OMEROS CORPORATION

CLINICAL PROTOCOL

PROTOCOL NO. OMS721-GNP-001
Amendment 02

Investigational New Drug
OMS721

PHASE2

# A Phase 2 Study to Evaluate the Safety and Effect on Proteinuria of OMS721 in Subjects with IgA Nephropathy, Lupus Nephritis, Membranous Nephropathy, or C3 Glomerulopathy including Dense Deposit Disease

24 May 2017

APPROVED BY:

[redacted]

## 1.1. Investigator Agreement

I have read Omeros Protocol No. OMS721-GNP-001 Amendment 02. I agree to conduct the study as described in this protocol, and provide the necessary assurances that this study will be conducted according to the stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable United States (US) federal regulations and International Conference on Harmonisation (ICH) guidelines.

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Principal Investigator Name

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Principal Investigator Signature

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Date

## 1.2. Contact Information

# 2. SYNOPSIS

| | |
|---|---|
| **Sponsor/Company:** Omeros Corporation | |
| **Investigational Product:** OMS721 | |
| **Active Ingredient(s):** OMS721 (MASP-2 monoclonal antibody) | |
| **Title of Study:** A Phase 2 Study to Evaluate the Safety and Effect on Proteinuria of OMS721 in Subjects with IgA Nephropathy, Lupus Nephritis, Membranous Nephropathy, or C3 Glomerulopathy including Dense Deposit Disease | |
| **Planned Number of Clinical Study Center(s):** Approximately 15 | |
| **Expected Duration of Study:** 48 months | **Phase of Development:** 2 |

**Objectives:**

The primary objective of this study is to describe the safety and tolerability of OMS721 administered to subjects with immunoglobulin A nephropathy (IgAN), lupus nephritis (LN), membranous nephropathy (MN), or complement component 3 (C3) glomerulopathy, including dense deposit disease, as assessed by adverse events (AEs), vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

The secondary objectives of this study are to describe the effect of OMS721 administered to subjects with IgAN, lupus nephritis, MN, or C3 glomerulopathy including dense deposit disease on:

- Proteinuria assessed by 24-hour urine protein collection by disease
- Urine albumin/creatinine ratio by disease
- Corticosteroid dose needed to maintain stable renal function by disease (Cohort 1)
- Pharmacokinetics (PK)
- Pharmacodynamics (PD)

The exploratory objectives of this study are to describe the effect of OMS721 administered to subjects with IgAN, lupus nephritis, MN, or C3 glomerulopathy including dense deposit disease on:

- Serum creatinine by disease
- Estimated glomerular filtration rate (eGFR) by disease calculated by the Modification of Diet in Renal Disease (MDRD) equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using serum creatinine, the CKD-EPI equation using cystatin C, and the CKD-EPI equation using creatinine – cystatin C
- Urine protein/creatinine ratio by disease
- Occurrence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb)
- Urine inflammatory markers by disease

- Duration of therapeutic response, if observed, defined as the number of consecutive weeks that 24-hour urine protein < 50% of baseline for up to 104 weeks (Cohort 3 only)

**Methodology:** This is a Phase 2, multicenter study of OMS721 in subjects with the following diseases: IgAN, lupus nephritis, MN, or C3 glomerulopathy including dense deposit disease. Three cohorts will be enrolled:

- Cohort 1 will be subjects with corticosteroid-dependent IgAN, LN, MN, or C3 glomerulopathy. All Cohort 1 subjects will be receiving a corticosteroid dose of ≥ 10 mg of prednisone or equivalent dose for at least 12 weeks. Cohort 1 subjects will all receive OMS721 4 mg/kg intravenously (IV) once weekly for 12 weeks.
- Cohort 2 will be subjects with IgA nephropathy who are not receiving corticosteroids. Cohort 2 subjects will receive either OMS721 4 mg/kg IV treatment or 5% dextrose in water (D5W) vehicle once weekly for 12 weeks in a randomized double blind design.
- Cohort 3 will be subjects with IgA nephropathy who are not receiving corticosteroids. Subjects in Cohort 3 will receive either OMS721 370 mg IV or 5% dextrose in water (D5W) vehicle in a randomized double blind design. Regardless of treatment assignment, subjects in Cohort 3 will be eligible for additional open-label OMS721 treatment if they fail to achieve a 24-hour urine protein < 50% of baseline or their 24-hr urine protein is > 1000mg/24-hours after 12 weeks of dosing [plus a 6-week follow-up period].

Cohorts 1 and 2 are ongoing at the time of this amendment. Upon approval of this amendment, subjects with IgAN in Cohort 1 and subjects in Cohort 2 who have started study drug and are on study will be offered the opportunity to roll into Cohort 3 for extended treatment and long-term follow-up. Subjects have to sign an informed consent and meet the eligibility criteria in order to participate in Cohort 3. The rollover subjects will not be randomized and will receive open-label OMS721 370 mg IV once per week for the remaining treatment period of their original cohort. Following rollover they will follow all study procedures for Cohort 3. Subjects with IgAN in Cohort 1 must have discontinued corticosteroids in order to roll into Cohort 3. Subjects with LN, MN or C3 glomerulopathy in Cohort 1 are not eligible rollover to Cohort 3.

Approximately 44 subjects will be enrolled (16 in Cohort 1, 10 in Cohort 2, and 18 in Cohort 3) from up to approximately 15 investigative sites.

For all subjects in Cohort 1 and Cohort 2, the study will consist of screening (4 weeks), treatment (12 weeks), and follow-up (6 weeks) periods.

For subjects in Cohort 3, the study will consist of screening (4 weeks), initial treatment (12 weeks) and initial follow-up (6 weeks). Cohort 3 subjects who have 24-hour urine protein ≥ 50% of baseline or > 1000 mg/24 hours at the end of the initial follow-up period (6-week follow-up visit) may elect to receive open-label OMS721 370 mg IV once weekly for 12 additional weeks. Follow-up for all Cohort 3 subjects will be 104 weeks from the first dose of study drug.

Subjects will have two screening visits within a 28-day screening period. Within the screening period and before the first study drug dose, consented subjects will provide three urine

samples (collected once daily) on each of two three-consecutive-day periods to establish baseline values of the albumin/creatinine ratio and protein/creatinine ratio. In addition, the subjects will provide one 24-hour urine protein sample to establish baseline values and confirm eligibility.

During the initial 4 weeks of treatment, Cohort 1 subjects will be maintained on their stable pre-study dose of corticosteroids. This initial 4-week treatment period will allow assessment of whether OMS721 can improve measures of renal function when administered to subjects with steroid-dependent disease when co-administered with corticosteroids. Investigators will be instructed to maintain subjects' dose of corticosteroids during the initial 4-week period unless an increase in corticosteroid dose is medically indicated.

At the end of the initial 4-week treatment period, Cohort 1 subjects will undergo corticosteroid taper over 4 weeks. The target will be a taper to ≤ 6 mg prednisone (or equivalent dose) daily. The taper schedule will be at the discretion of the Investigator. Over this period, the taper will be discontinued in subjects who have deterioration of renal function, as determined by the Investigator. Subjects will be treated with OMS721 through the corticosteroid taper and complete 12 weeks of treatment. The taper of steroids and OMS721 treatment will permit assessment of whether OMS721 allows a decrease in the dose of corticosteroid required to maintain stable renal function.

