

IMPROVED PROTOCOL FOR TREATMENT OF LUPUS NEPHRITIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Serial No. 15/835,219 filed 7 December 2017 and claims benefit under 35 U.S.C. Section 119(e) of U.S. Provisional Patent Application Nos. 62/505,734, filed 12 May 2017, and 62/541,612, filed 4 August 2017. The contents of the above patent applications are incorporated by reference herein in their entirety.

TECHNICAL FIELD

[0002] The invention relates to treatment of lupus nephritis and other proteinuric kidney diseases with voclosorin. More specifically it relates to pharmacodynamic dosing of subjects in accordance with an improved protocol for treatment.

BACKGROUND ART

[0003] Lupus nephritis (LN) one of a number of proteinuric kidney diseases wherein an inflammation of the kidneys is caused by systemic lupus erythematosus (SLE) whereby up to 60% of SLE patients develop LN. LN is a debilitating and costly disease often leading to renal failure which requires dialysis, or renal transplant and often results in death. Indeed, patients with renal failure have an over 60-fold increased risk of premature death compared to SLE patients in general. A clinical sign of LN is leakage of blood proteins into the urine and the disease can be diagnosed by a number of factors, including urinary protein/creatinine ratio (UPCR) wherein a UPCR of greater than 0.5mg/mg is indicative of the condition being in an active state. Further, certain markers in the blood can also be diagnostic--for example, complement 3 (C3), complement 4 (C4) and anti-dsDNA antibodies.

[0004] The standard of care for LN has not met with a great deal of success. The standard of care is use of mycophenolate mofetil (MMF) or intravenous cyclophosphamide. With these treatments partial remission was found only in approximately 50% of cases and complete remission was shown in less than 10% of the subjects. Thus, there is clearly a need for a treatment that improves these outcomes.

[0005] Voclosporin is an analog of cyclosporin A that has been found useful for treating autoimmune diseases and as an immunosuppressant in organ transplantation.

[0006] Mixtures of the E and Z isomers of voclosporin are described in U.S. Patent 6,998,385. Mixtures with a preponderance of the E-isomer are described in U.S. Patent 7,332,472. The '472 patent describes a number of indications which can be treated with the isomeric voclosporin mixture including glomerulonephritis. However, although some animal studies are described, no protocols in humans are disclosed.

[0007] Various formulations of voclosporin mixtures are also described in U.S. Patent Nos. 7,060,672; 7,429,562 and 7,829,533.

[0008] In October 2016, the results of a clinical study conducted on behalf of Aurinia Pharmaceuticals were published as an abstract. According to the abstract, the subjects, who were afflicted with lupus nephritis (LN), were dosed with 23.7mg of voclosporin twice daily in combination with mycophenolate mofetil (MMF) and reducing cortical steroid dose over 24 weeks for which data were presented. Entry criteria for the study included determination of a urine protein creatinine ratio (UPCR) of $\geq 1.0\text{mg/mg}$ or $\geq 1.5\text{mg/mg}$ depending on the classification of a renal biopsy and an eGFR (estimated glomerular filtration rate) of $\geq 45\text{ml/min/1.73m}^2$ as well as serologic evidence of LN. The results of this protocol showed complete remission or partial remission in a large percentage of subjects.

[0009] In addition, it was shown that subjects who achieved a $\geq 25\%$ reduction in UPCR at 8 weeks were likely to maintain benefit throughout the 24-week or 48 week protocol.

[0010] In a news release sent by Aurinia Pharmaceuticals on 1 March 2017, the results of more extensive clinical study involving mycophenolate mofetil (MMF) and reducing corticosterone dosages, but using in addition to 23.7mg of voclosporin twice daily, a higher dose of 39.5mg twice daily were described. The results of this study showed successful complete or partial remission in a large number of patients at 24 weeks and 48 weeks. It appeared that the lower dosage of 23.7mg twice daily (BID) was even more effective than the higher dosage of 39.5mg twice daily (BID).

[0011] Data regarding predictability of success with respect to complete remission (CR) based on various criteria measured after 8 weeks of treatment with 23.7 bid of Voclosporin along with MMF-1 and steroid taper were presented by the present inventors at the 12th International Congress on SLE on 27 March 2017. These criteria included UPCR (less than 25% reduction considered to show ineffectiveness) as well as normalization of complements

3 and 4 (C3 and C4) and of anti-dsDNA. However, the criteria for normalization of C3, C4 and anti-dsDNA were not disclosed.

[0012] An earlier study with respect to lupus treatment with cyclophosphamide rather than Voclosporin suggested normalization of C4 as a marker. Dall'Era, M. et al Arth. Care and Res. (2011) 63:351-357.

[0013] It has now been found that successful results, including a diminution in the number and severity of side effects can be obtained by altering the protocols disclosed in these publications by providing a pharmacodynamic dosing schedule based on individual patient responses. In addition, it has been found that even lower dosages of voclosporin—*i.e.*, 15.8mg of voclosporin twice daily or 7.9mg of voclosporin twice daily are effective.

DISCLOSURE OF THE INVENTION

[0014] The present invention, thus, provides an improved protocol for treatment of lupus nephritis and other proteinuric kidney diseases that takes advantage of assessments of parameters associated with the response of individual subjects. The invention is a personalized form of a protocol for treatment of proteinuric kidney diseases including protocols that employ low dosage of voclosporin. The voclosporin used is preferably a mixture of greater than about 80% E isomer and less than about 20% Z isomer, and more preferably greater than about 90% E isomer and less than about 10% Z isomer. The protocol employs daily dosages of voclosporin over a projected period of 24, 48, 52 weeks or longer wherein the voclosporin is administered twice daily (BID). Suitable dosages are in increments of 7.9 mg including 39.5 mg, 31.6 mg, 23.7 mg, 15.8 mg or 7.9 mg. Low dosages show superior results compared to a higher dose of 39.5 mg each of such administrations carried out twice daily. Doses as low as 15.8 mg or 7.9 mg twice daily are effective. The protocol preferably further includes administering to the subject an effective amount of MMF and/or an effective amount of a corticosteroid, typically prednisone, in a reducing dosage level across the time period of the study.

[0015] While it has been verified that the protocols of the invention are effective for lupus nephritis, such results indicate the same protocols can be used to generally treat proteinuric kidney diseases. Proteinuric kidney diseases that can be treated include: Diabetic nephropathy, nephrotic syndromes (*i.e.* intrinsic renal failure), nephritic syndromes, toxic lesions of kidneys, glomerular diseases, such as membranous glomerulonephritis, focal segmental glomerulosclerosis (FSGS), IgA nephropathy (*i.e.*, Berger's disease), IgM

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 invention 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 aspect, the invention 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.

[0018] In one specific embodiment, the invention 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/1.73m² 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/1.73m² between said first and second time points, administering a reduced dosage of voclosporin to said subject;

(iii) if the eGFR of said subject decreases by $\leq 20\%$ between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject.

[0019] The eGFR of 60 mL/min/1.73m² noted above is typically used; however, higher values such as 90 mL/min/1.73m² or 75 or 70 mL/min/1.73m² or lower value such as 50 mL/min/1.73m² or 55 mL/min/1.73m² could also be used.

[0020] The pharmacodynamic method may employ a third time point subsequent to the first and second time point wherein the target percentage reduction is again determined and if the percentage reduction as compared to the first time point is less than the target percentage, treatment may be restored, or if the percentage decrease is greater than the target percentage exhibited at the second time point, further reduction in dosage may be indicated.

[0021] A second embodiment relates to using blood pressure as an indicator rather than eGFR. In this second embodiment, the invention is directed to a pharmacodynamic method to treat lupus nephritis which method comprises administering to a subject diagnosed with lupus nephritis predetermined daily dosages of effective amounts of voclosporin over a projected treatment period of at least 24 weeks, said pharmacodynamic method further comprising:

(a) measuring the blood pressure (BP) of said subject at at least a first time point of said treatment period; and

(b) stopping the administering of voclosporin to the subject or administering a reduced dosage of voclosporin to said subject if either value of the systolic or diastolic component of the BP of said subject is $>130/80$.

[0022] In this case, an additional time point measuring BP may be employed and if both components of the BP of the subject are below 130/80, the administration of the predetermined daily dose of voclosporin may be resumed.

