinuric Glomerular Disease.

[00528] A phase 2, open-label, basket study of atrasentan was completed in patients with proteinuric glomerular disease as described in Example 1. Twenty patients with FSGS were enrolled in the study if the inclusion and exclusion criteria of Example 1 were met. Baseline characteristics of this cohort are shown in **Figure 3**. Patients were given 0.75 mg atrasentan daily. A reduction in urine protein to creatinine ratio (UPCR) was observed at least on weeks 6, 12, and 24 after the study start. For example, a reduction of 38.3% in UPCR was seen on week 24 compared the baseline measurement at week 0 (**Figure 4**).

What is claimed is:

1. A method of treating focal segmental glomerulosclerosis (FSGS) in a subject, comprising administering to the subject a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.
2. A method of decreasing renal inflammation and/or fibrosis in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
3. A method of reducing the rate of decline in estimated glomerular filtration rate (eGFR) in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
4. A method of delaying the onset of end-stage kidney disease (ESKD) in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
5. A method of decreasing proteinuria in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
6. A method of decreasing fatigue in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
7. A method of stabilizing functional podocyte mass in a subject having FSGS, comprising administering a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, to a subject in need thereof.
8. The method of Claim 2, wherein the renal inflammation and/or fibrosis comprises tubulointerstitial inflammation.

9. The method of Claim 2 or Claim 8, wherein the renal inflammation and/or fibrosis comprises tubulointerstitial fibrosis.
10. The method of any one of Claims 2, 8, or 9, wherein the renal inflammation and/or fibrosis comprises glomerular inflammation.
11. The method of any one of Claims 2, or 8-10, wherein the renal inflammation and/or fibrosis comprises glomerulosclerosis.
12. The method of any one of Claims 1-10, wherein the subject has biopsy-confirmed FSGS.
13. The method of any one of Claims 1-10, wherein the subject has been diagnosed with biopsy-confirmed FSGS.
14. The method of any one of Claims 1-10, wherein the subject has a mutation in a podocyte protein.
15. The method of any one of Claims 1-10, wherein the subject has a mutation in Apolipoprotein L1 (APOL1).
16. The method of any one of Claims 1-10, wherein the subject has a mutation in one or more of APOL1, NPHS1, NPHS2, CD2AP, TRPC6, ACTN4, INF2, MYO1E, ARHGAP24, PLCE1, WT1, LMX1B, COQ6, LAMB2, PAX2, ANLN, and/or CRB2.
17. The method of any one of Claims 1-16, wherein the FSGS comprises a nephrotic syndrome.
18. The method of Claim 17, wherein the nephrotic syndrome is selected from proteinuria, hypoalbuminemia, hypercholesterolemia, peripheral edema, or a combination of any of the foregoing.

19. The method of any one of Claims 1-18, wherein the FSGS is perihilar FSGS.
20. The method of any one of Claims 1-18, wherein the FSGS is tip lesion FSGS.
21. The method of any one of Claims 1-18, wherein the FSGS is cellular FSGS.
22. The method of any one of Claims 1-18, wherein the FSGS is collapsing FSGS.
23. The method of any one of Claims 1-18, wherein the FSGS is primary FSGS.
24. The method of any one of Claims 1-18, wherein the FSGS is FSGS not otherwise specified (NOS).
25. The method of any one of Claims 1-18, wherein the FSGS is virus-associated FSGS.
26. The method of Claim 25, wherein the virus-associated FSGS is not HIV-associated FSGS.
27. The method of any one of Claims 1-18, wherein the FSGS is toxin-associated FSGS.
28. The method of any one of Claims 1-18, wherein the FSGS is adaptive FSGS.
29. The method of any one of Claims 1-28, further comprising administering one or more additional agents to the subject.
30. The method of Claim 29, wherein the one or more additional agents are selected from calcineurin inhibitors, proteasome inhibitors, aminoquinolines, complement inhibitors, B-cell inhibitors, cytotoxic agents, mTOR inhibitors, and steroids, and combinations thereof.

31. The method of Claim 29, wherein the one or more additional agents comprises a calcineurin inhibitor.

32. The method of claim 31, wherein the calcineurin inhibitor is cyclosporin.

33. The method of any one of Claims 29-32, wherein the one or more additional agents comprises an immunosuppressant.

34. The method of Claim 33, wherein the immunosuppressant is mycophenolate mofetil (MMF), cyclophosphamide, or chlorambucil.

35. The method of any one of Claims 29-34, wherein the one or more additional agents comprises steroids.

36. The method of Claim 35, wherein the steroids are selected from the group consisting of prednisone, dexamethasone, hydrocortisone, cyclosporin, adrenocorticotrophic hormone (ACTH), and combinations of any of the foregoing.

37. The method of any one of Claims 29-35, wherein the one or more additional agents comprises aminoquinolines.

38. The method of Claim 37, wherein the one or more additional agents is hydroxychloroquine.

39. The method of any one of Claims 1-32, wherein the subject is not currently receiving one or more immunosuppressants.

40. The method of any one of Claims 29-39, wherein the one or more additional agents is administered at a dosage that is stable for at least 12 weeks prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

41. The method of Claim 29-40, wherein the dosage of the one or more additional agents is decreased after between about 15 days to about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

42. The method of any one of Claims 29-41, wherein the dosage of the one or more additional agents is reduced by about 25% to about 100%.

