PROTOCOL TO MINIMIZE CALCINEURIN INHIBITOR NEPHROTOXICITY

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Patent Application No. 63/138,325, filed January 15, 2021, entitled "PROTOCOL TO MINIMIZE CALCINEURIN INHIBITOR NEPHROTOXICITY," U.S. Provisional Patent Application No. 63/245,779, filed September 17, 2021, entitled "PROTOCOL TO MINIMIZE CALCINEURIN INHIBITOR NEPHROTOXICITY," and U.S. Provisional Patent Application No. 63/246,765, filed September 21, 2021, entitled "PROTOCOL TO MINIMIZE CALCINEURIN INHIBITOR NEPHROTOXICITY," the contents of which are incorporated by reference in their entirety.

FIELD

[0002] The present disclosure relates to methods of employing pharmacodynamics regimens to maximize effectiveness of voclosporin in treatment of proteinuric kidney diseases while minimizing undesirable side effects, such as but not limited to calcineurin inhibitor nephrotoxicity. Also provided are methods of assessments of renal functions and/or conditions, and corresponding protocols to modify, stop, restore and/or re-initiate voclosporin dosing and administrations to maximize effectiveness of voclosporin in treatment of proteinuric kidney diseases while minimizing undesirable side effects.

BACKGROUND

[0003] Calcineurin inhibitor drugs (CNI), such as cyclosporine and tacrolimus, both potent immunosuppressant, and have been tested for use in the treatment of a variety of conditions, including use in conjunction with tissue transplant. Both of these compounds show long term nephrotoxicity.

[0004] It would be beneficial to develop a CNI that was an effective immunosuppressant that is also tolerated for long term use. In particular, it would be beneficial to identify such a CNI and a method of administering same for prolonged periods of time.

SUMMARY

[0005] Provided herein in some ~~aspect~~examples are methods, compositions, devices, and systems for reducing chronic calcineurin inhibitor nephrotoxicity in the treatment of proteinuric

kidney disease or associated with a transplant, including identifying subjects as appropriate for said method, administering a predetermined daily dosage of effective amounts of voclosporin, and evaluating said subjects for renal function at a time point before, during and after the end of said treatment period.

[0006] In some of any ~~embodiment~~examples, the method to reduce chronic calcineurin inhibitor nephrotoxicity in treatment of a proteinuric kidney disease or associated with a transplant disclosed herein involves administering to a subject diagnosed with said disease or a subject that is receiving or is a candidate for receiving a transplant a predetermined daily dosage of effective amounts of voclosporin over a projected treatment period of at least 55 weeks. In some examples, the method further includes assessing the estimated Glomerular Filtration Rate (eGFR) of the subject at at least a first time point and a second time point on different days of said treatment period, and 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 by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some examples, the method further includes assessing the estimated Glomerular Filtration Rate (eGFR) of the subject at at least a first time point and a second time point on different days of said treatment period, and if the eGFR of the subject decreases by less than said target %, between said first and second time points, the method includes continuing administering the same predetermined daily dosage of voclosporin to said subject.

[0006a] In one aspect, the present disclosure refers to use of voclosporin in the manufacture of a medicament to reduce chronic calcineurin inhibitor nephrotoxicity for the treatment of a proteinuric kidney disease or associated with a transplant, 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: (a) 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, the daily dosage is to be reduced by increment(s) of 7.9 mg BID or the 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, the administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

[0007] In some of any ~~embodiment~~examples, the first time point is immediately preceding initiating said protocol. In some examples, the predetermined value is in the range of 50- 90 ml/min/1.73m^2. In some of any ~~embodiment~~examples, the target % is in the range of 20-45%. In some ~~aspect~~examples, the predetermined value is approximately 60ml/min/1.73m^2. In some examples, the target % is approximately 30%.

[0008] In some of any ~~embodiment~~examples, the method disclosed herein further includes identifying a subject as appropriate for said method prior to conducting said method on the subject by (a) determining that the urine protein creatinine ratio (UPCR) of the subject is > 1 mg/mg as measured by first morning void or 24 hour urine, and (b) determining that the subject has an eGFR as measured by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EP1) of > 45 ml/min/1.73m^2; if the conditions of (a) and (b) are met, the subject is identified as appropriate for said method.