[0023] Thus, blood measure elevation is an additional undesirable side-effect of treatment that can be used as a criterion for adjusting dosage.

[0024] It has also been found that the effectiveness of the protocol can be evaluated after only a portion of the treatment period has elapsed. This can be done in lieu of, or in addition to, the foregoing protocol. Therefore, because it is generally undesirable to continue an ineffective treatment an assessment at a time point earlier in the protocol than the end point planned is conducted and if the effectiveness of treatment is not confirmed, the treatment is

terminated. In the present case, such termination may be helpful since generally administration of an immunosuppressant is not recommended unless some benefit is achieved.

[0025] For example, the assessment may include determining the UPCR at first and second time points early in the protocol wherein the first point is determined at the outset of the protocol and stopping the administration of voclosporin to the subject if the UPCR has not been reduced by a predetermined amount, for example by 15% or 20% or 25% or 35% at the second time point. The UPCR can be determined by any standard technique, e.g., using first morning void or a 24 hour urine sample. This evaluation may be supplemented or substituted by evaluation of the concentration of C3 and C4 in the blood. Failure of the treatment to result in normalizing C3/C4 concentration indicates lack of success. The rule for stopping treatment if a combination of these factors is employed is that treatment will be stopped if neither criterion for success is met – i.e. the subject shows no satisfactory reduction in UPCR at the second time point and no normalization of C3/C4 at the second time point. In the alternative, either criterion could be used alone.

[0026] Alternatively, if it appears that the subject is in complete remission, it may be unnecessary to continue treatment.

[0027] In any of the protocols above, preferably, a dosage of MMF and a reducing dosage of corticosteroid is also administered during the treatment period. Typically, MMF is administered at the level of 2 grams daily and oral corticosteroids are administered in daily dosages diminishing from 20-25mg daily to 2.5mg daily over a period of 16 weeks. The reduced dosages then continue throughout the study. These protocols are shown in Figure 1.

[0028] In all cases, subjects who would be amenable to this treatment are identified by screening said subject prior to conducting said method on said subject by:

- (a) determining that the urine protein creatinine ratio (UPCR) of said subject is $\geq 1.5\text{mg/mg}$ or $\geq 1\text{mg/mg}$ depending on renal biopsy as preferably measured by first morning void; and
- (b) determining said subject has an eGFR as measured by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) of $\geq 45\text{ mL/min/1.73m}^2$ or any other suitable method such as the Modification of Diet in Renal Disease (MDRD) Study equation. If the determinations of subparagraphs (a) and (b) are positive, the subject is considered suitable for subjection to the protocol.

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

[0030] Thus, in another aspect, the invention 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.

[0031] It is also advantageous and part of the invention 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 embodiment 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 ≤ 0.5 mg/mg indicates complete response; alternatively, or in addition, an eGFR of ≥ 60 mL/min/1.73m² 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 ≤ 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.

MODES OF CARRYING OUT THE INVENTION

[0035] As noted above, the pharmacodynamic protocol of the invention relates to adjustment of administration of voclosporin depending on certain physiological indicators of the subjects. As further noted, the voclosporin administration is preferably conducted with a background of administration of MMF and of corticosteroids.

[0036] In general, the treatment protocols on which the invention is based show dramatically better results than the current standard of care—the rate of complete remission is almost 50% as compared to much lower levels achieved using the current standard of care treatment and the rate of partial remission after 48 weeks is even higher, wherein this rate (PR) includes the subjects with complete remission (CR). As shown below, a lower dosage of voclosporin is more effective than a higher dose in a comparable protocol wherein complete remission was obtained in 40% of the subjects at the higher dosage as opposed to 49% of the subjects in the lower dose group.

[0037] Critical to the present invention is pharmacodynamic administration of the voclosporin component. This pharmacodynamic administration is essential as the effects of this drug may be too intense and/or have undesirable side effects or the results may indicate lack of effectiveness and thus the dosage is reduced or interrupted to permit homeostasis to reestablish a suitable set of physiological parameters.

[0038] The protocols are designed to cover treatment periods of at least 24 weeks and may extend for longer periods of time, for example 48 weeks or 52 weeks. The regimens involve daily dosages of the voclosporin component, typically twice daily, although alternative frequencies could be employed, such as once a day, three times a day or four times a day based on reactions of the patient and convenience. As an illustration, the protocol will be described below in terms of a 23.7mg twice daily (BID) dosage; of course if the voclosporin preparation is administered four times daily, the dosage would be cut in half for each administration and if the administration were only once per day, the dosage for the once a day administration would be double the 23.7mg administered BID.

[0039] In addition, as to the pharmacodynamic protocols of the invention, the dosages may be any combination of the 7.9 mg basic units, and thus can be 7.9 mg, 15.8 mg, 31.6 mg, or 39.5 mg, as well as the exemplified 23.7 mg.

[0040] The dosage indicated, for example 23.7mg, (or any other specified dose) is subject to slight variations, typically $\pm 10\%$ or, alternatively, for 23.7mg specified between 21mg and

26mg BID. This is due to inconsistencies in pharmaceutical manufacture and the ideal dosage is the specified dose—*i.e.*, for example, 23.7mg BID. Comparable variations applied to the alternative dosages, and to the differential adjustment.

Adjustment Based on eGFR:

[0041] One critical parameter used to assess the desirability of dosage reduction is the eGFR using the CKD-EPI formula or other appropriate method. Chronic kidney disease is defined as eGFR as $\leq 60 \text{ mL/min/1.73m}^2$ for $\geq$ three months with or without kidney damage. As noted above, a further decrease in eGFR is a negative side effect that may occur during treatment. If the decrease is too severe, the protocol should be altered in accordance with the prescription of the invention. Typically, a baseline value of the eGFR is established either at the beginning of the protocol or at some “first time point” during the protocol. If the decrease is greater than a target percentage, which is typically between 20%-45% as compared to the first time point, a reduction in dosage is indicated, including a reduction to zero or stopping treatment. If the decrease is less than that target percentage maintenance of treatment at the same level as indicated. In addition to an indication that treatment should be reduced or terminated based on the eGFR reduction, reduction below a certain value is also indicative of a need to modify the treatment. This predetermined value is typically in the range of 50-90 mL/min/1.73m².

[0042] As stated above, a baseline value for eGFR is established at the outset of the treatment or during treatment. This is typically done on the first day of the treatment before any administration of the drugs in the protocol. This baseline is used as a criterion for adjusting dosage. However, a first time point could be established at any arbitrarily selected time during the protocol.

[0043] In one exemplary protocol, at a second time point subsequent to the first which can be on any day of the treatment, a subject with $\geq 30\%$ decrease in eGFR from the baseline to $< 60 \text{ mL/min/1.73m}^2$ (or, in some cases, a higher cut off) should have the treatment interrupted until a repeat test can be performed, but if the decrease is confirmed and not due to contributing factors (such as a high baseline eGFR, the addition or modification of non-steroidal anti-inflammatory drugs, angiotensin converting enzyme inhibitors, angiotensin 2 inhibitor blockers, or a concurrent state of dehydration, etc.), the treatment should be withheld until a third time point determination typically within 48 hours. If the $\geq 30\%$

decrease is not maintained, treatment is restored to two-thirds or one-third of the original dosage and increased as tolerated to the 23.7mg level BID.

[0044] For convenience, the 23.7mg administration is administered orally in the form of three capsules containing 7.9mg each. Thus, it is easy to provide two-thirds of the standard dosage by administering at any given time only two of the three capsules.

[0045] With regard to the second time point, in this exemplary protocol a subject having a decrease of $\geq 20\%$ in eGFR to $\leq 60\text{mL}/\text{min}/1.73\text{m}^2$ but a decrease of less than 30% reduction as compared to baseline, the treatment is not interrupted but the dosage is reduced. Reduction in increments of 7.9mg is preferred. Again, assessment at an additional time point at any subsequent day during the treatment showing baseline values are restored indicates that the original dosage level of 23.7mg BID can be resumed.

