CLAIMS

1. Use of voclosporin in the manufacture of a medicament ~~A method~~ to reduce chronic calcineurin inhibitor nephrotoxicity ~~in~~ for the treatment of a proteinuric kidney disease or associated with a transplant, ~~which method comprises administering to~~ in a subject diagnosed with said disease or a subject that is receiving or is a candidate for receiving a transplant, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered over a projected treatment period of at least 55 weeks, further wherein~~said method further comprising~~:

(a) ~~assessing the~~an estimated Glomerular Filtration Rate (eGFR) of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period; and

(b) (i) if the eGFR of said subject decreases by more than a target % to below a predetermined value, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the ~~administering~~ administration of voclosporin to said subject is to be stopped;

(ii) if the eGFR of said subject decreases by less than said target %, between said first and second time points, ~~continuing administering~~ the administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

2. The ~~method~~ use of claim 1, wherein the first time point is immediately preceding initiating said protocol.

3. The ~~method~~ use of claim 1 or 2, wherein the predetermined value is in the range of 50- 90 ml/min/1.73m^2.

4. The ~~method~~ use of claim 3, wherein the predetermined value is approximately 60ml/min/1.73m^2.

5. The ~~method~~ use of any one of claims 1-4, wherein the target % is in the range of 20-45%.

6. The ~~method~~ use of claim 5, wherein the target % is approximately 30%.

7. The ~~method~~ use of any one of claims 1-6, further comprising identifying said subject as appropriate for said ~~method~~ use prior to conducting said ~~method~~ use on said subject by:

(a) determining that the urine protein creatinine ratio (UPCR) of said subject is > 1mg/mg as measured by first morning void or 24 hour urine; and

(b) determining said subject has an eGFR as measured by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EP1) of > 45 ml/min/1.73m^2,

wherein if the conditions of (a) and (b) are met, said subject is identified as appropriate for said ~~method~~use.

8. Use of voclosporin in the manufacture of a medicament ~~A method~~ to reduce chronic calcineurin inhibitor nephrotoxicity ~~in~~ for the treatment of a proteinuric kidney disease or associated with a transplant, ~~which method comprises administering to~~ in a subject diagnosed with said disease, a subject that is receiving or is a candidate for receiving a transplant, wherein a predetermined daily dosages of effective amounts of voclosporin is to be administered over a projected treatment period to an end point, ~~further comprising~~further wherein:

(a) ~~measuring~~ a urinary protein creatinine ratio (UPCR) of said subject is to be measured at a first time point prior to said treatment period and a second time point occurring prior to the end point but after the start of the treatment period and determining any reduction of said UPCR, between said first and second time points, and

(b) if the UPCR of said subject fails to show a reduction of at least a predetermined amount at said second time point, ~~discontinuing administering~~ administration of voclosporin to the subject is to be discontinued and ~~continuing~~ said ~~administering~~ administration is to be continued if said predetermined amount of reduction is shown.

9. The ~~method~~ use of claim 8, further comprising measuring the concentration of C3/C4 in the blood of said subject at said first and second time points and determining whether the concentration of C3/C4 is normalized at said second time point and if said normalization is found, ~~reinstating or continuing administering~~ administration of voclosporin to the subject is to be reinstated or continued and if normalization has not occurred ~~maintaining~~ said ~~discontinuing~~discontinuation is to be maintained.

10. Use of voclosporin in the manufacture of a medicament ~~A method~~ to treat a proteinuric kidney disease, ~~which method comprises administering to~~in a subject diagnosed with the proteinuric kidney disease, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered over a projected treatment period of at least 8 weeks, wherein said effective amount is 15.8 mg BID or 7.9 mg voclosporin BID.

11. Use of voclosporin in the manufacture of a medicament ~~A method~~ to reduce chronic calcineurin inhibitor nephrotoxicity associated with a transplant~~, which method comprises administering to~~ in a subject that is receiving or is a candidate for receiving a transplant, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered over a projected treatment period of at least 8 weeks, wherein said effective amount is 15.8 mg BID or 7.9 mg voclosporin BID.

12. Use of voclosporin in the manufacture of a medicament~~A method~~ to reduce transplant rejection, ~~which method comprises administering to~~in a subject that is receiving or is a candidate for receiving a transplant, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered over a projected treatment period of at least 8 weeks, wherein said effective amount is 15.8 mg BID or 7.9 mg voclosporin BID.

13. The ~~method~~ use of any one of claims 1-10, wherein the proteinuric kidney disease is lupus nephritis.

14. The ~~method~~ use of any one of claims 1-9, 11 and 12, wherein the transplant is an organ transplant or a tissue transplant.