[0009] In some of any ~~embodiment~~examples, the method to reduce chronic calcineurin inhibitor nephrotoxicity in treatment of a proteinuric kidney disease or associated with a transplant disclosed herein involves administering to a subject diagnosed with said disease, a subject that is receiving or is a candidate for receiving a transplant, predetermined daily dosages of effective amounts of voclosporin over a projected treatment period to an end point, further comprising: (a) measuring urinary protein creatinine ratio (UPCR) of said subject 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 voclosporin to the subject and continuing said administering if said predetermined amount of reduction is shown.

[0009a] In one aspect, the present disclosure refers to use of voclosporin in the manufacture of a medicament to reduce chronic calcineurin inhibitor nephrotoxicity for the treatment of a proteinuric kidney disease or associated with a transplant, 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 wherein: (a) 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, administration of voclosporin to the subject is to be discontinued and said administration is to be continued if said predetermined amount of reduction is shown.

[0010] In some of any ~~embodiment~~examples, the method described herein further comprises 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 voclosporin to the subject and if normalization has not occurred maintaining said discontinuing.

[0011] In some of any ~~embodiment~~examples, the method to treat a proteinuric kidney disease disclosed herein involves administering to a subject diagnosed with the proteinuric kidney disease, a predetermined daily dosage of effective amounts of voclosporin 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.

[0011a] In one aspect, the present disclosure refers to use of voclosporin in the manufacture of a medicament to treat a proteinuric kidney disease, 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.

[0012] In some of any ~~embodiment~~examples, the method to reduce chronic calcineurin inhibitor nephrotoxicity associated with a transplant disclosed herein involves administering to a subject that is receiving or is a candidate for receiving a transplant, a predetermined daily dosage of effective amounts of voclosporin 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.

[0012a] In one aspect, the present disclosure refers to use of voclosporin in the manufacture of a medicament to reduce chronic calcineurin inhibitor nephrotoxicity associated with a transplant 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.

[0013] In some of any ~~embodiment~~examples, the method to reduce transplant rejection disclosed herein involves administering to a subject that is receiving or is a candidate for receiving a transplant, a predetermined daily dosage of effective amounts of voclosporin 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.

[0013a] In one aspect, the present disclosure refers to use of voclosporin in the manufacture of a medicament to reduce transplant rejection, 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.

[0014] In some of any ~~embodiment~~examples, the proteinuric kidney disease is lupus nephritis.

[0015] In some of any ~~embodiment~~examples, the transplant is an organ transplant or a tissue transplant. In some of any ~~embodiment~~examples, the organ transplant is a kidney (renal) transplant, a liver transplant, or a heart transplant. In some of any ~~embodiment~~examples, the organ transplant is a kidney (renal) transplant.

[0016] In some of any ~~embodiment~~examples, the subject has increased susceptibility to chronic calcineurin inhibitor nephrotoxicity. In some ~~aspect~~examples, the subject has increased susceptibility to chronic calcineurin inhibitor nephrotoxicity and exhibits one or more of (a) variability in P-glycoprotein expression and/or activity, (b) variability in CYP3A4/5 expression and activity, (c) older kidney age, (d) salt depletion, (e) the use of nonsteroidal anti-inflammatory drugs, (f) and has genetic polymorphisms in TGF-β and/or ACE. In some ~~aspect~~examples, the subject has increased susceptibility to chronic calcineurin inhibitor nephrotoxicity and exhibits one or more of (a) variability in P-glycoprotein expression and/or activity, (b) variability in CYP3A4/5 expression or activity, (c) older kidney age, (d) salt depletion, (e) the use of nonsteroidal anti-inflammatory drugs, (f) or has genetic polymorphisms in TGF-β and/or ACE.

[0017] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the interstitial fibrosis and tubular atrophy of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if interstitial fibrosis and tubular atrophy is observed in > 5% in cortical area, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the interstitial fibrosis and tubular atrophy of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if interstitial fibrosis and tubular atrophy is observed in < 5% in cortical area, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject.

[0018] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of medial arteriolar hyalinosis of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if medial

arteriolar hyalinosis is present, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of medial arteriolar hyalinosis of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if medial arteriolar hyalinosis is not present, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some ~~aspect~~examples, 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 the narrowing of the vascular lumen. In some ~~aspect~~examples, the 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, or the narrowing of the vascular lumen.