Adjustment Based on Blood Pressure

[0046] An alternative parameter that can be used to determine pharmacodynamic dosage is blood pressure. As voclosporin may increase blood pressure to undesirable levels, at any point during the treatment period if either component of the blood pressure *i.e.* the systolic or diastolic pressure of the subject is $\geq 130/80$, the treatment should be reduced, preferably by increments of 7.9mg. At a later time point if both components of the blood pressure are below 130/80, the treatment can be restored to the original level.

Adjustment Based on UPCR Reduction and/or C3/C4 Normalization

[0047] Suitable criteria for early evaluation of the probability of success – *i.e.* complete or partial remission by the end of a planned protocol, have been identified which permit discontinuation of the treatment earlier than the end point if it is highly unlikely that the subject will benefit from continuing on the dosage schedule. These criteria are reduction in UPCR and normalization of C3/C4. These can be used in combination or in the alternative. It has been found that a determination early in a 24-week or 48 week protocol of probable success can be used to determine whether treatment with voclosporin should continue; such findings are applicable to protocols of any substantial length. By way of illustration, if the UPCR has not been reduced by a satisfactory amount early in the regimen or if C3/C4 has not been normalized early in the regimen, one might conclude that the chances of improvement over an extended treatment period are diminished. Application of these criteria in an exemplary trial is shown in detail in Example 3.

[0048] However, a rule for stopping treatment is based either on UPCR reduction or C3/C4 normalization taken alone or in combination. If the combination is used, then failure with respect to both criteria would dictate termination of treatment. Decision would be based on the values of the sensitivity, specificity and positive and negative predictive values shown in the tables set forth in Example 3. These terms are defined in the Example.

[0049] As an illustration only, such determination can be made at approximately 8 weeks subsequent to the beginning of the regimen; a time frame of 6-10 weeks could be employed for the approximation of 8 weeks. If a decrease of, for example, $\geq 25\%$ of UPCR is not achieved, it appears unlikely the subject will benefit from further treatment and the protocol is stopped. As shown in the Example, this can be supplemented with evaluation of C3/C4 normalization – if this is done, it is desirable that both determinations be made at the same early time point.

Auxiliary Therapeutics

[0050] The voclosporin treatment of the invention is supplemented with MMF and reduced amounts of corticosteroids.

[0051] For example, with respect to corticosteroids, subjects who weigh 45kg or more may receive 0.5 grams of methylprednisolone on days 1 and 2 of the study intravenously and then beginning on day 3, oral corticosteroid therapy. Subjects weighing ≤ 45 kg receive only half these dosages.

[0052] For oral prednisone, the starting dosage for oral administration is 20mg/day for subjects < 45 kg and 25mg/day for subjects who weigh ≥ 45 kg. The dosage is reduced according to the protocol shown in Table 1.

Table 1 **Dosing Schedule for IV Methylprednisolone and Daily Oral Prednisone (mg)**

	Subjects <45 kg	Subjects ≥45 kg	In Case of Prior IV Steroids During Screening (Pre-randomization)
Weeks 1-2 ⁽¹⁾			
Days 1-2 ⁽²⁾	0.25 g (IV)	0.5 g (IV)	1 g minus prior IV steroids mg or (0.5 g minus prior IV steroids mg for subjects who weigh <45 kg) ⁽³⁾
Days 3-13	20 mg (oral)	25 mg (oral)	
Week 2 (Day 14)	15 mg (oral)	20 mg (oral)	
Week 4 (Day 28)	10 mg (oral)	15 mg (oral)	
Week 6 (Day 42) ⁽⁴⁾	10 mg (oral)	10 mg (oral)	
Week 8 (Day 56)	5 mg (oral)	5 mg (oral)	
Week 12 (Day 84)	5 mg (oral)	5 mg (oral)	
Week 16 (Day 112)	2.5 mg (oral)	2.5 mg (oral)	

1 Day 0-13: Oral steroids dosed according to subject weight and then tapered beginning at Day 14.

2 Oral corticosteroids may be commenced on Days 1 or 2 if corticosteroids are administered during screening.

3 It is recognized that dosing with IV methylprednisolone as described in Section 7.2.2.2, Corticosteroids may not be in the subject's best interest if they have already received therapy within the 3 months prior to screening. In this case, the Investigator may be permitted to omit the administration of further IV methylprednisolone but only after discussion with the Medical Monitor.

4 Week 6 is not a scheduled study visit, a phone call can be performed to decide further tapering for subjects

Notes: Oral prednisone taper should be done within ±3 days of specified timeframe. When clinically indicated, subjects are allowed to be completely titrated off of oral corticosteroids.

Abbreviation: IV = Intravenous.

[0053] In contrast to the reducing dose of corticosteroid, the same dose of MMF is maintained throughout the study at a twice daily dosage before meals with a glass of water. Typically, each individual dose is one gram resulting in a total dosage of two grams per day although in the alternative, the subject may be administered 500mg four times daily.

Low Dosage

[0054] In addition to the above-described pharmacodynamic protocols, applicants have found that a substantially lower dosage than expected is effective in large numbers of subjects such that a method to treat lupus nephritis in subjects either with or without pharmacodynamic adjustments can be based on a dosage level of either 15.8mg BID or 7.9mg BID. The increments of 7.9mg are dictated by the availability of capsules containing the 7.9mg dosage level which provides a convenient platform for dosage alterations.

[0055] One additional aspect of the invention is therefore a method to treat lupus nephritis wherein either a logically adjusted dosage or a constant dosage of either 15.8mg BID or 7.9mg BID is employed. In these protocols, as would be the case for higher dosages

of voclosporin, the above described background administration of MMF and corticosteroids is included in the protocol.

General Factors

[0056] In all cases, the subjects are evaluated for success of the treatment both on the completion of the treatment and at extended periods thereafter. Typical treatment periods are at least 24 weeks, but preferably 48 weeks or more. Reevaluation after the termination of the treatment period over a period of 1-2 weeks or longer is also employed. Subjects are evaluated for complete or partial remission. Complete remission (CR) is defined as: Confirmed protein/creatinine ratio of ≤ 0.5 mg/mg, and eGFR ≥ 60 mL/min/1.73 m² or no confirmed decrease from baseline in eGFR of $\geq 20\%$. Partial remission is defined as: 50% reduction in UPCR from baseline.

[0057] By establishing a pharmacodynamic dosing regimen, the effectiveness of the protocol in treatment of lupus nephritis can be maximized while minimizing undesirable side effects.

[0058] The length of the treatment protocol in all cases will vary from at least 8 weeks to for example 12, 16, 24 and 48 weeks or 52 weeks or even longer, up to 60 weeks including stopping points between the levels mentioned. For example, a treatment protocol of 10 or 11 or 15 or 20 or 29 or 31 or 36 or 43 or 51 or 55 weeks could be employed and is within the scope of the invention. The evaluation described above is conducted at the end of the protocol as well as at a suitable time period or multiple time periods thereafter. These time periods are generally 1-2 weeks to 4-5 months subsequent to terminating the dosage and intervening at time intervals are included within the scope of the invention as well.

[0059] This statement regarding time intervals applies to the invention pharmacodynamic treatment protocols, regardless of base dosage levels.

[0060] The following examples are to illustrate, not to limit the invention.

Example 1

48 Week Study of LN Treatment

[0061] The subjects enrolled in the study were divided into three groups, 88 subjects are in a control group who were administered 2g MMF daily as well as oral corticosteroids—*i.e.*, prednisone in a tapering dosage shown graphically in Figure 1—beginning at 20-25mg daily reduced gradually after the 12th week to 2.5mg daily. (Some subjects received lower doses

of MMF due to gastrointestinal problems). 89 subjects in the low dosage group received this background treatment, but in addition were administered three capsules containing 7.9mg (*i.e.* 23.7mg) of voclosporin each twice daily. The voclosporin used in this study comprised greater than 90% E isomer. A third group which was comprised of 88 subjects received a similar background treatment but in addition were dosed with five 7.9mg capsules *i.e.* 39.5mg twice daily. The study was conducted over a period of 48 weeks and safety was evaluated at 24 weeks.

[0062] Subjects were screened prior to admission to the study by (a) determining that the urine protein creatinine ratio (UPCR) as $>1.5\text{mg/mg}$ as measured by first morning void, and (b) that the eGFR as measured by Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) of $>45\text{ ml/min/1.73m}^2$. Subjects were assessed after 24 weeks and 48 weeks as well as a subsequent evaluation at 50 weeks.

