nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, minimal change disease, hypertensive nephrosclerosis and interstitial nephritis.

**[0016]** One of the side effects of treatment with voclosporin is an unwanted decrease in the estimated glomerular filtration rate (eGFR). One disclosure protocol is designed to reduce the incidence of this undesirable side effect by adjusting the dosage in accordance with the response of the subject.

**[0017]** Thus, in one example, the disclosure is directed to a pharmacodynamic method to treat a proteinuric kidney disease which method comprises administering to a subject diagnosed with said disease a predetermined daily dosage of effective amounts of voclosporin over a projected treatment period of at least 24 weeks, said pharmacodynamic method further comprising:

(a) assessing the estimated Glomerular Filtration Rate (eGFR) 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 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 7.9mg BID or stopping the administering of voclosporin to said subject;

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

**[0017a]** In one aspect, the present disclosure refers to use of a composition comprising volclospoin in the manufacture of a medicament for pharmacodynamic treatment of lupus nephritis, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered to a subject diagnosed with lupus nephritis over a projected treatment period of at least 24 weeks, and wherein:

(a) the 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, both said time points occurring prior to the end of the treatment period, and

(b) (i) if the eGFR of said subject decreases by more than a target % in the range of 20-45% to below a predetermined value in the range of 50-90 ml/min/1.73m$^2$ between said first and second time points, the daily dosage is to be reduced by increment(s) of 7.9mg 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, administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

**[0017b]** In another example, the present disclosure refers to use of a composition comprising volclospoin in the manufacture of a medicament for pharmacodynamic treatment of a proteinuric kidney disease, wherein predetermined daily dosages of effective amounts of voclosporin are to be administered to a subject diagnosed with a proteinuric kidney disease over a projected treatment period to an end point, wherein:

(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 any reduction of said UPCR between said first and second time points is to be determined, and

(b) if the UPCR of said subject fails to show a reduction of at least a predetermined amount in the range of 15%-35% 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.

**[0018]** In one specific example, the disclosure includes a pharmacodynamic method to treat lupus nephritis which method comprises 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 24 weeks, said pharmacodynamic method further comprising:

(a) assessing the glomerular filtration rate (eGFR) 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 eGFR of said subject decreases by $\geq$30% to a value of below 60 mL/min/1.73m$^2$ between said first and second time points, stopping the administering of voclosporin to said subject;

(ii) if the eGFR of said subject decreases by between 20% to 30% to a value of below 60 ml/min/1.73m$^2$ between said first and second time points, administering a reduced dosage of voclosporin to said subject;

**[0029]** In addition, lowered levels of voclosporin dosage have been shown to be effective.

**[0030]** Thus, in another example, the disclosure is directed to a method to treat lupus nephritis which method comprises administering to a subject diagnosed with lupus nephritis a predetermined daily dosage of effective amounts of voclosporin wherein said effective amount is either 15.8mg BID or 7.9mg BID. Surprisingly, it has been found that these lower dosages are effective in a majority of patients, especially if the treatment is prolonged beyond 24 weeks. A dosage of 31.6 mg BID (4 capsules) could also be employed. Pharmacodynamic dosing can be applied in these instances as well.

**[0030a]** In another example, the present disclosure refers to use of a composition comprising volclospoin in the manufacture of a medicament for treating a proteinuric kidney disease, wherein a predetermined daily dosage of voclosporin is to be administered to a subject diagnosed with lupus nephritis over a protocol that consists of a projected treatment period of at least 8 weeks, wherein said the dosage of voclosporin is15.8/mg BID or 7.9/mg voclosporin BID and does not exceed 15.8 mg BID over the entire protocol and wherein said subject is to be administered voclosporin only in said protocol.

**[0031]** It is also advantageous and part of the disclosure to evaluate a subject who has been treated with the protocol at the end of the treatment period to determine whether a complete or partial remission has occurred. Further evaluations are included at a time subsequent to termination of the treatment to assess whether the remission achieved according to the measurement at the end of the treatment is being maintained. Such evaluation may also be done at intermediate times during treatment to determine whether dosage can be reduced. In an exemplary example used simply for illustration a dosage of 23.6 mg voclosporin BID may be reduced to 15.8 mg or 7.9 mg BID based on such results.

**[0032]** The evaluation for effectiveness can be based on the protein/creatinine ratio in urine (UPCR) where a ratio of $\leq 0.5$ mg/mg indicates complete response; alternatively, or in addition, an eGFR of $\geq 60$ mL/min/1.73m$^2$ or no decrease from baseline and eGFR of $\geq 20\%$ is shown. Other indications of complete response include lack of need for rescue medications such as intravenous steroids, cyclophosphamide or a need for $\leq 10$ mg prednisone for more than three consecutive days or more than seven days total. These evaluations may be performed at any point in the treatment.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0033]** Figure 1 shows graphically the design of a protocol for treatment of lupus nephritis with voclosporin upon which the pharmacodynamic treatment of the invention is superimposed.

**[0034]** Figure 2 is a bar graph showing a comparison of complete remission (CR) at 48 weeks and partial remission (PR) at 48 weeks for low dose as compared to high dose of voclosporin (VCS). The PR percentages include the CR percentages.

# CLAIMS

1. Use of a composition comprising volclospoin in the manufacture of a medicament for pharmacodynamic treatment of lupus nephritis, wherein a predetermined daily dosage of effective amounts of voclosporin is to be administered to a subject diagnosed with lupus nephritis over a projected treatment period of at least 24 weeks, and wherein:

(a) the 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, both said time points occurring prior to the end of the treatment period, and

(b) (i) if the eGFR of said subject decreases by more than a target % in the range of 20-45% to below a predetermined value in the range of 50-90 ml/min/1.73m$^2$ between said first and second time points, the daily dosage is to be reduced by increment(s) of 7.9mg 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, administration of the same predetermined daily dosage of voclosporin to said subject is to be continued.

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

3. The use of claim 1 or 2, wherein the predetermined value is approximately 60ml/min/1.73m$^2$.

4. The use of any of claims 1-3, wherein the target % is approximately 30%.

5. The use of any of claims 1-4, wherein said subject as appropriate for said use is identified prior to said use on said subject by:

(a) determining that the urine protein creatinine ratio (UPCR) of said subject is $\geq$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 $\geq$45 ml/min/1.73m$^2$,

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

6. The use of any of claims 1-5, wherein said predetermined daily dosage is 39.5mg voclosporin BID or 31.6mg voclosporin BID or 23.7mg voclosporin BID or 15.8mg voclosporin BID or 7.9mg voclosporin BID.

7. The use of any of claims 1-6, wherein said subject is to be evaluated for renal function at a time point after the end of said treatment period by assessing eGFR.

8. The use of claim 7, 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.

9. The use of any of claims 1-8, wherein an effective amount of mycophenolate mofetil (MMF) is to be further administered to said subject.

10. The use of any of claims 1-9, wherein an effective amount of a corticosteroid is to be further administered to said subject.

11. The use of any of claims 1-10, wherein said treatment period is at least 48 weeks.

12. The use of any of claims 1-11, wherein 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 % in the range of 20-45%, administration of said predetermined daily dosage of voclosporin is to be resumed.

13. The use of claim 12, wherein the target % is approximately 30%.