CLAIMS

1. Use of Atrasentan, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of focal segmental glomerulosclerosis (FSGS), wherein a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof, is to be administered to a subject in need thereof, wherein the use is characterized by
(i) decreasing proteinuria,
(ii) reducing the rate of decline in estimated glomerular filtration rate (eGFR),
(iii) decreasing renal inflammation and/or fibrosis,
(iv) delaying the onset of end-stage kidney disease (ESKD),
(iv) decreasing fatigue, and/or
(v) stabilizing functional podocyte mass.

2. The use according to claim 1, wherein
a) the renal inflammation and/or fibrosis comprises tubulointerstitial inflammation, tubulointerstitial fibrosis, glomerular inflammation or glomerulosclerosis;
b) the FSGS comprises a nephrotic syndrome selected from proteinuria, hypoalbuminemia, hypercholesterolemia, peripheral edema, or a combination of any of the foregoing; and/ or
c) i) the FSGS is perihilar FSGS, tip lesion FSGS, cellular FSGS, collapsing FSGS, or primary FSGS; or
c) ii) the FSGS is virus-associated FSGS, not HIV-associated FSGS, toxin-associated FSGS, or adaptive FSGS.

3. The use according to claim 1 or claim 2, further comprising one or more additional agents selected from calcineurin inhibitors, proteasome inhibitors, aminoquinolines, complement inhibitors, B-cell inhibitors, cytotoxic agents, mTOR inhibitors, immunosuppressants (e.g., mycophenolate mofetil (MMF), cyclophosphamide, or chlorambucil), steroids (e.g., prednisone, dexamethasone, hydrocortisone, cyclosporin, or adrenocorticotropic hormone (ACTH)), and combinations thereof to be administered.

4. The use according to claim 3, wherein the one or more additional agents are to be 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.

5. The use according to claim 3 or claim 4, wherein the dosage of the one or more additional agents is reduced by about 25% to about 100%, or by about 50% to about 100%, or by about 75% to about 100% after between about 15 days to about 30 days of treatment with atrasentan, or a pharmaceutically acceptable salt thereof.

6. The use according to claim 1 or claim 2, wherein the subject is not currently receiving one or more immunosuppressants.

7. The use according to any one of claims 1 to 5, wherein the subject is concomitantly receiving a) 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; or b) an ACE inhibitor, an ARB, or a combination thereof.

8. The use according to claim 7, 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, and
the ARB is selected from candesartan, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan, olmesartan medoxomil, telmisartan, valsartan, azilsartan medoxomil, and BRA-657.

9. The use according to claim 7, wherein
the statin is selected from atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin, and pitavastatin, and
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.

10. The use according to any one of claims 1 to 9, wherein atrasentan is to be administered as
a) a pharmaceutically acceptable salt;
b) atrasentan hydrochloride or atrasentan mandelate; c) atrasentan hydrochloride; and/ ord) the free base.

11. The use according to any one of claims 1 to 10, wherein the subject is at a high risk of progression to ESKD.

12. The use according to any one of claims 1 to 11, wherein the subject has been diagnosed with FSGS, 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.

13. The use according to claim 12, wherein the subject has biopsy-confirmed FSGS.

14. The use according to any one of claims 1 to 13, wherein
the subject is excreting an average of from about 1.0 g/g to about 3.5 g/g or more, or 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,
the subject has an average eGFR of from about 20 to about 120 mL/min/1.73 m^2, or from about 20 to about 90 mL/min/1.73 m^2, or from about 20 to about 60 mL/min/1.73 m^2 for at least about 3 months prior to the first administration of atrasentan, or a pharmaceutically acceptable salt thereof,
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,
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,
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,
the subject maintains a potassium level within a normal physiologic range,

the subject maintains a sodium level within a normal physiologic range,
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, and/or
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.

15. The use according to any one of claims 1 to 14, wherein fluid retention in the subject is manageable with diuretics.

16. The use according to any one of claims 1 to 15, wherein
a) the amount of protein in the urine of the subject is reduced by about 20% to about 80% after about 10 weeks, or about 12 weeks, or from about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof;
b) the amount of protein in the urine of the subject is reduced by at least about 30%, or from about 35% to about 80% after treatment with atrasentan, or a pharmaceutically acceptable salt thereof;
c) the UPCR of the subject is reduced to less than about 1.5 g/g after about 10 weeks, or about 12 weeks, or from about 12 weeks to about 24 weeks of treatment with atrasentan, or a pharmaceutically acceptable salt thereof;
d) the risk of the subject developing ESKD is reduced by about 20% to about 99% after between about 6 months and about 24 months, or between about 12 months and about 60 months of treatment with atrasentan, or a pharmaceutically acceptable salt thereof;
e) the average rate of decrease in eGFR is from about 0.75 mL/min/year to about 75 mL/min/year, or from about 3 mL/min/year to about 6 mL/min/year, or 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; and/or
f) 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.

17. The use according to any one of claims 1 to 16, wherein the therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof,
is from about 0.75 mg to about 1.5 mg, or from about 1.0 mg to about 1.5 mg, or from about 1.25 mg to about 1.5 mg; and/or
is about 0.75 mg or about 1.5 mg.

18. The use according to any one of claims 1 to 17, wherein atrasentan, or a pharmaceutically acceptable salt thereof, is to be administered to the subject at a dose of about 0.75 mg once per day.

19. The use according to any one of claims 1 to 18, wherein atrasentan, or a pharmaceutically acceptable salt thereof, is to be administered to the subject orally.

20. The use according to any one of claims 1 to 19, further comprising a therapeutically effective amount of a SGLT-2 inhibitor to be administered.

21. The use according to claim 20, wherein the SGLT-2 inhibitor is selected from bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin, sergliflozin, licogliflozin, sotagliflozin, and tofogliflozin.

22. The use according to any one of claims 1 to 21, 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.

23. The use according to any one of claims 1 to 22, 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.

24. The use according to any one of claims 1 to 23, wherein the subject is to be concurrently administered a maximally tolerated stable dose of a RAS inhibitor and a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

25. The use according to any one of claims 1 to 24, wherein the subject has been determined to have an eGFR of at least 30 mL/min/1.73 m^2 prior to administration of a therapeutically effective amount of atrasentan, or a pharmaceutically acceptable salt thereof.

26. The use according to any one of claims 1 to 25, 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.

27. The use according to any one of claims 1 to 26, wherein the FSGS is associated with one or more genetic mutations in a gene encoding a podocyte protein associated with FSGS.

28. The use according to claim 27, 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, ARHGDIA, PLCE1, PTPRO, WT1, LXMB1, $tRNA^{leu}$, COQ2, COQ6, ITGB4, PDSS2, CD151, CUBN, LAMB2, PAX2, ANLN, CRB2, APOL1, and a combination of any of the foregoing.

29. The use according to claim 27 or claim 28, wherein the one or more genetic mutations is in APOL1.

30. The use according to any one of claims 1 to 29, wherein the subject has been administered a prior therapy for FSGS and was not responsive to the prior therapy, wherein the prior therapy is a standard of care therapy for FSGS, 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.

31. The use according to any one of claims 1 to 30, wherein
the subject has not been treated or is not being treated with a sodium glucose co-transporter 2 (SGLT2) inhibitor and/or an antiretroviral therapy,
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,
the subject has not been previously diagnosed with HIV-related nephropathy,
the subject has not been previously diagnosed with HIV,
the subject is not currently diagnosed with HIV,
the subject is not currently being treated for HIV,
the subject has not been previously diagnosed with renovascular hypertension, and/or
the subject is not currently being treated for renovascular hypertension.