[0063] As shown in Figure 2, the low dosage administration achieved better results than administration of voclosporin at higher dosages. After 48 weeks of treatment, 49% of low dosage subjects showed complete remission at 48 weeks, compared to 40% of high dosage subjects. In the same study, but after 24 weeks of treatment, 32.6% of low dosage patients, but only 27% of high dosage patients showed complete remission (CR) compared to 19.3% of controls. At 24 weeks, 70% of low dosage patients and 66% of high dosage patients showed partial remission (PR) compared to 49% of controls.

[0064] CR in this example is a composite end-point which includes efficacy, safety and low-dose steroids: $\text{UPCR} \leq 0.5\text{mg/mg}$ (confirmed); $\text{eGFR} >60\text{ml/min/1.73m}^2$ or within 20% of baseline; steroids $\leq 10\text{mg/day}$; no administration of rescue medication.

[0065] PR is a composite end-point that includes safety and efficacy: UPCR reduction of 50% from baseline and no use of rescue medication

[0066] To determine the efficacy of the pharmacodynamic protocol wherein dosage is reduced or stopped according to the presence or absence of indicators of the decrease in eGFR experienced as a side effect, these three groups of patients were assessed after 24 weeks and 48 weeks of treatment with respect to whether treatment was altered according to the invention protocol. In all three groups, the patients were evaluated according to the criteria set forth in the exemplary protocol above—*i.e.*, wherein the eGFR of each patient was measured immediately prior to administering the first dose of voclosporin and at a second time point at least a day later and

(i) if the eGFR of said subject decreased by $\geq 30\%$ to a value of below 60 mL/min/1.73m² between said first and second time points, stopping the administering of Voclosporin or reducing dosage thereof to said subject;

(ii) if the eGFR of said subject decreased by between 20% to 30% to a value of below 60 ml/min/1.73m² between said first and second time points, administering a reduced dosage of voclosporin to said subject;

(iii) if the eGFR of said subject decreased by $\leq 20\%$ between said first and second time points, continuing administering the same predetermined daily dosage of voclosporin to said subject.

[0067] The results are shown in Tables 2 and 3 below. Table 2 shows percentages with complete remission (CR) or partial remission (PR) after 24 weeks and Table 3 shows these values after 48 weeks for patients that had no dose reduction and those who did have dose reduction.

Table 2

Patients with a No Dose Reductions (24 weeks):

Group	Patient number (n)	Patients with no Dose Reduction n(%)	Patients with CR at 24 weeks n(%)	Patients with PR at 24 weeks n(%)
Placebo	88	77 (87.5)	14 (18.2)	36 (46.8)
Low Dose	89	50 (56.2)	15 (30.0)	34 (68.0)
High Dose	88	41 (46.6)	11 (26.8)	24 (58.5)

Patients with Dose Reductions (pharmacodynamically dosed):

Group	Patient number (n)	Patients with Dose Reduction n(%)	Patients with CR at 24 weeks n(%)	Patients with PR at 24 weeks n(%)
Placebo	88	11 (12.5)	3 (27.3)	7 (63.6)
Low Dose	89	39 (43.8)	14 (35.9)	28 (71.8)
High Dose	88	47 (53.4)	13 (27.7)	34 (72.3)

Table 3

Patients with No Dose Reductions (48 weeks):

Group	Patient number (n)	Patients with no Dose Reduction n(%)	Patients with CR at 48 weeks n(%)	Patients with PR at 48 weeks n(%)
Placebo	88	74 (84.1)	18 (24.3)	38 (51.4)
Low Dose	89	43 (48.3)	20 (46.5)	26 (60.5)
High Dose	88	35 (39.8)	11 (31.4)	22 (62.9)

Patients with Dose Reductions (pharmacodynamically dosed):

Group	Patient number (n)	Patients with Dose Reduction n(%)	Patients with CR at 48 weeks n(%)	Patients with PR at 48 weeks n(%)
Placebo	88	14 (15.9)	3 (21.4)	4 (28.6)
Low Dose	89	46 (51.7)	24 (52.2)	35 (76.1)
High Dose	88	53 (60.2)	24 (45.3)	41 (77.4)

[0068] In this study, CR was defined as a composite of UPCR ≤ 0.5 mg/mg; eGFR > 60 mL/min/1.73m² or within 20% of baseline, steroids at ≤ 10 mg/day and no administration of rescue medication. PR is defined as UPCR reduction of 50% from baseline and no use of rescue medication.

[0069] As shown in Table 2, 12.5% of patients on placebo, 43.8% of patients on low dose and 53.4% of patients on high dose voclosporin underwent dose reduction during the treatment. The percentage of patients with complete response after 24 weeks was not affected in either dosage groups by the pharmacodynamic dosage and the percentage with partial response was also roughly the same, although with the high dose group, the percentage

with partial reduction improved. Table 3 shows similar results at 48 weeks, although a higher percentage of patients were subjected to dose reduction. Again, no drastic effect on the overall response was exhibited.

Example 2

Low Dosage Protocol

[0070] In the course of clinical studies similar to those in Example 1, it was observed that a substantial portion of subjects showed substantial remission at a dosage reduced almost immediately to 15.8 mg voclosporin administered twice daily (BID). Accordingly, applicants have analyzed these data and have concluded that a dosage protocol providing 15.8 mg or 7.9 mg voclosporin BID is effective with or without the pharmacodynamic aspects of the protocol.

[0071] As the capsules contain 7.9mg voclosporin, 1 cap represents 7.9mg voclosporin, 2 caps represent 15.8mg voclosporin and 3 caps represent 23.7mg voclosporin, etc. Substantial numbers of subjects showed complete or partial remission even when the dosage was lowered to 7.9mg voclosporin BID quite early in the treatment and similar results were obtained for administration of 15.8mg BID.

Example 3

Predictability based on Early Responses

[0072] In the study reported in Example 1, the predictability of outcomes based on markers at early time points were determined. These results are shown in Tables 4-12.

[0073] In the study described in Example 1, data were obtained to ascertain whether markers evaluated after various time-points during treatment would predict an ultimate favorable outcome or show that continuing treatment was likely to be futile. This is important because it is undesirable to subject a patient to unnecessary treatment, even if the treatment is relatively safe. These data are shown in the tables below.

[0074] Based on these data, the sensitivity and specificity of the evaluation of each marker and their counterparts positive predictive value and negative predictive value were determined with respect to whether the patient would or would not show partial remission (PR) after 48 weeks of the treatment protocol. PR is defined as at least 50% reduction in

proteinuria (i.e. UPCR). This would also include subjects who showed complete remission (CR).

[0075] Sensitivity is defined as the probability that a subject showing PR at 48 weeks would have shown a favorable result with regard to the marker at the designated early time point. In the tables below, this is the ratio of the number of subjects with favorable marker results (early drop or normalization) to the total subjects with 48 week PR.

[0076] Specificity is defined as the probability that a subject not showing PR at 48 weeks would have shown an unfavorable result with regard to the marker at the designated early time point. In the tables below, this is the ratio of the number of subjects with unfavorable marker results (no early drop or no normalization) to the total subjects with no 48 week PR.

[0077] Positive predictive value is defined as the probability that a subject showing a favorable result with respect to the marker at an earlier time point would show PR at 48 weeks. In the tables below, this is the ratio of the number of subjects with favorable marker results who have 48 week PR to those with favorable marker results (early reduction or yes column).

[0078] Negative predictive value is defined as the probability that a subject showing an unfavorable result with respect to the marker at an earlier time point would not show PR at 48 weeks. In the tables below, this is the ratio of the number of subjects with unfavorable marker results who have no PR at 48 weeks to the total subjects with unfavorable marker results (no early reduction or no column).

[0079] An ideal marker would show a value of 100 for all of these, but this is generally unattainable. As high as possible value is desirable.

[0080] Based on the results in these tables, the protocol will be designed to stop treatment at an earlier time point when the parameters set forth above are the most favorable, but at a reasonable time before the 48 week end point. (Obviously the closer to the end point, the more favorable the indicators become, but the advantage to stopping treatment is correspondingly reduced).