[0019] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of glomerular injury of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if glomerular injury is present, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of glomerular injury of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if glomerular injury is not present, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some ~~aspect~~examples, the glomerular injury comprises global and segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arteriosclerosis. In some ~~aspect~~examples, the glomerular injury comprises global and segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, or arteriosclerosis. In some examples, the glomerular injury is present when total renal chronicity score is > 1.

[0020] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of juxtaglomerular apparatus (JGA) hyperplasia of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if JGA hyperplasia is present, between said first and second time points, reducing the

daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of juxtaglomerular apparatus (JGA) hyperplasia of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if JGA hyperplasia is not present, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some examples, JGA hyperplasia includes enlargements of juxtaglomerular apparatus components comprising one or more of: the vascular components, the mesangial cell components, the tubular components (the macula densa), and the presence of intracellular renin granules. In some examples, the JGA hyperplasia includes enlargements of juxtaglomerular apparatus components comprising one or more of: the vascular components, the mesangial cell components, the tubular components (the macula densa), or the presence of intracellular renin granules.

[0021] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of tubular microcalcifications of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if tubular microcalcifications is present, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the presence of tubular microcalcifications of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if tubular microcalcifications is not present, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject.

[0022] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the P-glycoprotein (P-gp) expression of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if loss of expression of P-gp is more than a predetermined value, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the P-glycoprotein (P-gp) expression of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if loss of expression of P-gp is less than the predetermined value, between said first and second

time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some examples, the predetermined value for loss of expression of P-gp is 10% loss of P-gp expression in tubules in the cortical area.

[0023] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the Calcineurin Inhibitor (CNI) Nephrotoxicity and/or Banff Scores of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if the CNI Nephrotoxicity and/or Banff Scores are outside of predetermined ranges, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing the Calcineurin Inhibitor (CNI) Nephrotoxicity and/or Banff Scores of said subject by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if the CNI Nephrotoxicity and/or Banff Scores are within predetermined ranges, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some ~~aspect~~examples, the predetermined range of CNI Nephrotoxicity Score is 0-3, and the predetermined range of Banff Score is 0-3. In some ~~aspect~~examples, the predetermined range of CNI Nephrotoxicity Score is 0-3, or the predetermined range of Banff Score is 0-3.

[0024] In some of any ~~embodiment~~examples, the method disclosed herein further includes 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 by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and 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 by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes 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 by renal biopsies at at least a first time point and a second time point on different days of said treatment period, and if the NIH-AI, NIH-CI, and/or TIAI are within predetermined ranges, between said first and second time points, continuing administering the same predetermined

daily dosage of voclosporin to said subject. In some of any ~~embodiment~~examples, the predetermined range of NIH-AI is 0-6, and the predetermined range of NIH-CI is 0-3, and the predetermined range of TIAI is 0-5. In some of any ~~embodiment~~examples, the predetermined range of NIH-AI is 0-6, or the predetermined range of NIH-CI is 0-3, and the predetermined range of TIAI is 0-5. In some of any ~~embodiment~~examples, the predetermined range of NIH-AI is 0-6, and the predetermined range of NIH-CI is 0-3, or the predetermined range of TIAI is 0-5. In some of any ~~embodiment~~examples, the predetermined range of NIH-AI is 0-6, or the predetermined range of NIH-CI is 0-3, or the predetermined range of TIAI is 0-5.

[0025] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing urine anion gap (UAG) in urinary specimens of said subject at at least a first time point and a second time point on different days of said treatment period, and if the UAG is outside of a predetermined range, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing urine anion gap (UAG) in urinary specimens of said subject at at least a first time point and a second time point on different days of said treatment period, and if the UAG is within the predetermined range, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some ~~aspect~~examples, the predetermined range of UAG is between 20-90 mEq/L.