Subjects in Cohort 1 and Cohort 2 will remain in the study for 6 weeks following their last study drug dose. Subjects in Cohort 3 will remain in the study for 104 weeks following their first blinded study drug dose.

Clinic visits for subjects in Cohort 1 and Cohort 2 will occur at screening, weekly through the treatment period, and 1, 4, and 6 weeks following the last dose of study drug. Cohort 1 and Cohort 2 subjects will be in the study for approximately 22 weeks.

Clinic visits for subjects in Cohort 3 will occur at screening, weekly through the treatment period and 1, 4, and 6 weeks following the 12$^{th}$ blinded study drug dose at Week 12. Cohort 3 subjects who have 24-hour urine protein < 500 mg will enter the follow-up period with visits at weeks 26, 39, 52, 65, 78, 91 and 104. Cohort 3 subjects who have 24-hour urine protein > 1000 mg or 24-hour urine protein ≥ 50% of baseline anytime between weeks 18-91 during the follow-up period may elect, with the agreement of the Investigator, to receive open-label OMS721 370 mg IV once weekly for 12 weeks. Additional 12-week OMS721 treatment courses may be administered as often as subjects have 24-hour urine protein > 1000 mg or 24-hour urine protein ≥ 50% of baseline during weeks 18-91. Subjects in Cohort 3 will be in the study approximately 25 months.

In Cohort 3, data analyses will be performed after the 6-week follow-up period of the initial 12 weeks of study drug treatment for both the exclusive Asian and non-exclusive Asian groups.

Clinical and laboratory assessments will be done at each study visit.

**Number of Subjects (Planned):** Approximately 44 (approximately 16 in Cohort 1, approximately 10 in Cohort 2, and approximately 18 in Cohort 3)

**Inclusion Criteria:**

Subjects may be included in the study only if they meet all of the following criteria:

1. Competent to provide informed consent.
2. Voluntarily provide informed consent in accordance with regulations and governing institutional review board (IRB) or independent ethics committee (IEC) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.
3. Are age ≥ 18 years at the Screening Visit 1.
4. Have a diagnosis of one of the following:
   - IgAN diagnosed on kidney biopsy
   - Lupus nephritis diagnosed on kidney biopsy (Cohort 1 only)
   - Primary MN diagnosed on kidney biopsy (Cohort 1 only)
   - C3 glomerulopathy including Dense Deposit Disease diagnosed on kidney biopsy (Cohort 1 only)
5. Have 24-hour urine protein > 1000 mg/24 hours.
6. For subjects in Cohort 1, have been on ≥ 10 mg of prednisone or equivalent dose for at least 12 weeks prior to Screening Visit 1.
7. If on immunosuppressive treatment (e.g., cyclophosphamide, mycophenolate mofetil), have been on a stable dose for at least 2 months prior to Screening Visit 1 with no expected change in the dose for the study duration.
8. Have an eGFR ≥ 30 mL/min/1.73 $m^2$ calculated by the MDRD equation.
9. Are on physician-directed, stable, optimized treatment with angiotensin converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB) and have a systolic blood pressure of < 150 mmHg and a diastolic blood pressure of < 90 mmHg at rest.
10. If female, are either a) not of childbearing potential (i.e., surgically sterilized or postmenopausal for > 1 year), b) have a negative pregnancy test and if sexually active must agree to use two medically reliable forms of contraception throughout the study, or c) have a medically sterilized male partner. Acceptable methods of contraception include a reliable intrauterine device, hormonal contraception, or a barrier method.
11. If male, are either a) not of reproductive potential or b) if sexually active must agree to use a medically reliable form of contraception throughout the study. Acceptable methods of birth control include spermicide in combination with a barrier method, or subject's female partner is willing to use medically acceptable methods of birth control (intrauterine device, hormonal contraception, or a barrier method).

**Exclusion Criteria:**

1. Have a known hypersensitivity to any constituent of the investigational product.
2. Have a hemoglobin < 9.0 g/dL.
3. Have a platelet count < 100,000/$mm^3$.
4. Have an absolute neutrophil count < 500 cells/$mm^3$.
5. Have an alanine transaminase (ALT) or aspartate transaminase (AST) > 5.0 x the upper limit of normal.
6. Have systemic manifestations of Henoch-Schonlein purpura (e.g., joint pain, gastrointestinal bleeding, abdominal pain) within 2 years prior to Screening Visit 1.
7. Have used belimumab, eculizumab, or rituximab within 6 months of Screening Visit 1.
8. Have a history of renal transplant.
9. Have a diagnosis of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection, or positive serology at Screening Visit 1 for HIV, hepatitis B, or hepatitis C.
10. Have any significant infection requiring antibiotic treatment at Screening Visit 1.
11. Have a malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated in situ disease, or other cancer from which the patient has been disease-free for ≥ 5 years.
12. Have an expectation of survival of less than 24 months.
13. If female, are pregnant or breastfeeding.
14. Have received any other investigational drug or device or experimental procedures within 30 days of Screening Visit 1.
15. Are an employee of Omeros, the investigative site, a study staff member, or their immediate family member.
16. Have any condition that the Investigator believes would put the subject at risk from participation.
17. For subjects in Cohort 2 and Cohort 3, have received corticosteroids within the 3 months prior to screening. Subjects in Cohort 1 rolling into Cohort 3 must have IgAN and must have discontinued corticosteroids prior to entry into Cohort 3, but the discontinuation may occur at any time prior to Cohort 3 entry.

**Investigational Product, Dosage, and Mode of Administration:**

[redacted]

**Duration of Treatment:** 12 weeks for Cohorts 1 and 2; Initially 12 weeks with potential additional treatment for Cohort 3

**Reference Therapy, Dosage, and Mode of Administration:** Intravenous D5W for Cohort 2 and 3 only

**Study Endpoints:**

1. Safety and tolerability of OMS721 as assessed by AEs, vital signs, clinical laboratory tests, and ECGs
2. Change from baseline in 24-hour urine protein
3. Change from baseline in urine albumin/creatinine ratio by disease
4. Corticosteroid dose required to maintain stable renal function by disease (Cohort 1)
5. OMS721 PK
6. OMS721 PD
7. Urine protein/creatinine ratio change from baseline to 12 weeks by disease
8. Change from baseline in serum creatinine by disease
9. Change from baseline in eGFR calculated using the following equations by disease state: MDRD equation, CKD-EPI using serum creatinine, CKD-EPI using cystatin C, and CKD-EPI using creatinine – cystatin C
10. Occurrence of ADA and NAb
11. Urine inflammatory markers by disease
12. Duration of therapeutic response, if observed, defined as 24-hour urine protein < 50% of baseline for up to 104 weeks (Cohort 2 only)

**Statistical Methods:**

Sample Size Determination

The primary objective of the study is to assess safety and tolerability of OMS721. The sample size has been empirically determined for each cohort.