Table 4 – Early 15% reduction in UPCR

Table 4		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
2	Placebo	27	15	19	25	46	40	64.3	56.8	58.7	62.5
	Voclosporin 23.7mg BID	45	16	10	14	55	30	73.8	58.3	81.8	46.7
	Voclosporin 39.5mg BID	39	21	15	9	54	30	65.0	37.5	72.2	30.0
4	Placebo	36	5	18	23	54	28	87.8	56.1	66.7	82.1
	Voclosporin 23.7mg BID	50	9	12	11	62	20	84.7	47.8	80.6	55.0
	Voclosporin 39.5mg BID	49	12	16	5	65	17	80.3	23.8	75.4	29.4
6	Placebo	35	7	22	17	57	24	83.3	43.6	61.4	70.8
	Voclosporin 23.7mg BID	53	6	12	6	65	12	89.8	33.3	81.5	50.0
	Voclosporin 39.5mg BID	53	10	16	4	69	14	84.1	20.0	76.8	28.6
8	Placebo	38	4	22	18	60	22	90.5	45.0	63.3	81.8
	Voclosporin 23.7mg BID	55	5	12	7	67	12	91.7	36.8	82.1	58.3
	Voclosporin 39.5mg BID	56	5	17	4	73	9	91.8	19.0	76.7	44.4
12	Placebo	39	3	19	21	58	24	92.9	52.5	67.2	87.5
	Voclosporin 23.7mg BID	59	2	15	4	74	6	96.7	21.1	79.7	66.7
	Voclosporin 39.5mg BID	57	5	14	4	71	9	91.9	22.2	80.3	44.4
16	Placebo	39	3	19	20	58	23	92.9	51.3	67.2	87.0
	Voclosporin 23.7mg BID	58	3	13	5	71	8	95.1	27.8	81.7	62.5
	Voclosporin 39.5mg BID	57	6	15	5	72	11	90.5	25.0	79.2	45.5
20	Placebo	38	4	21	16	59	20	90.5	43.2	64.4	80.0
	Voclosporin 23.7mg BID	60	0	13	3	73	3	100.0	18.8	82.2	100.0
	Voclosporin 39.5mg BID	58	4	15	5	73	9	93.5	25.0	79.5	55.6
24	Placebo	37	3	18	17	55	20	92.5	48.6	67.3	85.0
	Voclosporin 23.7mg BID	60	0	12	2	72	2	100.0	14.3	83.3	100.0
	Voclosporin 39.5mg BID	57	5	14	5	71	10	91.9	26.3	80.3	50.0
26	Placebo	36	3	16	14	52	17	92.3	46.7	69.2	82.4
	Voclosporin 23.7mg BID	55	0	9	3	64	3	100.0	25.0	85.9	100.0
	Voclosporin 39.5mg BID	61	0	12	4	73	4	100.0	25.0	83.6	100.0
36	Placebo	41	1	18	13	59	14	97.6	41.9	69.5	92.9
	Voclosporin 23.7mg BID	60	1	10	3	70	4	98.4	23.1	85.7	75.0
	Voclosporin 39.5mg BID	62	1	12	6	74	7	98.4	33.3	83.8	85.7
48	Placebo	37	1	10	16	47	17	97.4	61.5	78.7	94.1
	Voclosporin 23.7mg BID	58	0	9	2	67	2	100.0	18.2	86.6	100.0
	Voclosporin 39.5mg BID	61	0	10	6	71	6	100.0	37.5	85.9	100.0

Table 5 – Early 20% reduction in UPCR

Table 5		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
2	Placebo	24	18	15	29	39	47	57.1	65.9	61.5	61.7
	Voclosporin 23.7mg BID	44	17	8	16	52	33	72.1	66.7	84.6	48.5
	Voclosporin 39.5mg BID	36	24	14	10	50	34	60.0	41.7	72.0	29.4
4	Placebo	32	9	13	28	45	37	78.0	68.3	71.1	75.7
	Voclosporin 23.7mg BID	49	10	12	11	61	21	83.1	47.8	80.3	52.4
	Voclosporin 39.5mg BID	47	14	16	5	63	19	77.0	23.8	74.6	26.3
6	Placebo	34	8	22	17	56	25	81.0	43.6	60.7	68.0
	Voclosporin 23.7mg BID	53	6	11	7	64	13	89.8	38.9	82.8	53.8
	Voclosporin 39.5mg BID	53	10	15	5	68	15	84.1	25.0	77.9	33.3
8	Placebo	38	4	19	21	57	25	90.5	52.5	66.7	84.0
	Voclosporin 23.7mg BID	55	5	11	8	66	13	91.7		83.3	61.5
	Voclosporin 39.5mg BID	55	6	17	4	72	10	90.2	19.0	76.4	40.0
12	Placebo	38	4	19	21	57	25	90.5	52.5	66.7	84.0
	Voclosporin 23.7mg BID	59	2	14	5	73	7	96.7	26.3	80.8	71.4
	Voclosporin 39.5mg BID	57	5	14	4	71	9	91.9	22.2	80.3	44.4
16	Placebo	39	3	17	22	56	25	92.9	56.4	69.6	88.0
	Voclosporin 23.7mg BID	58	3	12	6	70	9	95.1	33.3	82.9	66.7
	Voclosporin 39.5mg BID	57	6	15	5	72	11	90.5	25.0	79.2	45.5
20	Placebo	38	4	20	17	58	21	90.5	45.9	65.5	81.0
	Voclosporin 23.7mg BID	60	0	12	4	72	4	100.0	25.0	83.3	100.0
	Voclosporin 39.5mg BID	58	4	15	5	73	9	93.5	25.0	79.5	55.6
24	Placebo	37	3	16	19	53	22	92.5	54.3	69.8	86.4
	Voclosporin 23.7mg BID	59	1	11	3	70	4	98.3	21.4	84.3	75.0
	Voclosporin 39.5mg BID	56	6	14	5	70	11	90.3	26.3	80.0	45.5
26	Placebo	36	3	15	15	51	18	92.3	50.0	70.6	83.3
	Voclosporin 23.7mg BID	55	0	9	3	64	3	100.0	25.0	85.9	100.0
	Voclosporin 39.5mg BID	61	0	12	4	73	4	100.0	25.0	83.6	100.0
36	Placebo	41	1	16	15	57	16	97.6	48.4	71.9	93.8
	Voclosporin 23.7mg BID	60	1	10	3	70	4	98.4	23.1	85.7	75.0
	Voclosporin 39.5mg BID	61	2	12	6	73	8	96.8	33.3	83.6	75.0
48	Placebo	37	1	9	17	46	18	97.4	65.4	80.4	94.4
	Voclosporin 23.7mg BID	58	0	9	2	67	2	100.0	18.2	86.6	100.0

Table 5		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
	Voclosporin 39.5mg BID	61	0	10	6	71	6	100.0	37.5	85.9	100.0