43. The method of any one of Claims 29-42, wherein the dosage of the one or more additional agents is reduced by about 50% to about 100%.

44. The method of any one of Claims 29-43, wherein the dosage of the one or more additional agents is reduced by about 75% to about 100%.

45. The method of any one of Claims 1-38, wherein the subject is concomitantly receiving an ACE inhibitor, an ARB, a statin, a diuretic, a calcium channel blocker, a beta blocker, an aldosterone antagonist, fish oil, hydroxychloroquine, or a combination of any of the foregoing.

46. The method of any one of Claims 1-39, wherein the subject is concomitantly receiving an ACE inhibitor, an ARB, or a combination thereof.

47. The method of Claim 45 or Claim 46, wherein the statin is selected from: atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin.

48. The method of Claim 45 or Claim 46, wherein the diuretic is selected from: hydrochlorothiazide, trichlormethiazide, hydroflumethiazide, quinethazone, metolazone, chlorothiazide, chlorthalidone, indapamide, methyclothiazide bumetanide, torsemide, piretanide, ethacrynic acid, bumetanide, furosemide, triamterene, spironolactone, eplerenone, and amiloride.

49. The method of any one of Claims 46-48, wherein the ACE inhibitor is selected from: quinapril, fosinopril perindopril, captopril, enalapril, enalaprilat, ramipril, cilazapril, delapril, fosinopril, zofenopril, indolapril, benazepril, lisinopril, spirapril,trandolapril, perindep, pentopril, moexipril, rescinnamine, and pivopril.

50. The method of any one of Claims 46-49, wherein the ARB is selected from: candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan, olmesartan medoxomil, telmisartan, valsartan, azilsartan medoxomil, and BRA-657.

51. The method of any one of Claims 1-50, wherein the atrasentan is administered as a pharmaceutically acceptable salt.

52. The method of any one of Claims 1-51, wherein the atrasentan is administered as atrasentan hydrochloride or atrasentan mandelate.

53. The method of any one of Claims 1-52, wherein the atrasentan is administered as atrasentan hydrochloride.

54. The method of any one of Claims 1-50, wherein the atrasentan is administered as the free base.

55. The method of any one of Claims 1-54, wherein the subject is at a high risk of progression to ESKD.

56. The method of any one of Claims 1-55, wherein the subject has been diagnosed with FSGS.

57. The method of Claim 56, wherein the diagnosis of FSGS comprises a kidney biopsy, a genetic test for mutations in a podocyte protein associated with FSGS, or a combination of any of the foregoing.

58. The method of Claim 55 or 56, wherein diagnosis of FSGS comprises examination of a kidney biopsy.

59. The method of any one of Claims 1-58, wherein the subject is excreting an average of about 1.0 g/g to about 3.5 g/g or more of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

60. The method of any one of Claims 1-59, wherein the subject is excreting an average of above about 3.5 g/g to about 10 g/g of protein in the urine per day for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

61. The method of any one of Claims 1-60, wherein the subject has an average eGFR of about 20 to about 120 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

62. The method of any one of Claims 1-61, wherein the subject has an average eGFR of about 20 to about 90 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

63. The method of any one of Claims 1-62, wherein the subject has an average eGFR of about 20 to about 60 mL/min/1.73m² for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

64. The method of any one of Claims 1-63, wherein the subject has a urine protein to creatinine ratio (UPCR) of greater than about 1.5 g/g to about 11 g/g for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

65. The method of any one of Claims 1-64, wherein the subject has an average HbA1c of about 4% to about 6% for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

66. The method of any one of Claims 1-65, wherein the subject has an average fasting blood glucose level of about 125 mg/dL or less for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

67. The method of any one of Claims 1-66, wherein the subject maintains a potassium level within a normal physiologic range.

68. The method of any one of Claims 1-67, wherein the subject maintains a sodium level within a normal physiologic range.

69. The method of any one of Claims 1-68, wherein the subject has alanine transaminase/aspartate transaminase (ALT/AST) levels during the administration of atrasentan, or a pharmaceutically acceptable salt thereof, that are about the same as the ALT/AST levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

70. The method of any one of Claims 1-69, wherein the subject has bilirubin levels during the administration of atrasentan, or a pharmaceutically acceptable salt thereof, that are about the same as the bilirubin levels prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

71. The method of any one of Claims 1-70, wherein fluid retention in the subject is manageable with diuretics.

72. The method of any one of Claims 1-71, wherein the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 10 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

73. The method of any one of Claims 1-72, wherein the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 12 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

74. The method of any one of Claims 1-73, wherein the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

75. The method of Claim 74, wherein the amount of protein in the urine of the subject is reduced by about 35% to about 80%.