Analysis Populations

Safety analyses will be based on the safety population, which includes all subjects who receive any amount of study drug.

Efficacy analyses will be based on the efficacy population, which includes all subjects who receive any amount of study drug and have a baseline and at least one post-baseline 24-hour urine protein.

Statistical analyses will group subjects according to their assigned cohort, except for the rollover subjects who will constitute their own cohort.

Safety Analyses

The safety endpoints will be descriptively summarized. Adverse events will be coded according to preferred term and system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA) AE coding dictionary. Laboratory tests and vital signs will be summarized by visit.

Efficacy Analyses

The efficacy endpoints will be descriptively summarized by visit, disease and cohort.

Pharmacokinetic Analyses

Serum drug concentration will be summarized by visit, disease, and cohort. Non-compartmental models will be used to estimate the PK parameters. ADA information will be summarized by visit.

# 3. TABLE OF CONTENTS AND LIST OF FIGURES

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# 4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

| Abbreviation or Specialist Term | Explanation |
|---|---|
| ACEI | Angiotensin-converting-enzyme inhibitor |
| ADA | Anti-drug antibody |
| AE | Adverse event |
| aHUS | Atypical hemolytic uremic syndrome |
| ALT | Alanine aminotransferase |
| AP | Alternative complement pathway |
| ARB | Angiotensin receptor blockers |
| AST | Aspartate aminotransferase |
| AUC | Area under time-concentration curve |
| BP | Blood pressure |
| C1q | Complement component 1q |
| C1r | Complement component 1r |
| C1s | Complement component 1s |
| C2 | Complement component 2 |
| C3 | Complement component 3 |
| C4 | Complement component 4 |
| C4d | Complement component 4d |
| CKD-EPI | Chronic Kidney Disease Epidemiology Collaboration |
| CL | Clearance |
| $C_{max}$ | Maximum plasma concentration |
| CRF | Case report form |
| CTCAE | Common Terminology Criteria for Adverse Events |
| D5W | 5% dextrose in water |
| dL | Deciliter |
| DNA | Deoxyribonucleic acid |
| EC | Ethics committee |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic data capture |
| eGFR | Estimated glomerular filtration rate |
| EMA | European Medicines Agency |
| ESRD | End-stage renal disease |
| FDA | Food and Drug Administration |
| g | Gram |
| GCP | Good clinical practice |
| GLP | Good laboratory practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| $IC_{50}$ | Inhibitory concentration 50% |
| ICH | International Conference on Harmonisation |
| IDMS | Isotope-dilution mass spectrometry |

| Abbreviation or Specialist Term | Explanation |
|---|---|
| IEC | Independent ethics committee |
| IgA | Immunoglobulin A |
| IgA1 | Sub-class of the Immunoglobulin A antibody |
| IgAN | Immunoglobulin A nephropathy |
| IgG | Immunoglobulin G |
| IgG4 | Immunoglobulin G4 |
| IgM | Immunoglobulin M |
| INR | International normalized ratio |
| IB | Investigator's Brochure |
| IRB | Institutional review board |
| IV | Intravenous |
| kg | Kilogram |
| $\lambda z$ | Elimination rate constant |
| LLOQ | Lower limit of quantitation |
| mAb | Monoclonal antibody |
| MASP | Mannan-binding lectin-associated serine protease |
| MBL | Mannan-binding lectin |
| MDRD | Modification of Diet in Renal Disease |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mg | Milligram |
| Min | Minute |
| mL | Milliliter |
| mM | Millimolar |
| mm | Millimeter |
| mmHg | Millimeter of mercury |
| MN | Membranous nephropathy |
| NAb | Neutralizing antibodies |
| ng | Nanogram |
| nM | Nanomolar |
| NOAEL | No observed adverse effect level |
| PD | Pharmacodynamic |
| PK | Pharmacokinetic |
| pM | Picomolar |
| PT | Prothrombin time |
| PTT | Partial thromboplastin time |
| RNA | Ribonucleic acid |
| RR | Respiratory rate |
| SAE | Serious adverse event |
| SC | Subcutaneous |
| SCr | Serum creatinine |
| SLE | Systemic lupus erythematosus |
| $t_{½}$ | Elimination half-life |
| TEAE | Treatment-emergent adverse event |
| TMA | Thrombotic Microangiopathy |
| $T_{max}$ | Time to maximum concentration |
| US | United States |

# 5. INTRODUCTION

## 5.1. Background

### 5.1.1. Description of OMS721

Omeros Corporation (Omeros, Sponsor) is developing OMS721, a human immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that binds to and inhibits mannan-binding lectin-associated serine protease 2 (MASP-2), for the treatment of lectin complement pathway-mediated diseases.

The primary function of the complement system is to protect the host against infectious agents [Ricklin 2010]. This complex system targets immune and inflammatory responses to surfaces that display molecular patterns not usually present on healthy host cells. Activation of the complement system initiates a series of proteolytic steps that culminate in the formation of a membrane attack complex, which disrupts the membranes of targeted cells, causing lysis and cell death. In addition, complement activation triggers opsonization and the recruitment of phagocytic cells to further engage the infectious agents.

Three pathways activate complement in response to distinct initiating events: the classical, lectin, and alternative pathways. The classical pathway is triggered by immune complexes and mediates important immune effector functions. The lectin pathway can be activated by specific types of cell-surface carbohydrate patterns that are usually found on microbes but not on healthy host cell surfaces. These carbohydrate patterns are also found on injured host tissue. Members of the MASP enzyme family initiate lectin pathway activation. These proteases are synthesized as proenzymes that form a complex in blood with lectins, such as the mannan-binding lectin (MBL), ficolins, and collectins. These lectins bind to carbohydrate patterns on foreign or injured host cell surfaces, targeting MASPs to their site(s) of action and leading to activation of MASPs. There are three known MASPs: MASP-1, MASP-2, and MASP-3 [Yongqing 2012]. MASP-2 is thought to be the key enzyme responsible for activation of the lectin pathway; upon activation, it cleaves its substrates, complement component 2 (C2) and complement component 4 (C4), both of which contribute to the formation of the complement component 3 (C3) convertase, a central component of complement activation.

### 5.1.2. Complement Associated Kidney Diseases and Scientific Rationale

Chronic kidney diseases affect more than 20 million people in the United States (US) [Drawz 2015]. In many of these diseases, complement is believed to contribute to the pathophysiology and evidence of lectin pathway activation has been observed. Although treatments exist for these diseases, many patients have persistent renal inflammation and progressive deterioration. Often these patients must be treated with chronic corticosteroids or immunosuppressive agents, which have many serious long-term adverse consequences. Many patients continue to deteriorate even on these treatments. Alternative treatments that could decrease or eliminate the need for such chronic therapies would address an unmet medical need.