Table 6 – Early 25% reduction in UPCR

Table 6		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
2	Placebo	18	24	15	29	33	53	42.9	65.9	54.5	54.7
	Voclosporin 23.7mg BID	39	22	8	16	47	38	63.9	66.7	83.0	42.1
	Voclosporin 39.5mg BID	33	27	14	10	47	37	55.0	41.7	70.2	27.0
4	Placebo	30	11	11	30	41	41	73.2	73.2	73.2	73.2
	Voclosporin 23.7mg BID	48	11	12	11	60	22	81.4	47.8	80.0	50.0
	Voclosporin 39.5mg BID	45	16	16	5	61	21	73.8	23.8	73.8	23.8
6	Placebo	33	9	20	19	53	28	78.6	48.7	62.3	67.9
	Voclosporin 23.7mg BID	51	8	10	8	61	16	86.4	44.4	83.6	50.0
	Voclosporin 39.5mg BID	49	14	15	5	64	19	77.8	25.0	76.6	26.3
8	Placebo	35	7	17	23	52	30	83.3	57.5	67.3	76.7
	Voclosporin 23.7mg BID	54	6	10	9	64	15	90.0	47.4	84.4	60.0
	Voclosporin 39.5mg BID	55	6	17	4	72	10	90.2	19.0	76.4	40.0
12	Placebo	37	5	17	23	54	28	88.1	57.5	68.5	82.1
	Voclosporin 23.7mg BID	57	4	13	6	70	10	93.4	31.6	81.4	60.0
	Voclosporin 39.5mg BID	57	5	14	4	71	9	91.9	22.2	80.3	44.4
16	Placebo	39	3	17	22	56	25	92.9	56.4	69.6	88.0
	Voclosporin 23.7mg BID	58	3	11	7	69	10	95.1	38.9	84.1	70.0
	Voclosporin 39.5mg BID	56	7	14	6	70	13	88.9	30.0	80.0	46.2
20	Placebo	38	4	17	20	55	24	90.5	54.1	69.1	83.3
	Voclosporin 23.7mg BID	59	1	11	5	70	6	98.3	31.3	84.3	83.3
	Voclosporin 39.5mg BID	58	4	15	5	73	9	93.5	25.0	79.5	55.6
24	Placebo	37	3	13	22	50	25	92.5	62.9	74.0	88.0
	Voclosporin 23.7mg BID	59	1	11	3	70	4	98.3	21.4	84.3	75.0
	Voclosporin 39.5mg BID	55	7	12	7	67	14	88.7	36.8	82.1	50.0
26	Placebo	36	3	14	16	50	19	92.3	53.3	72.0	84.2
	Voclosporin 23.7mg BID	55	0	8	4	63	4	100.0	33.3	87.3	100.0
	Voclosporin 39.5mg BID	60	1	12	4	72	5	98.4	25.0	83.3	80.0
36	Placebo	41	1	16	15	57	16	97.6	48.4	71.9	93.8

Table 6		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
48	Voclosporin 23.7mg BID	60	1	10	3	70	4	98.4	23.1	85.7	75.0
	Voclosporin 39.5mg BID	61	2	12	6	73	8	96.8	33.3	83.6	75.0
	Placebo	37	1	9	17	46	18	97.4	65.4	80.4	94.4
	Voclosporin 23.7mg BID	58	0	9	2	67	2	100.0	18.2	86.6	100.0
	Voclosporin 39.5mg BID	61	0	7	9	68	9	100.0	56.3	89.7	100.0

Table 7 – Early 30% reduction in UPCR

Table 7		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
2	Placebo	14	28	13	31	27	59	33.3	70.5	51.9	52.5
	Voclosporin 23.7mg BID	37	24	6	18	43	42	60.7	75.0	86.0	42.9
	Voclosporin 39.5mg BID	31	29	11	13	42	42	51.7	54.2	73.8	31.0
4	Placebo	27	14	10	31	37	45	65.9	75.6	73.0	68.9
	Voclosporin 23.7mg BID	47	12	11	12	58	24	79.7	52.2	81.0	50.0
	Voclosporin 39.5mg BID	45	16	15	6	60	22	73.8	28.6	75.0	27.3
6	Placebo	32	10	16	23	48	33	76.2	59.0	66.7	69.7
	Voclosporin 23.7mg BID	49	10	10	8	59	18	83.1	44.4	83.1	44.4
	Voclosporin 39.5mg BID	47	16	15	5	62	21	74.6	25.0	75.8	23.8
8	Placebo	34	8	15	25	49	33	81.0	62.5	69.4	75.8
	Voclosporin 23.7mg BID	53	7	10	9	63	16	88.3	47.4	84.1	56.3
	Voclosporin 39.5mg BID	54	7	17	4	71	11	88.5	19.0	76.1	36.4
12	Placebo	36	6	16	24	52	30	85.7	60.0	69.2	80.0
	Voclosporin 23.7mg BID	56	5	12	7	68	12	91.8	36.8	82.4	58.3
	Voclosporin 39.5mg BID	55	7	14	4	69	11	88.7	22.2	79.7	36.4
16	Placebo	39	3	16	23	55	26	92.9	59.0	70.9	88.5
	Voclosporin 23.7mg BID	58	3	11	7	69	10	95.1	38.9	84.1	70.0
	Voclosporin 39.5mg BID	55	8	13	7	68	15	87.3	35.0	80.9	46.7
20	Placebo	38	4	16	21	54	25	90.5	56.8	70.4	84.0
	Voclosporin 23.7mg BID	57	3	9	7	66	10	95.0	43.8	86.4	70.0
	Voclosporin 39.5mg BID	57	5	15	5	72	10	91.9	25.0	79.2	50.0
24	Placebo	37	3	11	24	48	27	92.5	68.6	77.1	88.9
	Voclosporin 23.7mg BID	59	1	11	3	70	4	98.3	21.4	84.3	75.0

Table 7		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
	Voclosporin 39.5mg BID	53	9	12	7	65	16	85.5	36.8	81.5	43.8
26	Placebo	34	5	12	18	46	23	87.2	60.0	73.9	78.3
	Voclosporin 23.7mg BID	54	1	7	5	61	6	98.2	41.7	88.5	83.3
	Voclosporin 39.5mg BID	58	3	11	5	69	8	95.1	31.3	84.1	62.5
36	Placebo	41	1	14	17	55	18	97.6	54.8	74.5	94.4
	Voclosporin 23.7mg BID	60	1	10	3	70	4	98.4	23.1	85.7	75.0
	Voclosporin 39.5mg BID	61	2	11	7	72	9	96.8	38.9	84.7	77.8
48	Placebo	37	1	5	21	42	22	97.4	80.8	88.1	95.5
	Voclosporin 23.7mg BID	58	0	8	3	66	3	100.0	27.3	87.9	100.0
	Voclosporin 39.5mg BID	61	0	5	11	66	11	100.0	68.8	92.4	100.0

Table 8 – Early 35% reduction in UPCR

Table 8		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
2	Placebo	13	29	13	31	26	60	31.0	70.5	50.0	51.7
	Voclosporin 23.7mg BID	36	25	6	18	42	43	59.0	75.0	85.7	41.9
	Voclosporin 39.5mg BID	28	32	11	13	39	45	46.7	54.2	71.8	28.9
4	Placebo	26	15	9	32	35	47	63.4	78.0	74.3	68.1
	Voclosporin 23.7mg BID	46	13	11	12	57	25	78.0	52.2	80.7	48.0
	Voclosporin 39.5mg BID	43	18	13	8	56	26	70.5	38.1	76.8	30.8
6	Placebo	30	12	14	25	44	37	71.4	64.1	68.2	67.6
	Voclosporin 23.7mg BID	47	12	9	9	56	21	79.7	50.0	83.9	42.9
	Voclosporin 39.5mg BID	47	16	14	6	61	22	74.6	30.0	77.0	27.3
8	Placebo	34	8	14	26	48	34	81.0	65.0	70.8	76.5
	Voclosporin 23.7mg BID	52	8	9	10	61	18	86.7	52.6	85.2	55.6
	Voclosporin 39.5mg BID	53	8	17	4	70	12	86.9	19.0	75.7	33.3
12	Placebo	35	7	14	26	49	33	83.3	65.0	71.4	78.8
	Voclosporin 23.7mg BID	54	7	10	9	64	16	88.5	47.4	84.4	56.3
	Voclosporin 39.5mg BID	52	10	14	4	66	14	83.9	22.2	78.8	28.6
16	Placebo	39	3	13	26	52	29	92.9	66.7	75.0	89.7
	Voclosporin 23.7mg BID	57	4	11	7	68	11	93.4	38.9	83.8	63.6
	Voclosporin 39.5mg BID	55	8	13	7	68	15	87.3	35.0	80.9	46.7