76. The method of any one of Claims 1-75, wherein the UPCR of the subject is reduced to less than about 1.5 g/g after about 10 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

77. The method of any one of Claims 1-76, wherein the UPCR of the subject is reduced to less than about 1.5 g/g after about 12 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

78. The method of any one of Claims 1-77, wherein the UPCR of the subject is reduced to less than about 1.5 g/g after about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

79. The method of any one of Claims 1-78, wherein the risk of the subject developing ESKD is reduced by about 20% to about 99% after between about 6 months and about 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

80. The method of any one of Claims 1-79, wherein the risk of the subject developing ESKD is reduced by about 20% to about 99% after between about 12 months and about 60 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

81. The method of any one of Claims 1-80, wherein the average rate of decrease in eGFR is from about 0.75 mL/min/year to about 75 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

82. The method of any one of Claims 1-81, wherein the average rate of decrease in eGFR is from about 3 mL/min/year to about 6 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

83. The method of any one of Claims 1-82, wherein the average rate of decrease in eGFR is from about 4 mL/min/year to about 5 mL/min/year for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof.

84. The method of any one of Claims 1-83, wherein the average rate of decrease in eGFR is reduced by from about 15% to about 70% after between about 6 months and about 24 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

85. The method of any one of Claims 1-84, wherein the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 0.75 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

86. The method of any one of Claims 1-85, wherein the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 1.0 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

87. The method of any one of Claims 1-86, wherein the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is from about 1.25 mg to about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

88. The method of any one of Claims 1-87, wherein the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is about 1.5 mg of atrasentan, or an equivalent amount of a pharmaceutically acceptable salt thereof.

89. The method of any one of Claims 1-88, further comprising administering a therapeutically effective amount of a SGLT-2 inhibitor.

90. The method of Claim 89, wherein the SGLT-2 inhibitor is selected from bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, licogliflozin, sotagliflozin, and tofogliflozin.

91. The method of Claim 89 or 90, wherein the SGLT-2 inhibitor is canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin.

92. The method of any one of Claims 1-91, wherein the subject has been determined to have proteinuria of at least 1 g/day in at least two of three consecutive readings over the year prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

93. The method of any one of Claims 1-92, wherein the subject has been administered a maximally tolerated stable dose of a RAS inhibitor for at least 12 weeks prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

94. The method of any one of Claims 1-93, wherein the subject is concurrently administered a maximally tolerated stable dose of a RAS inhibitor and a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

95. The method of any one of Claims 1-94, wherein the subject has been determined to have an eGFR of at least 30 mL/min/1.73 m² prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

96. The method of any one of Claims 1-95, wherein the FSGS comprises non-nephrotic range proteinuria of less than 3.5 grams of protein in the urine per day for at least about 3 months prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

97. The method of any one of Claims 1-96, wherein the FSGS is associated with one or more genetic mutations.

98. The method of any one of Claims 1-97, wherein the one or more genetic mutations is in gene encoding a podocyte protein associated with FSGS.

99. The method of Claim 98, wherein the one or more genetic mutations is selected from one or more mutations in a gene selected from the group consisting of: NPHS1, NPHS2, CD2AP, TRPC6, ACTN4, INF2, MYO1E, ARHGAP24, ARHGDI1, PLCE1, PTPRO, WT1,

LXMB1, tRNA^{leu}, COQ2, COQ6, ITGB4, PDSS2, CD151, CUBN, LAMB2, APOL1, and a combination of any of the foregoing.

100. The method of Claim 98 or 99, wherein the one or more genetic mutations is in APOL1.

101. The method of any one of Claims 1-100, wherein the subject has been administered a prior therapy for FSGS and was not responsive to the prior therapy.

102. The method of Claim 101, wherein the prior therapy is a standard of care therapy for FSGS.

103. The method of Claim 101 or 102, wherein the prior therapy is selected from: acthar, sparsentan, rituximab with plasmaphoresis, volcosporin, 10-nitro-9(E)-octadec-9-enoic acid (CXA-10), PF-06730512, 4-Chloro-N-[5-methyl-2-[7H-pyrrolo[2,3-d]pyrimidine-4-carbonyl]-3-pyridyl]-3-(trifluoromethyl)benzenesulfonamide (CCX140-B), abatacept, bardoxolone, or a combination of any of the foregoing

104. The method of any one of Claims 1-103, wherein the subject has not been treated or is not being treated with a sodium glucose co-transporter 2 (SGLT2) inhibitor.

105. The method of any one of Claims 1-104, wherein the subject has not been treated or is not being treated with antiretroviral therapy.

106. The method of any one of Claims 1-105, wherein the subject has not been previously diagnosed with one or more of diabetic nephropathy, IgA nephropathy, sickle cell nephropathy, HIV/AIDS, or acute kidney failure.

107. The method of any one of Claims 1-106, wherein the subject has not been previously diagnosed with HIV-related nephropathy.

108. The method of any one of Claims 1-107, wherein the subject has not been previously diagnosed with HIV.

109. The method of any one of Claims 1-108, wherein the subject is not currently diagnosed with HIV.

110. The method of any one of Claims 1-109, wherein the subject is not currently being treated for HIV.

111. The method of any one of Claims 1-110, wherein the subject has not been previously diagnosed with renovascular hypertension.

112. The method of any one of Claims 1-111, wherein the subject is not currently being treated for renovascular hypertension.