[0026] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing hyperkalemia, hypomagnesemia, magnesium wasting and hyperuricemia in serum and urine samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if hyperkalemia, hypomagnesemia, magnesium wasting and hyperuricemia are detected, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing hyperkalemia, hypomagnesemia, magnesium wasting and/or hyperuricemia in serum and urine samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if hyperkalemia, hypomagnesemia, magnesium wasting or hyperuricemia are detected, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any

~~embodiment~~examples, the method disclosed herein further includes assessing hyperkalemia, hypomagnesemia, magnesium wasting and hyperuricemia in serum and urine samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if hyperkalemia, hypomagnesemia, magnesium wasting and hyperuricemia are not detected, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing hyperkalemia, hypomagnesemia, magnesium wasting and hyperuricemia in serum and urine samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if hyperkalemia, hypomagnesemia, magnesium wasting or hyperuricemia are not detected, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some ~~aspect~~examples, hyperkalemia is determined by a serum potassium level of > 5 mmol/L. In some ~~aspect~~examples, hypomagnesemia is determined by a serum magnesium level less than 1.4 mg/dL. In some ~~aspect~~examples, magnesium wasting is determined by a urine magnesium level of more than 2 mEq. In some ~~aspect~~examples, hyperuricemia is determined by a serum uric acid level of > 7.0 mg/dL

[0027] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing serum creatinine (SCr) and serum cystatin C (SCysC) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the SCr and SCysC levels are elevated above predetermined ranges, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing serum creatinine (SCr) and serum cystatin C (SCysC) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the SCr or SCysC levels are elevated above predetermined ranges, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing serum creatinine (SCr) and serum cystatin C (SCysC) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the SCr and SCysC levels are within predetermined ranges, between said first and second time points, continuing administering the

same predetermined daily dosage of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing serum creatinine (SCr) and serum cystatin C (SCysC) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the SCr or SCysC levels are within predetermined ranges, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some examples, the predetermined range of SCr level is 0.84-1.21 mg/dL, and the predetermined range of SCysC level is below 1 mg/L. In some examples, the predetermined range of SCr level is 0.84-1.21 mg/dL, or the predetermined range of SCysC level is below 1 mg/L.

[0028] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing creatinine clearance (CrCl) and blood urea nitrogen (BUN) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the CrCl level is decreased below a first predetermined range and if BUN level is elevated above a second predetermined range, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing creatinine clearance (CrCl) and blood urea nitrogen (BUN) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the CrCl level is decreased below a first predetermined range or if BUN level is elevated above a second predetermined range, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing creatinine clearance (CrCl) and blood urea nitrogen (BUN) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the CrCl and BUN levels are within predetermined ranges, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing creatinine clearance (CrCl) and blood urea nitrogen (BUN) in serum samples of said subject at at least a first time point and a second time point on different days of said treatment period, and if the CrCl or BUN levels are within predetermined ranges, between said first and second time points, continuing administering the same predetermined daily dosage of

voclosporin to said subject. In some ~~aspect~~examples, the first predetermined range of CrCl level is 137-150 mL/min in males and 128-130 mL/min in females, and the second predetermined range of BUN level is 7 to 20 mg/dL.

[0029] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing renal vascular resistance and renal plasma flow (RPF) of said subject at at least a first time point and a second time point on different days of said treatment period, and if the renal vascular resistance and RPF are altered outside of predetermined values, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing renal vascular resistance and renal plasma flow (RPF) of said subject at at least a first time point and a second time point on different days of said treatment period, and if the renal vascular resistance or RPF are altered outside of predetermined values, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing renal vascular resistance and renal plasma flow (RPF) of said subject at at least a first time point and a second time point on different days of said treatment period, and if the renal vascular resistance and RPF remain within predetermined values, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing renal vascular resistance and renal plasma flow (RPF) of said subject at at least a first time point and a second time point on different days of said treatment period, and if the renal vascular resistance or RPF remain within predetermined values, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some examples, the predetermined value of RPF is 600mL/min.

[0030] In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing albuminuria in morning and random urinary specimens of said subject at at least a first time point and a second time point on different days of said treatment period, and if the albuminuria is detected, between said first and second time points, reducing the daily dosage by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject. In some of any ~~embodiment~~examples, the method disclosed herein further includes assessing albuminuria in

morning and random urinary specimens of said subject at at least a first time point and a second time point on different days of said treatment period, and if the albuminuria is not detected, between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some ~~aspect~~examples, albuminuria is determined by the presence of albumin/creatinine ratios of > 30 mg/g.

[0031] In some of any ~~embodiment~~examples, the methods described herein do not substantially decrease or increase urinary electrolyte levels, between said first and second time points. In some of any ~~embodiment~~examples, the method 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.