#### 5.1.2.1. Immunoglobulin A Nephropathy

Immunoglobulin A nephropathy (IgAN) is an autoimmune kidney disease resulting in intrarenal inflammation and kidney injury. IgAN is the most common type of glomerulonephritis in the world [D'Amico 1987, Levy 1988] and causes end-stage renal disease (ESRD) in a significant percentage of patients [D'Amico 2000, Donadio 2002]. There are approximately 92,000 – 165,000 cases in the US and there is a higher prevalence in Asia, Europe, and Australia [D'Amico 2000]. It is less common in populations of African descent.

Patients typically present with microscopic hematuria with mild to moderate proteinuria and variable levels of renal insufficiency [Wyatt 2013]. Clinical markers such as impaired kidney function, sustained hypertension, and heavy proteinuria (over 1g per day) are associated with poor prognosis [Berthoux 2011, Goto 2009]. Proteinuria is the strongest prognostic factor independent of other risk factors in multiple large observational studies and prospective trials [Coppo 2005, Reich 2007]. It is estimated that 40% of patients reach ESRD within 20 years of disease onset if left untreated [Lai 2016].

The diagnostic hallmark of IgAN is the predominance of immunoglobulin A (IgA) deposits, alone or with IgG, immunoglobulin M (IgM), or both, in the glomerular mesangium. The frequency of IgA without IgG or IgM varies greatly, from 0% to more than 85% across centers. Complement components C3 and properdin are almost always present. Complement components C4 or C4d, MBL, and the terminal complement complex (C5b–C9) are frequently detected, whereas the absence of C1q suggests that the classical pathway is not activated [Wyatt 2013]. At the molecular level, IgAN is linked to the abnormal glycosylation of IgA1 subclass antibodies characterized by reduced terminal galactose residues on N-linked and O-glycans of IgA1. Abnormally glycosylated IgA form pathogenic immune complexes with anti-glycan antibodies

that deposit in the renal mesangium [Maillard 2015]. IgA1 lacking terminal galactose have exposed oligomannose moieties [Oortwijn 2006], a known ligand for MBL binding, and activate the lectin pathway of complement [Maillard 2015, Ohsawa 2012, Oortwijn 2006, Roos 2001].

Glomerular MBL deposition, usually co-localized with IgA and other hallmarks of complement activation, is associated with an unfavorable prognosis; patients with glomerular MBL deposition have more severe proteinuria, decreased renal function, lower levels of serum albumin, and more severe histological changes and mesangial proliferation than patients without MBL deposition [Liu 2013, Matsuda 1998, Roos 2006]. Follow-up data further demonstrates a lower renal remission rate for patients with MBL deposition [Liu 2013].

The current treatment strategies including blood pressure (BP) control with angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) lead to a reduction of proteinuria. The Kidney Disease Improving Global Outcomes guidelines [KDIGO 2012] suggest that corticosteroids should be given in patients with proteinuria of greater than or equal to 1g/day and the usual treatment duration is 6 months. Other strategies to control intra-renal inflammation include the administration of fish oil (controversial) and the administration of immunosuppressive agents such as cyclophosphamide, azathioprine, or mycofenolate mofetil for severe disease (e.g., crescentic IgAN). However, no specific treatment is available for IgAN.

#### 5.1.2.2. Lupus Nephritis

A main complication of systemic lupus erythematosus (SLE) is nephritis, also known as lupus nephritis, which is classified as a secondary form of glomerulonephritis. Up to 60% of adults with SLE have some form of kidney involvement later in the course of the disease [Koda-Kimble 2012] with a prevalence of 20-70 per 100,000 people in the US. Lupus nephritis often presents in patients with other symptoms of active SLE, including fatigue, fever, rash, arthritis, serositis, or central nervous system disease [Pisetsky 1997]. Some patients have asymptomatic lupus nephritis; however, during regular follow-up, laboratory abnormalities such as elevated serum creatinine levels, low albumin levels, or urinary protein or sediment suggest active lupus nephritis.

Autoimmunity plays a major role in the pathogenesis of lupus nephritis. These autoantibodies form pathogenic immune complexes intravascularly, which are deposited in glomeruli. Autoantibodies may also bind to antigens already located in the glomerular basement membrane, forming immune complexes *in situ*. Immune complexes promote an inflammatory response by activating complement and attracting inflammatory cells [D'Agati 2007]. Thus, immune complex-mediated complement activation plays a key role in the pathogenesis of lupus nephritis. C4d deposits are present in renal tissue and are usually associated with immune complex deposits, C1q, and C3, invoking the classical pathway. In some cases C4d deposits are present without C1q, indicating possible lectin pathway involvement [Kim 2013]. In further support of an important contribution for the lectin pathway, deposits of MBL occur in skin lesions of SLE patients [Wallim 2014]. Additionally, robust deposition of MBL and ficolins in the majority of renal biopsies from patients with lupus nephritis has been observed [Nisihara 2013]. Renal MBL deposition was most evident in patients with high proteinuria. Furthermore, plasma MBL levels were significantly higher in SLE patients than in healthy controls and MBL levels correlated with disease activity, suggesting that MBL levels may represent a biomarker for SLE disease activity [Panda 2012].

Corticosteroids are the major conventional treatment option for patients with mild lupus nephritis. For more severe cases, high-dose prednisone, methylprednisolone, mycophenolate mofetil, cyclophosphamide, azathioprine, and cyclosporine have been used in clinical practice. Treatment options for SLE and lupus nephritis have high associated morbidity and mortality. Side effects, particularly from long-term corticosteroid usage, limit patient adherence with subsequent impact on treatment efficacy. There is a need to develop better tolerated treatment regimens.

#### 5.1.2.3. Primary Membranous Nephropathy

Membranous nephropathy (MN) has an estimated incidence in the Western world at 1.2 per 100,000 persons/year [McGrogan 2011]. Initial manifestations of the disease are related to the nephrotic syndrome: proteinuria, hypoalbuminemia, hyperlipidemia, and edema. Membranous nephropathy is more likely than other causes of the nephrotic syndrome to lead to venous thromboembolic events such as deep vein or renal vein thrombosis, and pulmonary embolism [Kerlin 2012].

Membranous nephropathy is an immune-mediated glomerular disease and one of the most common causes of the nephrotic syndrome in adults. The disease is characterized by the formation of immune deposits on the outer aspect of the glomerular basement membrane, which contain podocyte antigens and antibodies specific to those antigens, resulting in complement activation. On immunofluorescence staining, IgG is nearly always accompanied by C3 in a fine granular pattern demonstrating complement activation. The observed IgG is IgG4, which does not activate the classical pathway of complement. This suggests that the classical pathway is not activated. In over 90% of patients with primary MN anti-PLA2R antibody is detected on biopsy [Qin 2011]. These autoantibodies are associated with clinically active disease, and decline or disappear with spontaneous or treatment-induced remission. However, evidence indicates that IgG4 anti-PLA2R autoantibodies can bind mannan-binding lectin and, thus, may activate complement via the lectin pathway [Ma 2013]. The mechanism by which the lectin pathway might be activated in MN is incompletely understood. The N-linked carbohydrate moieties on autoreactive IgG4 in MN patients may be hypogalactosylated, resulting in exposure of terminal GlcNAc residues, allowing MBL to bind and thereby activate complement by the lectin pathway [Beck 2010, Ma 2011, Salant 2013].