Table 8		Week 48 Partial Remission		No Week 48 Partial Remission		Early Reduction		Sensi- tivity	Specifi- city	Positive Predic- tive Value	Negative Predic- tive Value
Week	Treatment Group	Early Drop	No Early Drop	Early Drop	No Early Drop	Yes	No				
20	Placebo	38	4	15	22	53	26	90.5	59.5	71.7	84.6
	Voclosporin 23.7mg BID	57	3	8	8	65	11	95.0	50.0	87.7	72.7
	Voclosporin 39.5mg BID	56	6	15	5	71	11	90.3	25.0	78.9	45.5
24	Placebo	37	3	10	25	47	28	92.5	71.4	78.7	89.3
	Voclosporin 23.7mg BID	59	1	8	6	67	7	98.3	42.9	88.1	85.7
	Voclosporin 39.5mg BID	53	9	12	7	65	16	85.5	36.8	81.5	43.8
26	Placebo	34	5	11	19	45	24	87.2	63.3	75.6	79.2
	Voclosporin 23.7mg BID	52	3	7	5	59	8	94.5	41.7	88.1	62.5
	Voclosporin 39.5mg BID	55	6	11	5	66	11	90.2	31.3	83.3	45.5
36	Placebo	41	1	12	19	53	20	97.6	61.3	77.4	95.0
	Voclosporin 23.7mg BID	60	1	9	4	69	5	98.4	30.8	87.0	80.0
	Voclosporin 39.5mg BID	61	2	11	7	72	9	96.8	38.9	84.7	77.8
48	Placebo	37	1	3	23	40	24	97.4	88.5	92.5	95.8
	Voclosporin 23.7mg BID	58	0	7	4	65	4	100.0	36.4	89.2	100.0
	Voclosporin 39.5mg BID	61	0	4	12	65	12	100.0	75.0	93.8	100.0

[0081] Thus it appears the 8 week or 12 week results, for example, are predictions of ultimate outcome, and it is beneficial to stop treatment if there was no reduction in UPCR by >15% at that time.

[0082] For completeness, Tables 9a and 9b show similar results for an 8 week early time point when a 25% UPCR reduction is used as a criterion and the protocol extends for 24 or 48 weeks.

Table 9a: Probability of attaining a CR by Proteinuria if UPCR reduction of 25% or greater is achieved at 8 weeks:					
Group	# of patients in treatment arm (number with week 8 assessment)	# of CRs by Proteinuria at 24 weeks	# of patients with UPCR reduction of $\geq 25\%$ at 8 weeks	#(%) of patients who had a reduction of UPCR of $\geq 25\%$ who went on to be a CR by UPCR at 24 weeks	#(%) of patients who had a reduction of UPCR of $\geq 25\%$ who went on to be a CR by UPCR at 48 weeks
Placebo	88 (83)	17	52	16/52 (30.8)	18/52 (34.6)
Low Dose	89 (80)	29	64	29/64 (45.3)	40/64 (62.5)
High Dose	88 (84)	24	72	24/72 (33.3)	32/72 (44.4)
Table 9b: Probability of attaining a CR by Proteinuria if UPCR reduction of 25% or greater is <u>not</u> achieved at 8 weeks:					
Group	# of patients in treatment arm (number with week 8 assessment)	# of CRs by Proteinuria at 24 weeks	# of patients without UPCR reduction of $\geq 25\%$ at 8 weeks	#(%) of patients who did not have a reduction of UPCR of $\geq 25\%$ who went on to be a CR by UPCR at 24 weeks	#(%) of patients who did not have a reduction of UPCR of $\geq 25\%$ who went on to be a CR by UPCR at 48 weeks
Placebo	88 (83)	17	31	1/31 (3.2)	3/31 (9.7)
Low Dose	89 (80)	29	16	0/16 (0.0)	4/16 (25.0)
High Dose	88 (84)	24	12	0/12 (0.0)	3/12 (25.0)

[0083] Another criterion for effectiveness is normalization of C3 and/or C4 concentration in blood. The normal concentration of C3 is 90 mg/dl or greater and for C4 16 mg/dl or greater. Subjects for the treatment of the invention generally have concentrations below these values. Normalization of C3 is defined as an increase from below 90 mg/dl to above that level or a 25% increase from the baseline (below 90) exhibited by the subject and normalization of C4 is defined as an increase from below 16 mg/dl to above that level or a 25% increase from the baseline (below 16) exhibited by the subject.

[0084] Tables 10 – 12 provide similar data for these criteria to the data in Tables 4-9 for UPCR.

Table 10 – Early C3 normalization

Table 10		Week 48 Partial Remission		No Week 48 Partial Remission		Normal-ization		Sensi-tivity	Specifi-city	Positive Predic-tive Value	Negative Predic-tive Value
Week	Treatment Group	Normal-ization	No Normal-ization	Normal-ization	No Normal-ization	Yes	No				
12	Placebo	16	24	15	22	31	46	40.0	59.5	51.6	47.8
	Voclosporin 23.7mg BID	23	34	8	10	31	44	40.4	55.6	74.2	22.7
	Voclosporin 39.5mg BID	34	28	7	10	41	38	54.8	58.8	82.9	26.3
24	Placebo	17	22	16	18	33	40	43.6	52.9	51.5	45.0
	Voclosporin 23.7mg BID	24	33	6	8	30	41	42.1	57.1	80.0	19.5
	Voclosporin 39.5mg BID	35	26	6	12	41	38	57.4	66.7	85.4	31.6
48	Placebo	15	23	14	13	29	36	39.5	48.1	51.7	36.1
	Voclosporin 23.7mg BID	25	30	2	8	27	38	45.5	80.0	92.6	21.1
	Voclosporin 39.5mg BID	34	29	7	9	41	38	54.0	56.3	82.9	23.7

Table 11 – Early C4 normalization

Table 11		Week 48 Partial Remission		No Week 48 Partial Remission		Normal-ization		Sensi-tivity	Specifi-city	Positive Predic-tive Value	Negative Predic-tive Value
Week	Treatment Group	Normal-ization	No Normal-ization	Normal-ization	No Normal-ization	Yes	No				
12	Placebo	15	25	19	18	34	43	37.5	48.6	44.1	41.9
	Voclosporin 23.7mg BID	27	29	10	8	37	37	48.2	44.4	73.0	21.6
	Voclosporin 39.5mg BID	40	22	8	9	48	31	64.5	52.9	83.3	29.0
24	Placebo	16	23	18	16	34	39	41.0	47.1	47.1	41.0
	Voclosporin 23.7mg BID	32	25	8	6	40	31	56.1	42.9	80.0	19.4
	Voclosporin 39.5mg BID	39	22	5	13	44	35	63.9	72.2	88.6	37.1
48	Placebo	16	22	14	13	30	35	42.1	48.1	53.3	37.1
	Voclosporin 23.7mg BID	29	26	5	5	34	31	52.7	50.0	85.3	16.1
	Voclosporin 39.5mg BID	36	27	5	11	41	38	57.1	68.8	87.8	28.9

Table 12 – Early C3/C4 normalization

Table 12		Week 48 Partial Remission		No Week 48 Partial Remission		Normal-ization		Sensi-tivity	Specifi-city	Positive Predic-tive Value	Negative Predic-tive Value
Week	Treatment Group	Normal-ization	No Normal-ization	Normal-ization	No Normal-ization	Yes	No				
12	Placebo	11	29	14	23	25	52	27.5	62.2	44.0	44.2
	Voclosporin 23.7mg BID	20	37	6	12	26	49	35.1	66.7	76.9	24.5
	Voclosporin 39.5mg BID	29	33	7	10	36	43	46.8	58.8	80.6	23.3
24	Placebo	12	27	14	20	26	47	30.8	58.8	46.2	42.6
	Voclosporin 23.7mg BID	23	34	4	10	27	44	40.4	71.4	85.2	22.7
	Voclosporin 39.5mg BID	26	35	5	13	31	48	42.6	72.2	83.9	27.1

Table 12		Week 48 Partial Remission		No Week 48 Partial Remission		Normal-ization		Sensi-tivity	Specifi-city	Positive Predic-tive Value	Negative Predic-tive Value
Week	Treatment Group	Normal-ization	No Normal-ization	Normal-ization	No Normal-ization	Yes	No				
48	Placebo	10	28	10	17	20	45	26.3	63.0	50.0	37.8
	Voclosporin 23.7mg BID	20	35	2	8	22	43	36.4	80.0	90.9	18.6
	Voclosporin 39.5mg BID	27	36	5	11	32	47	42.9	68.8	84.4	23.4

[0085] Tables 13-17 make similar calculations for the combined results of UPCR and C3/C4 at 12 weeks. In these tables, the data from the 12 week determinations in Tables 4-8 are meshed with the data from the 12 week time point in Table 12.