[0032] In some of any ~~embodiment~~examples, provided herein is a method involving (a) assessing the level of one or more urinary electrolytes of said subject 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 by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject; (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 administering the same predetermined daily dosage of voclosporin to said subject.

[0033] In some of any ~~embodiment~~examples, the urinary electrolyte is selected from one or more of magnesium, sodium and potassium. In some of any ~~embodiment~~examples, the urinary electrolyte is magnesium, and the predetermined value is about 20 mg/dL. In some of any ~~embodiment~~examples, the urinary electrolyte is sodium, and the predetermined value is about 50 mmol/L. In some of any ~~embodiment~~examples, the urinary electrolyte is potassium, and the predetermined value is about 10 mmol/L.

[0034] In some of any ~~embodiment~~examples, the methods described herein do not result in a substantial dyslipidemia, or the level of one or more lipids is within a predetermined range, at said second time point.

[0035] In some of any ~~embodiment~~examples, the method disclosed herein further includes (a) assessing the level of one or more lipids of said subject 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 by increment(s) of 7.9 mg BID or stopping the administering of voclosporin to said subject; (ii) if the level of the one or more lipid is within a predetermined range, at said second time point, continuing administering the same predetermined daily dosage of voclosporin to said subject. In some of any ~~embodiment~~examples, the one or more lipid is selected from one or more of total cholesterol, low density lipoprotein (LDL) cholesterol, and triglyceride. In some of any ~~embodiment~~examples, the lipid is total cholesterol, and the predetermined range is 100-200 mg/dL. In some of any ~~embodiment~~examples, the lipid is triglycerides, and the predetermined range is 50-150 mg/dL. In some of any ~~embodiment~~examples, the lipid is LDL, and the predetermined range is 50-130 mg/dL.

[0036] In any of the provided ~~embodiment~~examples, the first time point is immediately provided initiating said protocol. In some of any ~~embodiment~~examples, the second time point is after the first time point and initiating said protocol. In some of any ~~embodiment~~examples, the second time point is after the mid-point of the projected treatment period. In some of any ~~embodiment~~examples, the second time point is after the end of the projected treatment period.

[0037] In any of the provided ~~embodiment~~examples, the 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.

[0038] In any of the provided ~~embodiment~~examples, the method further includes evaluating said subject for renal function at a time point after the end of said treatment period by assessing eGFR. In some of any ~~embodiment~~examples, the method further includes evaluating said subject for efficacy by assessing protein/creatinine ratio (UPCR) at a time point after the end of said treatment period.

[0039] In any of the provided ~~embodiment~~examples, the method further includes administering to said subject an effective amount of mycophenolate mofetil (MMF). In some of any ~~embodiment~~examples, the method further includes administering to said subject an effective amount of a corticosteroid. In some of any ~~embodiment~~examples, the treatment period is at least 100 weeks. In some of any ~~embodiment~~examples, the treatment period is at least 150 weeks.

[0040] In any of the provided ~~embodiment~~examples, the method further includes determining the eGFR of the subject 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 said predetermined daily dosage of voclosporin. In some examples, the target % is 20-45%. In some examples, the target % is approximately 30%.

[0041] In some of any ~~embodiment~~examples, disclosed herein is a method to reduce chronic calcineurin inhibitor nephrotoxicity in treatment of a proteinuric kidney disease, in which the method includes administering to a subject diagnosed with said disease predetermined daily dosages of effective amounts of voclosporin over a projected treatment period to an end point, and further includes measuring urinary protein creatinine ratio (UPCR) of said subject 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, if the UPCR of said subject fails to show a reduction of at least a predetermined amount at said second time point, discontinuing administering voclosporin to the subject and continuing said administering if said predetermined amount of reduction is shown.

[0042] In some of any ~~embodiment~~examples, the method described herein further comprises 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 voclosporin to the subject and if normalization has not occurred maintaining said discontinuing. In some ~~aspect~~examples, the method further includes administering to said subject an effective amount of mycophenolate mofetil (MMF). In some examples, the method further includes administering to the subject an effective amount of a corticosteroid. In some of any ~~embodiment~~examples, the 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.

[0043] In some of any ~~embodiment~~examples, disclosed herein is a method to treat a proteinuric kidney disease which includes administering to a subject diagnosed with lupus nephritis a predetermined daily dosage of effective amounts of voclosporin 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.