Although MN may spontaneously remit without treatment, as many as one third of patients have progressive loss of kidney function and may progress to ESRD at a median of 5 years after diagnosis. Often, corticosteroids are used to treat MN and there is a need to develop alternate therapies. Additionally, patients determined to be at moderate to high risk for progression, based on severity of proteinuria, are treated with prednisone in conjunction with cyclophosphamide or a calcineurin inhibitor, and these two treatments together are often associated with severe systemic adverse effects.

#### 5.1.2.4. C3 glomerulopathy including dense deposit disease

Complement component 3 (C3) glomerulopathies have glomerular deposits made solely of C3 and no immunoglobulin. They are caused by dysregulation of the AP through inherited or acquired defects. The prevalence is approximately 1 – 2 cases per million [Medjeral-Thomas 2014]. The clinical presentation often includes persistent microscopic hematuria with or without

episodes of macroscopic hematuria [Bennett 1989]. Invariably there is progression of disease and in one study with a median follow-up of 28 months, 29% of patients had developed ESRD [Medjeral-Thomas 2014].

It is thought that C3 glomerulopathy may share genetic risk factors with atypical hemolytic uremic syndrome (aHUS) [Servais 2012], suggesting commonalities in pathogenesis. One striking observation in patients with C3 glomerulopathy is that the clinical presentation is often preceded by an infectious episode. This suggests that the infectious episode may trigger the initial complement activation, which is then amplified uncontrollably due to AP dysregulation to induce manifestations of C3 glomerulopathy in predisposed individuals.

Treatment is not well described and corticosteroids may be used. There are case reports on treatment with eculizumab, a complement factor 5 inhibitor [Bomback 2012, Herlitz 2012]. Few therapies are available and there is a medical need for therapies that work at the level of C3.

## 5.2. Previous Experience

### 5.2.1. Nonclinical Experience

[redacted]

### 5.2.2. Clinical Experience

[redacted]

## 5.3. Potential Risk and Benefits

### 5.3.1. Known and Potential Risks

#### 5.3.1.1. Human MASP-2 Deficiency

MASP-2 deficiency has been reported to occur in humans and the clinical phenotype of MASP-2 deficiency may be relevant to risk assessment of MASP-2 inhibition with OMS721. The literature contains conflicting reports as to whether subjects with MASP-2 deficiency are at risk for adverse effects.

Two case reports described individuals with MASP-2 deficiency due to a homozygous mutation (D120G) with clinical associations with autoimmunity or recurrent bacterial infections; one

patient was healthy until 13 years of age and the other patient had cystic fibrosis [Olesen 2006, Stengaard-Pedersen 2003]. A genetic screen of 335 Polish children with recurrent respiratory tract infections identified one child with MASP-2 deficiency [Cedzynski 2004]. In contrast, in a genetic screen of 868 healthy Spaniards, two homozygous D120G individuals were identified; both subjects were healthy without clinical evidence of recurrent infections or autoimmune disorders and both had normal levels of circulating complement [Garcia-Laorden 2006].

The gene frequency of the D120G mutation is 2-4% in European populations, which would predict that approximately 1 in 625 to 2000 individuals in this population would be homozygotes with MASP-2 deficiency [Garcia-Laorden 2006, Thiel 2007]. Polymorphisms in the MASP-2 gene as well as the plasma concentration of MASP-2 are influenced by race. For example, the D120G mutation is the most common one in Caucasians, but it is not found in Chinese or Africans [Thiel 2007]. Moreover, the circulating levels of MASP-2 were lowest in Africans (median 196 ng/mL), followed by Chinese (262 ng/mL), and Amerindian (290 ng/mL), and highest in Caucasian Danes (416 ng/mL) [Thiel 2007]. The initial studies were in Danes and a plasma concentration below 100 ng/mL was suggested as indicating MASP-2 deficiency since only individuals homozygous for the D120G mutation had this level. Subsequent studies in broader populations showed that this cutoff was inappropriate since 5% of Chinese and 19% of Africans tested had values below 100 ng/mL.

Several studies have examined the relationship between MASP-2 concentration and susceptibility to infections. In a Swiss study of 94 pediatric cancer patients, MASP-2 deficiency defined as serum levels below 200 ng/mL was identified in nine children [Schlapbach 2007]. Patients with low MASP-2 levels had significantly more episodes of febrile neutropenia with no identified microbial etiology and had longer duration of IV antibacterial therapy than those with normal MASP-2 levels. In a Polish study of 1788 neonates, cord blood serum MASP-2 concentration correlated with gestational age and birth weight and was significantly lower in premature babies and other pre-term babies compared with term babies [St Swierzko 2009]. Neonates with low MASP-2 concentrations did not have a higher incidence of perinatal infections when compared with those with normal MASP-2. Indeed, there was a trend towards higher MASP-2 concentrations among babies with infections. A study in Spain evaluated the frequency of D120G mutation in 868 healthy subjects as well as 967 adult patients with community-acquired pneumonia, 43 children with recurrent respiratory infections, and 130 patients with SLE and found that the allelic frequency of the D120G mutation was similar in all of these clinical groups [Garcia-Laorden 2006]. These investigators conducted a follow-up study in which they evaluated the significance of MASP-2 deficiency in the susceptibility and outcome of community-acquired pneumonia in adults and found similar MASP-2 alleles and genotypes among patients and control subjects, leading to the conclusion that MASP-2 deficiency was not associated with an increased risk of community-acquired pneumonias [Garcia-Laorden 2008].

In summary, the literature does not provide a clear indication as to the risk for increased susceptibility to infections in individuals with MASP-2 deficiency. The researchers in Denmark who were the first to describe MASP-2 deficiency and have done the most work in this area stated in one article [Thiel 2007] that “One must conclude that (MASP-2) deficiency in itself does not result in disease, rather, it is a modifier, which may penetrate when also other elements are compromised.”

#### 5.3.1.2. Animal Models of Infection

The role of MASP-2 in bacterial infection has been evaluated in animal models and the results vary depending on the model, ranging from disease worsening to no effect to protection. In a murine model of pneumococcal infection, inhibition of MASP-2 with a MASP-2 mAb prior to nasal inoculation of *Streptococcus pneumonia* resulted in increased severity of disease compared to isotype control mAb [Ali 2012]. In this model, antibiotic treatment was effective in MASP-2 mAb-treated animals, resulting in a similar outcome to that in untreated controls. In contrast, in a murine model of pneumococcal meningitis, MASP-2-deficient mice had a better outcome compared to wild-type littermates [van de Beek D, unpublished observations]. In a murine model of *Pseudomonas aeruginosa* infection, MASP-2-deficient mice had no significant survival disadvantage compared to wild-type littermates [Kenawy 2012]. In a murine model of meningococcal infection, treatment with a MASP-2 mAb prior to bacterial challenge resulted in increased survival compared to treatment with isotype control mAb, demonstrating a protective effect [Omeros data on file].