[0086] Based on the levels of sensitivity, specificity, positive predictive value and negative predicted value shown, decision to stop or continue treatment is made.

Table 13 – Early 15% reduction in UPCR or C3/C4 normalization

Table 13		Week 48 Partial Remission		No Week 48 Partial Remission		Early Drop or Normal		Sensi-tivity	Specifi-city	Positive Predic-tive Value	Negative Predic-tive Value
Week	Treatment Group	Early Drop or Normal	No Early Drop or Normal	Early Drop or Normal	No Early Drop or Normal	Yes	No				
12	Placebo	39	3	26	12	65	15	92.9	31.6	60.0	80.0
	Voclosporin 23.7mg BID	60	1	18	1	78	2	98.4	5.3	76.9	50.0
	Voclosporin 39.5mg BID	60	3	16	3	76	6	95.2	15.8	78.9	50.0
24	Placebo	39	2	27	8	66	10	95.1	22.9	59.1	80.0
	Voclosporin 23.7mg BID	61	0	13	1	74	1	100.0	7.1	82.4	100.0
	Voclosporin 39.5mg BID	57	5	15	4	72	9	91.9	21.1	79.2	44.4
48	Placebo	37	1	18	9	55	10	97.4	33.3	67.3	90.0
	Voclosporin 23.7mg BID	58	0	10	1	68	1	100.0	9.1	85.3	100.0
	Voclosporin 39.5mg BID	62	0	12	4	74	4	100.0	25.0	83.8	100.0

Table 14 – Early 20% reduction in UPCR or C3/C4 normalization

Table 14		Week 48 Partial Remission		No Week 48 Partial Remission		Early Drop or Normal		Sensi-tivity	Specifi-city	Positive Predic-tive Value	Negative Predic-tive Value
Week	Treatment Group	Early Drop or Normal	No Early Drop or Normal	Early Drop or Normal	No Early Drop or Normal	Yes	No				
12	Placebo	38	4	26	12	64	16	90.5	31.6	59.4	75.0
	Voclosporin 23.7mg BID	60	1	17	2	77	3	98.4	10.5	77.9	66.7
	Voclosporin 39.5mg BID	60	3	16	3	76	6	95.2	15.8	78.9	50.0

Table 14		Week 48 Partial Remission		No Week 48 Partial Remission		Early Drop or Normal		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop or Normal	No Early Drop or Normal	Early Drop or Normal	No Early Drop or Normal	Yes	No				
24	Placebo	39	2	25	10	64	12	95.1	28.6	60.9	83.3
	Voclosporin 23.7mg BID	61	0	13	1	74	1	100.0	7.1	82.4	100.0
	Voclosporin 39.5mg BID	57	5	15	4	72	9	91.9	21.1	79.2	44.4
48	Placebo	37	1	17	10	54	11	97.4	37.0	68.5	90.9
	Voclosporin 23.7mg BID	58	0	10	1	68	1	100.0	9.1	85.3	100.0
	Voclosporin 39.5mg BID	62	0	12	4	74	4	100.0	25.0	83.8	100.0

Table 15 – Early 25% reduction in UPCR or C3/C4 normalization

Table 15		Week 48 Partial Remission		No Week 48 Partial Remission		Early Drop or Normal		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop or Normal	No Early Drop or Normal	Early Drop or Normal	No Early Drop or Normal	Yes	No				
12	Placebo	38	4	24	14	62	18	90.5	36.8	61.3	77.8
	Voclosporin 23.7mg BID	58	2	16	3	74	5	96.7	15.8	78.4	60.0
	Voclosporin 39.5mg BID	60	3	16	3	76	6	95.2	15.8	78.9	50.0
24	Placebo	39	2	23	12	62	14	95.1	34.3	62.9	85.7
	Voclosporin 23.7mg BID	61	0	13	1	74	1	100.0	7.1	82.4	100.0
	Voclosporin 39.5mg BID	57	5	14	5	71	10	91.9	26.3	80.3	50.0
48	Placebo	37	1	17	10	54	11	97.4	37.0	68.5	90.9
	Voclosporin 23.7mg BID	58	0	10	1	68	1	100.0	9.1	85.3	100.0
	Voclosporin 39.5mg BID	62	0	10	6	72	6	100.0	37.5	86.1	100.0

Table 16 – Early 30% reduction in UPCR or C3/C4 normalization

Table 16		Week 48 Partial Remission		No Week 48 Partial Remission		Early Drop or Normal		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop or Normal	No Early Drop or Normal	Early Drop or Normal	No Early Drop or Normal	Yes	No				
12	Placebo	37	5	24	14	61	19	88.1	36.8	60.7	73.7
	Voclosporin 23.7mg BID	58	2	16	3	74	5	96.7	15.8	78.4	60.0
	Voclosporin 39.5mg BID	59	4	16	3	75	7	93.7	15.8	78.7	42.9
24	Placebo	39	2	22	13	61	15	95.1	37.1	63.9	86.7
	Voclosporin 23.7mg BID	61	0	13	1	74	1	100.0	7.1	82.4	100.0
	Voclosporin 39.5mg BID	57	5	14	5	71	10	91.9	26.3	80.3	50.0
48	Placebo	37	1	13	14	50	15	97.4	51.9	74.0	93.3

Table 16		Week 48 Partial Remission		No Week 48 Partial Remission		Early Drop or Normal		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop or Normal	No Early Drop or Normal	Early Drop or Normal	No Early Drop or Normal	Yes	No				
	Voclosporin 23.7mg BID	58	0	9	2	67	2	100.0	18.2	86.6	100.0
	Voclosporin 39.5mg BID	62	0	8	8	70	8	100.0	50.0	88.6	100.0

Table 17 – Early 35% reduction in UPCR or C3/C4 normalization

Table 17		Week 48 Partial Remission		No Week 48 Partial Remission		Early Drop or Normal		Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Week	Treatment Group	Early Drop or Normal	No Early Drop or Normal	Early Drop or Normal	No Early Drop or Normal	Yes	No				
12	Placebo	36	6	23	15	59	21	85.7	39.5	61.0	71.4
	Voclosporin 23.7mg BID	56	4	14	5	70	9	93.3	26.3	80.0	55.6
	Voclosporin 39.5mg BID	57	6	16	3	73	9	90.5	15.8	78.1	33.3
24	Placebo	39	2	21	14	60	16	95.1	40.0	65.0	87.5
	Voclosporin 23.7mg BID	61	0	10	4	71	4	100.0	28.6	85.9	100.0
	Voclosporin 39.5mg BID	57	5	14	5	71	10	91.9	26.3	80.3	50.0
48	Placebo	37	1	12	15	49	16	97.4	55.6	75.5	93.8
	Voclosporin 23.7mg BID	58	0	8	3	66	3	100.0	27.3	87.9	100.0
	Voclosporin 39.5mg BID	62	0	7	9	69	9	100.0	56.3	89.9	100.0

Example 4Low Dose Corticosteroid

[0087] Applicants have also found that the dosage of corticosteroid can effectively be reduced as compared to “standard of care” as shown in Tables 8 and 9, and can be reduced further to 4mg per day or less.

Table 18

Standard of Care Dosing Schedule for IV methylprednisolone and daily oral prednisone:

Time	Patients < 45 kg (daily dosage)	Patients ≥ 45 kg (daily dosage)
Days 1-3	0.5 g IV methylprednisolone	1 g IV methylprednisolone
Days 3-112	1 mg/kg tapered down	1 mg/kg (maximum 80 mg) tapered down

Table 19

Lowered Dosing Schedule for IV methylprednisolone and daily oral prednisone:

Time	Patients < 45 kg (daily dosage)	Patients ≥ 45 kg (daily dosage)
Days 1-2	0.25 g IV methylprednisolone	0.5 g IV methylprednisolone
Days 3-13	20 mg oral prednisone	25 mg oral prednisone
Week 3	15 mg oral prednisone	20 mg oral prednisone
Week 4	10 mg oral prednisone	15 mg oral prednisone
Week 6	10 mg oral prednisone	10 mg oral prednisone
Week 8	5 mg oral prednisone	5 mg oral prednisone
Week 12	5 mg oral prednisone	5 mg oral prednisone
Week 16	2.5 mg oral prednisone	2.5 mg oral prednisone