15. The ~~method~~ use of claim 14, wherein the organ transplant is a kidney (renal) transplant, a liver transplant, or a heart transplant.

16. The ~~method~~ use of claim 14 or 15, wherein the organ transplant is a kidney (renal) transplant.

17. The ~~method~~ use of any one of claims 1-16, wherein said subject has increased susceptibility to chronic calcineurin inhibitor nephrotoxicity.

18. The ~~method~~ use of any one of claims 1-17, wherein said subject exhibits glomerulonephropathy.

19. The ~~method~~ use of any one of claims 1-18, wherein said subject exhibits one or more of:

(a) variability in P-glycoprotein expression and/or activity;

(b) variability in CYP3A4/5 expression and/or activity;

(c) older kidney age;

(d) salt depletion;

(e) the use of nonsteroidal anti-inflammatory drugs;

(f) genetic polymorphisms in TGF-β and/or ACE; and/or

(g) glomerulonephropathy.

20. The ~~method~~ use of any one of claims 1-19, further ~~comprising~~wherein:

(a) ~~assessing the~~ interstitial fibrosis and tubular atrophy of said subject are to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period; and

(b) (i) if interstitial fibrosis and tubular atrophy is observed in > 5% in cortical area, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the ~~administering~~ administration of voclosporin to said subject is to be stopped;

(ii) if interstitial fibrosis and tubular atrophy is observed in < 5% in cortical area, between said first and second time points, ~~continuing administering~~ administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

21. The ~~method~~ use of any one of claims 1-20, further ~~comprising~~wherein:

(a) ~~assessing the~~ presence of medial arteriolar hyalinosis of said subject is to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period; and

(b) (i) if medial arteriolar hyalinosis is present, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the ~~administering~~ administration of voclosporin to said subject is to be stopped;

(ii) if medial arteriolar hyalinosis is not present, between said first and second time points, ~~continuing administering~~ administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

22. The ~~method~~ use of claim 21, wherein medial arteriolar hyalinosis is identified by the replacement of necrotic smooth muscle cells with focal, circular lumpy protein (hyaline) deposits at the periphery of the wall of afferent arterioles, and/or the narrowing of the vascular lumen.

23. The ~~method~~ use of any one of claims 1-22, further ~~comprising~~wherein:

(a) ~~assessing the~~ presence of glomerular injury of said subject is to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if glomerular injury is present, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the ~~administering~~ administration of voclosporin to said subject is to be stopped;

(ii) if glomerular injury is not present, between said first and second time points, ~~continuing administering~~ the administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

24. The ~~method~~ use of claim 23, wherein glomerular injury comprises global and segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, and/or arteriosclerosis.

25. The ~~method~~ use of claim 23 or 24, wherein glomerular injury is present when total renal chronicity score is > 1.

26. The ~~method~~ use of any one of claims 1-25, further ~~comprising~~wherein:

(a) ~~assessing the~~ presence of juxtaglomerular apparatus (JGA) hyperplasia of said subject is to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if JGA hyperplasia is present, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if JGA hyperplasia is not present, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

27. The ~~method~~ use of claim 26, wherein JGA hyperplasia comprises:

(a) enlargements of juxtaglomerular apparatus components comprising one or more of: the vascular components, the mesangial cell components, the tubular components (the macula densa); and/or

(b) the presence of intracellular renin granules.

28. The ~~method~~ use of any one of claims 1-27, further ~~comprising~~wherein:

(a) ~~assessing the~~ presence of tubular microcalcifications of said subject is to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if tubular microcalcifications are present, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if tubular microcalcifications are not present, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

29. The ~~method~~ use of any one of claims 1-28, further ~~comprising~~wherein:

(a) ~~assessing the~~ P-glycoprotein (P-gp) expression of said subject is to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if loss of expression of P-gp is more than a predetermined value, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if loss of expression of P-gp is less than the predetermined value, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

30. The ~~method~~ use of claim 29, wherein the predetermined value for loss of expression of P-gp is 10% loss of P-gp expression in tubules in the cortical area.

31. The ~~method~~ use of any one of claims 1-30, further ~~comprising~~wherein:

(a) ~~assessing the~~ Calcineurin Inhibitor (CNI) Nephrotoxicity and/or Banff Scores of said subject is to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the CNI Nephrotoxicity and/or Banff Scores are outside of predetermined ranges, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or stopping the administration ~~administering~~ of voclosporin to said subject;

(ii) if the CNI Nephrotoxicity and/or Banff Scores are within predetermined ranges, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

32. The ~~method~~ use of claim 31, wherein:

(a) the predetermined range of CNI Nephrotoxicity Score is 0-3; and/or

(b) the predetermined range of Banff Score is 0-3.