### 5.3.2. Potential Benefits

[redacted]

### 5.3.3. Risk – Benefit Summary

[redacted]

# 6. STUDY PURPOSE AND OBJECTIVES

The purpose of this Phase 2 study is to evaluate the safety, efficacy, pharmacokinetics (PK), and pharmacodynamics (PD) of OMS721 in subjects with glomerulonephropathies. Three cohorts will be evaluated: one cohort who is corticosteroid-dependent and two cohorts that are not receiving corticosteroids.

## 6.1. Primary Objective(s)

The primary objective of this study is to describe the safety and tolerability of OMS721 administered to subjects with IgAN, lupus nephritis, MN, or C3 glomerulopathy, including dense deposit disease, as assessed by adverse events (AEs), vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

## 6.2. Secondary Objective(s)

The secondary objectives of this study are to describe the effect of OMS721 administered to subjects with IgAN, lupus nephritis, MN, or C3 glomerulopathy including dense deposit disease on:

- Proteinuria assessed by 24-hour urine protein excretion by disease
- Urine albumin/creatinine ratio by disease
- Corticosteroid dose needed to maintain stable renal function by disease (Cohort 1)
- PK
- PD

## 6.3. Exploratory Objectives

The exploratory objectives of this study are to describe the effect of OMS721 administered to subjects with IgAN, lupus nephritis, MN, or C3 glomerulopathy including dense deposit disease on:

- Serum creatinine by disease
- Estimated glomerular filtration rate (eGFR) by disease state calculated by the Modification of Diet in Renal Disease (MDRD) equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using serum creatinine, the CKD-EPI equation using cystatin C, and the CKD-EPI equation using creatinine – cystatin C
- Urine protein/creatinine ratio by disease
- Occurrence of anti-drug antibodies (ADA) and neutralizing antibodies (NAb)
- Urine inflammatory markers by disease
- Duration of therapeutic response, if observed, defined as the number of consecutive weeks that 24-hour urine protein < 50% of baseline for up to 104 weeks (Cohort 3 only)

# 7. STUDY DESIGN AND PROCEDURES

## 7.1. Summary of Study Design

This is a Phase 2, multicenter study of OMS721 in subjects with the following diseases: IgAN, lupus nephritis, MN, or C3 glomerulopathy including dense deposit disease. Three cohorts will be enrolled:

- Cohort 1 will be subjects with corticosteroid-dependent IgAN, LN, MN, or C3 glomerulopathy. All Cohort 1 subjects will be receiving a corticosteroid dose of ≥ 10 mg of prednisone or equivalent dose for at least 12 weeks. Cohort 1 subjects will all receive OMS721 4 mg/kg intravenously (IV) once weekly for 12 weeks.
- Cohort 2 will be subjects with IgA nephropathy who are not receiving corticosteroids. Cohort 2 subjects will receive either OMS721 4 mg/kg IV treatment or 5% dextrose in water (D5W) vehicle once weekly for 12 weeks in a randomized double blind design.
- Cohort 3 will be subjects with IgA nephropathy who are not receiving corticosteroids. Subjects in Cohort 3 will receive either OMS721 370 mg IV or 5% dextrose in water (D5W) vehicle in a randomized double blind design. Regardless of treatment assignment, subjects in Cohort 3 will be eligible for additional open-label OMS721 treatment if they fail to achieve a 24-hour urine protein < 50% of baseline or their 24-hr urine protein is > 1000mg/24-hours after 12 weeks of dosing [plus a 6-week follow-up period].

Cohorts 1 and 2 are ongoing at the time of this amendment. Upon approval of this amendment, subjects with IgAN in Cohort 1 and subjects in Cohort 2 who have started study drug and are on study will be offered the opportunity to roll into Cohort 3 for extended treatment and long-term follow-up. Subjects have to sign an informed consent and meet the eligibility criteria in order to participate in Cohort 3. The rollover subjects will not be randomized and will receive open-label OMS721 370 mg IV once per week for the remaining treatment period of their original cohort. Following rollover they will follow all study procedures for Cohort 3. Subjects with IgAN in Cohort 1 must have discontinued corticosteroids in order to roll into Cohort 3. Subjects with LN, MN or C3 glomerulopathy in Cohort 1 are not eligible rollover into Cohort 3.

Approximately 44 subjects will be enrolled (16 in Cohort 1, 10 in Cohort 2, and 18 in Cohort 3) from up to approximately 15 investigative sites.

For all subjects in Cohort 1 and Cohort 2, the study will consist of screening (4 weeks), treatment (12 weeks), and follow-up (6 weeks) periods.

For subjects in Cohort 3, the study will consist of screening (4 weeks), initial treatment (12 weeks) and initial follow-up (6 weeks). Cohort 3 subjects who have 24-hour urine protein ≥ 50% of baseline or > 1000 mg/24 hours at the end of the initial follow-up period (6-week follow-up visit) may elect to receive open-label OMS721 370 mg IV once weekly for 12 additional weeks. Follow-up for all Cohort 3 subjects will be 104 weeks from the first dose of study drug.

Subjects will have two screening visits within a 28-day screening period. Within the screening period and before the first study drug dose, consented subjects will provide three urine samples

(collected once daily) on each of two three-consecutive-day periods to establish baseline values of the albumin/creatinine ratio and protein/creatinine ratio. In addition, the subjects will provide one 24-hour urine protein sample to establish baseline values and confirm eligibility.

During the initial 4 weeks of treatment, Cohort 1 subjects will be maintained on their stable pre-study dose of corticosteroids. This initial 4-week treatment period will allow assessment of whether OMS721 can improve measures of renal function when administered to subjects with steroid-dependent disease when co-administered with corticosteroids. Investigators will be instructed to maintain subjects' dose of corticosteroids during the initial 4-week period unless an increase in corticosteroid dose is medically indicated.

At the end of the initial 4-week treatment period, Cohort 1 subjects will undergo corticosteroid taper over 4 weeks. The target will be a taper to ≤ 6 mg prednisone (or equivalent dose) daily. The taper schedule will be at the discretion of the Investigator. Over this period, the taper will be discontinued in subjects who have deterioration of renal function, as determined by the Investigator. Subjects will be treated with OMS721 through the corticosteroid taper and complete 12 weeks of treatment. The taper of steroids and OMS721 treatment will permit assessment of whether OMS721 allows a decrease in the dose of corticosteroid required to maintain stable renal function.

Subjects in Cohort 1 and Cohort 2 will remain in the study for 6 weeks following their last study drug dose. Subjects in Cohort 3 will remain in the study for 104 weeks following their first blinded study drug dose.

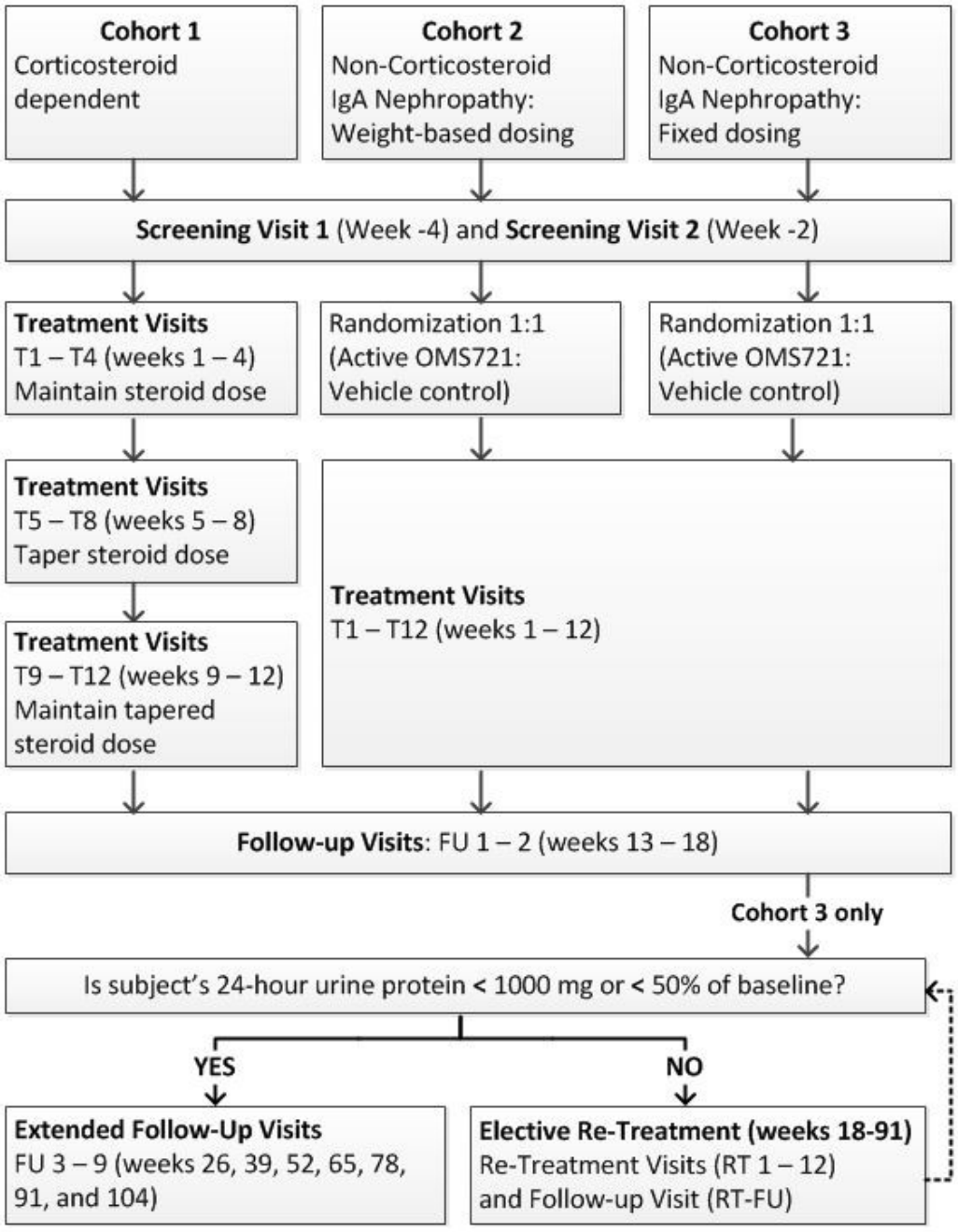
Clinic visits for subjects in Cohort 1 and Cohort 2 will occur at screening, weekly through the treatment period, and 1, 4, and 6 weeks following the last dose of study drug. Cohort 1 and Cohort 2 subjects will be in the study for approximately 22 weeks.

Clinic visits for subjects in Cohort 3 will occur at screening, weekly through the treatment period and 1, 4, and 6 weeks following the 12$^{th}$ blinded study drug dose at Week 12. Cohort 3 subjects who have 24-hour urine protein < 500 mg will enter the follow-up period with visits at weeks 26, 39, 52, 65, 78, 91 and 104. Cohort 3 subjects who have 24-hour urine protein > 1000 mg or 24-hour urine protein ≥ 50% of baseline anytime between weeks 18-91 during the follow-up period may elect, with the agreement of the investigator, to receive open-label OMS721 370 mg IV once weekly for 12 weeks. Additional 12-week OMS721 treatment courses may be administered as often as subjects have 24-hour urine protein > 1000 mg or 24-hour urine protein ≥ 50% of baseline during weeks 18-91. Subjects in Cohort 3 will be in the study approximately 25 months.

In Cohort 3, data analyses will be performed after the 6-week follow-up period of the initial 12 weeks of study drug treatment for both the exclusive Asian and non-exclusive Asian groups.

Clinical and laboratory assessments will be done at each study visit as shown in Figure 1.

**Figure 1: Study Design Schematic**




## 7.2. Study Rationale

This is the first study of OMS721 in subjects with complement-associated nephropathies, including IgAN, lupus nephritis, MN, and C3 glomerulopathy including dense deposit disease. The study is designed to evaluate whether OMS721 may improve renal function and/or reduce corticosteroid needs in subjects with these nephropathies. Each of these diseases has glomerular inflammation and evidence of lectin pathway activation. Persistent renal inflammation is

associated with progressive deterioration in renal function. Treatment often involves chronic corticosteroids and many patients require high-dose corticosteroids. Many patients have serious long-term adverse consequences on chronic high-dose corticosteroid treatment. OMS721 may improve proteinuria, which is associated with improved outcomes, and decrease the corticosteroid needs.

Measurement of urinary protein or albumin is routinely used to assess kidney involvement and persistent high levels of urinary protein correlate with disease progression. The 24-hour urine protein is used clinically to assess proteinuria and has been demonstrated to be predictive of outcome in patients with IgAN.

Results from nonclinical toxicity and clinical studies of OMS721 indicate that there is an adequate safety margin to conduct this study at the proposed dose in subjects with complement-associated kidney diseases. Subjects treated to date have tolerated OMS721 treatment well.

Cohort 3 is being added to ensure that all subjects may receive active therapy if they have significant proteinuria following treatment with blinded study drug. Also, because continued suppression of urinary protein has been observed in IgAN subjects treated with OMS721, subjects in Cohort 3 will undergo extended follow-up to determine the duration of the urine protein suppression. Subjects may receive open-label OMS721 treatment if they do not achieve a therapeutic response with the initial 12-week blinded study drug treatment course or if their urinary protein increases after achieving a therapeutic response. Chronic toxicology has been completed and supports indefinite dosing. Follow-up through 24 months with visits approximately every 13 weeks will allow assessment of duration of therapeutic response with minimal burden to subjects. Subjects with IgAN in Cohort 1 and subjects in Cohort 2 who have not completed the study may roll into Cohort 3 to be able to receive extended OMS721 treatment.

Asian subjects with IgAN residing in Asia have been added to provide initial evaluation of OMS721 in this population. The literature reports that IgAN in the Asian population may be more severe due to genetic or environmental conditions [Magistroni 2015].