33. The ~~method~~ use of any one of claims 1-32, further ~~comprising~~wherein:

(a) ~~assessing~~ one or more of the National Institutes of Health Activity Index (NIH-AI), the National Institutes of Health Chronicity Index (NIH-CI), and the Tubulointerstitial Activity Index (TIAI) of said subject are to be assessed by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the NIH-AI, NIH-CI, and/or TIAI are outside of predetermined ranges, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the NIH-AI, NIH-CI, and/or TIAI are within predetermined ranges, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

34. The ~~method~~ use of claim 33, wherein:

(a) the predetermined range of NIH-AI is 0-6; and/or

(b) the predetermined range of NIH-CI is 0-3; and/or

(c) the predetermined range of TIAI is 0-5.

35. The ~~method~~ use of any one of claims 1-34, further ~~comprising~~wherein:

(a) ~~assessing~~ urine anion gap (UAG) in urinary specimens of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the UAG is outside of a predetermined range, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the UAG is within the predetermined range, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

36. The ~~method~~ use of claim 35, wherein the predetermined range of UAG is between 20-90 mEq/L.

37. The ~~method~~ use of any one of claims 1-36, further ~~comprising~~wherein:

(a) ~~assessing~~ hyperkalemia, hypomagnesemia, magnesium wasting and/or hyperuricemia in serum and urine samples of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if hyperkalemia, hypomagnesemia, magnesium wasting and/or hyperuricemia are detected, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if hyperkalemia, hypomagnesemia, magnesium wasting and hyperuricemia are not detected, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

38. The ~~method~~ use of claim 37, wherein:

(a) hyperkalemia is to be determined by a serum potassium level of > 5 mmol/L;

(b) hypomagnesemia is to be determined by a serum magnesium level less than 1.4 mg/dL;

(c) magnesium wasting is to be determined by a urine magnesium level of more than 2 mEq;

(d) hyperuricemia is to be determined by a serum uric acid level of > 7.0 mg/dL.

39. The ~~method~~ use of any one of claims 1-38, further ~~comprising~~wherein:

(a) ~~assessing~~ serum creatinine (SCr) and/or serum cystatin C (SCysC) in serum samples of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the SCr and/or SCysC levels are elevated above predetermined ranges, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the SCr and/or SCysC levels are within predetermined ranges, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

40. The ~~method~~ use of claim 39, wherein:

(a) the predetermined range of SCr level is 0.84-1.21 mg/dL; and/or

(b) the predetermined range of SCysC level is below 1 mg/L.

41. The ~~method~~ use of any one of claims 1-40, further ~~comprising~~wherein:

(a) ~~assessing~~ creatinine clearance (CrCl) and/or blood urea nitrogen (BUN) in serum samples of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the CrCl level is decreased below a first predetermined range and/or if BUN level is elevated above a second predetermined range, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the CrCl and/or BUN levels are within predetermined ranges, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

42. The ~~method~~ use of claim 41, wherein:

(a) the first predetermined range of CrCl level is 137-150 mL/min in males and 128-130 mL/min in females;

(b) the second predetermined range of BUN level is 7 to 20 mg/dL.

43. The ~~method~~ use of any one of claims 1-42, further ~~comprising~~wherein:

(a) ~~assessing~~ renal vascular resistance and/or renal plasma flow (RPF) of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the renal vascular resistance and/or RPF are altered outside of predetermined values, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the renal vascular resistance and/or RPF remain within predetermined values, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

44. The ~~method~~ use of claim 43, wherein the predetermined value of RPF is 600mL/min.

45. The ~~method~~ use of any one of claims 1-44, further ~~comprising~~wherein:

(a) ~~assessing~~ albuminuria in morning/random urinary specimens of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the albuminuria is detected, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the albuminuria is not detected, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

46. The ~~method~~ use of claim 45, wherein albuminuria is to be determined by the presence of albumin/creatinine ratios of > 30 mg/g.

47. The ~~method~~ use of any one of claims 1-46, wherein the ~~method~~ use does not result in a substantial increase or decrease of the level of one or more urinary electrolytes, or the level of one or more urinary electrolytes is decreased or increased by less than the predetermined value, between said first and second time points.

48. The ~~method~~ use of any one of claims 1-47, further ~~comprising~~wherein:

(a) ~~assessing the~~a level of one or more urinary electrolytes of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the level of the one or more urinary electrolyte is decreased or increased by more than a predetermined value, between said first and second time points, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the level of the one or more urinary electrolyte is decreased or increased by less than the predetermined value, between said first and second time points, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

49. The ~~method~~ use of claim 47 or 48, wherein the urinary electrolyte is selected from one or more of magnesium, sodium and potassium.

50. The ~~method~~ use of claim 47 or 48, wherein the urinary electrolyte is magnesium, and the predetermined value is about 20 mg/dL.

51. The ~~method~~ use of claim 47 or 48, wherein the urinary electrolyte is sodium, and the predetermined value is about 50 mmol/L.

52. The ~~method~~ use of claim 47 or 48, wherein the urinary electrolyte is potassium, and the predetermined value is about 10 mmol/L.

53. The ~~method~~ use of any one of claims 1-52, wherein the ~~method~~ use does not result in a substantial dyslipidemia, or the level of one or more lipids is within a predetermined range, at said second time point.

54. The ~~method~~ use of any one of claims 1-53, further ~~comprising~~wherein:

(a) ~~assessing the~~a level of one or more lipids of said subject is to be assessed at at least a first time point and a second time point on different days of said treatment period, and

(b) (i) if the level of the one or more lipid is outside of a predetermined range, at said second time point, ~~reducing~~ the daily dosage is to be reduced by increment(s) of 7.9 mg BID or ~~stopping~~ the administration ~~administering~~ of voclosporin to said subject is to be stopped;

(ii) if the level of the one or more lipid is within a predetermined range, at said second time point, ~~continuing~~ the administration of ~~administering~~ the same predetermined daily dosage of voclosporin to said subject is to be continued.

55. The ~~method~~ use of claim 53 or 54, wherein the one or more lipid is selected from one or more of total cholesterol, low density lipoprotein (LDL) cholesterol, and triglyceride.

56. The ~~method~~ use of claim 53 or 54, wherein the lipid is total cholesterol, and the predetermined range is 100-200 mg/dL.

57. The ~~method~~ use of claim 53 or 54, wherein the lipid is triglycerides, and the predetermined range is 50-150 mg/dL.

58. The ~~method~~ use of claim 53 or 54, wherein the lipid is LDL, and the predetermined range is 50-130 mg/dL.

59. The ~~method~~ use of any one of claims 1-9 and 13-58, wherein the first time point is immediately preceding initiating said protocol.

60. The ~~method~~ use of any one of claims 1-9 and 13-59, wherein the second time point is after the first time point and initiating said protocol.

61. The ~~method~~ use of any one of claims 1-9 and 13-59, wherein the second time point is after the mid-point of the projected treatment period.

62. The ~~method~~ use of any one of claims 1-9 and 13-59, wherein the second time point is after the end of the projected treatment period.

63. The ~~method~~ use of any one of claims 1-62, wherein said predetermined daily dosage is 39.5 mg voclosporin BID or 31.6 mg voclosporin BID or 23.7 mg voclosporin BID or 15.8 mg voclosporin BID or 7.9 mg voclosporin BID.

64. The ~~method~~ use of any one of claims 1-63, further ~~comprising~~ wherein ~~evaluating~~ said subject is to be evaluated for renal function at a time point after the end of said treatment period by assessing eGFR.

65. The ~~method~~ use of claim 64, further ~~comprising evaluating~~wherein said subject is to be evaluated for efficacy by assessing protein/creatinine ratio (UPCR) at a time point after the end of said treatment period.

66. The ~~method~~ use of any one of claims 1-65, wherein ~~further comprising administering to said subject~~ an effective amount of mycophenolate mofetil (MMF) is to be further administered to said subject.

67. The ~~method~~ use of any one of claims 1-66, ~~further comprising administering to said subject~~ wherein an effective amount of a corticosteroid is to be further administered to said subject.

68. The ~~method~~ use of any one of claims 1-67, wherein said treatment period is at least 100 weeks.

69. The ~~method~~ use of any one of claims 1-68, wherein said treatment period is at least 150 weeks.

70. The ~~method~~ use of any one of claims 1-9 and 13-69, further ~~comprising~~ wherein ~~determining~~ the eGFR of said subject is to be determined at a third time point and if the eGFR is determined at said third time point to differ from the eGFR determined at said first time point by less than said target %, ~~resuming administering~~ the administration of said predetermined daily dosage of voclosporin is to be resumed.

71. The ~~method~~ use of claim 70, wherein the target % is 20-45%.

72. The ~~method~~ use of claim 70, wherein the target % is approximately 30%.