### 7.2.1. Rationale for Dose Selection

The dose level of OMS721 370 mg IV in this study inhibits the lectin pathway for approximately one week and provides high levels of lectin pathway inhibition for approximately 4 to 5 days. Prior doses of 4 mg/kg were associated with marked improvement in urinary protein measures in subjects with aHUS, IgA nephropathy, MN, and lupus nephritis. This dose was well tolerated. The fixed dose is within the range of doses provided previously in this study.

## 7.3. Study Endpoints

### 7.3.1. Primary Endpoints

The primary endpoints are:

- Safety and tolerability of OMS721 as assessed by AEs, vital signs, clinical laboratory tests, and ECGs

### 7.3.2. Secondary Endpoint

The secondary endpoints are:

- Proteinuria from baseline to 12 weeks assessed by 24-hour urine protein collection by disease
- Urine albumin/creatinine ratio by disease
- Corticosteroid dose needed to maintain stable renal function by disease (Cohort 1)
- PK
- PD

### 7.3.3. Exploratory Endpoint

The exploratory endpoints are:

- Urine protein/creatinine ratio by disease
- Serum creatinine by disease
- eGFR by disease calculated by the MDRD equation, the CKD-EPI equation using serum creatinine, the CKD-EPI equation using cystatin C, and the CKD-EPI equation using creatinine – cystatin C
- Occurrence of ADA and NAb
- Urine inflammatory markers by disease
- Duration of therapeutic response, if observed, defined as the number of consecutive weeks that 24-hour urine protein < 50% of baseline for up to 104 weeks (Cohort 3 only)

# 8. SELECTION AND WITHDRAWAL OF SUBJECTS

## 8.1. Subject Inclusion Criteria

Subjects may be included in the study only if they meet all of the following criteria:

1. Competent to provide informed consent.
2. Voluntarily provide informed consent in accordance with regulations and governing institutional review board (IRB) or independent ethics committee (IEC) requirements prior to any procedures or evaluations performed specifically for the sole purpose of the study.
3. Are age ≥ 18 years at Screening Visit 1.
4. Have a diagnosis of one of the following:
   - IgAN diagnosed on kidney biopsy
   - Lupus nephritis diagnosed on kidney biopsy (Cohort 1 only)

- Primary MN diagnosed on kidney biopsy (Cohort 1 only)
- C3 glomerulopathy including dense deposit disease diagnosed on kidney biopsy (Cohort 1 only)

5. Have 24-hour urine protein > 1000 mg/24 hours.
6. For subjects in Cohort 1, have been on $\geq$ 10 mg of prednisone or equivalent dose for at least 12 weeks prior to Screening Visit 1.
7. If on immunosuppressive treatment (e.g., cyclophosphamide, mycophenolate mofetil), have been on a stable dose for at least 2 months prior to Screening Visit 1 with no expected change in the dose for the study duration.
8. Have an eGFR $\geq$ 30 mL/min/1.73 $m^2$ calculated by the MDRD equation.
9. Are on physician-directed, stable, optimized treatment with ACEIs and/or ARBs and have a systolic blood pressure of < 150 mmHg and a diastolic blood pressure of < 90 mmHg at rest.
10. If female, are either a) not of childbearing potential (i.e., surgically sterilized or postmenopausal for > 1 year), b) have a negative pregnancy test and if sexually active must agree to use two medically reliable forms of contraception throughout the study, or c) have a medically sterilized male partner. Acceptable methods of contraception include a reliable intrauterine device, hormonal contraception, or a barrier method.
11. If male, are either a) not of reproductive potential or b) if sexually active must agree to use a medically reliable form of contraception throughout the study. Acceptable methods of birth control include spermicide in combination with a barrier method, or subject's female partner is willing to use medically acceptable methods of birth control (intrauterine device, hormonal contraception, or a barrier method).

## 8.2. Subject Exclusion Criteria

Subjects will be excluded from the study for any of the following reasons:

1. Have a known hypersensitivity to any constituent of the investigational product.
2. Have a hemoglobin < 9.0 g/dL.
3. Have a platelet count < 100,000/$mm^3$.
4. Have an absolute neutrophil count < 500 cells/$mm^3$.
5. Have an ALT or AST > 3.0 x the upper limit of normal.
6. Have systemic manifestations of Henoch-Schonlein purpura (e.g., joint pain, gastrointestinal bleeding, abdominal pain) within 2 years prior to Screening Visit 1.
7. Have used belimumab, eculizumab, or rituximab within 6 months of Screening Visit 1.
8. Have a history of renal transplant.
9. Have a diagnosis of human immunodeficiency virus (HIV), hepatitis B, or hepatitis C infection or positive serology at Screening Visit 1 for HIV, hepatitis B, or hepatitis C.

10. Have any significant infection requiring antibiotic treatment at Screening Visit 1.
11. Have a malignancy except for adequately treated and cured basal or squamous cell skin cancer, curatively treated *in situ* disease, or other cancer from which the patient has been disease-free for ≥ 5 years.
12. Have an expectation of survival of less than 24 months.
13. If female, are pregnant or breastfeeding.
14. Have received any other investigational drug or device or experimental procedures within 30 days of Screening Visit 1.
15. Are an employee of Omeros, the investigative site, a study staff member, or their immediate family member.
16. Have any condition that the Investigator believes would put the subject at risk from participation.
17. For subjects in Cohort 2 and Cohort 3, have received corticosteroids within the 3 months prior to screening. Subjects in Cohort 1 rolling into Cohort 3 must have IgAN and must have discontinued corticosteroids prior to entry into Cohort 3, but the discontinuation may occur at any time prior to Cohort 3 entry.

## 8.3. Subject Withdrawal Criteria

### 8.3.1. Early Discontinuation of Study Drug

Subjects may voluntarily withdraw from the study at any time and for any reason without prejudice to further treatment. A subject must permanently discontinue study drug under any of the following circumstances:

- The subject becomes pregnant. Study drug must be discontinued immediately and the pregnancy reported to the Sponsor.
- The subject wishes to discontinue study drug treatment for any reason.
- The subject experiences a medical emergency that necessitates discontinuing study drug treatment.
- The Investigator, Sponsor, or subject's primary care physician decides to discontinue treatment for medical reasons or due to the subject's noncompliance with the protocol.
- For Cohort 1 subjects, the subject experiences deterioration of renal function during corticosteroid tapering period, as determined by the Investigator.

The reason for termination of study drug before study completion must be recorded in the subject's case report form (CRF). The subject should complete all scheduled study visits provided written consent to do so has not been withdrawn.

### 8.3.2. Subject Withdrawal from the Study

A subject must be withdrawn from the study and discontinue study drug under the following circumstances:

- The subject withdraws consent to participate in the study.
- The Investigator or subject's primary care physician decides that the subject should be withdrawn from the study.
- The Sponsor decides that the subject should be withdrawn or the Sponsor discontinues the study for any reason.

The reason for withdrawal must be recorded in the subject's CRF. The subject should complete the evaluations scheduled for the Follow-Up Visit 1, provided written consent to do so has not been withdrawn. Subjects who are withdrawn may be replaced at the discretion of the Sponsor in consultation with the Investigator in order to meet study objectives.

### 8.3.3. Notification of Withdrawal

When a study participant is withdrawn from the study protocol, voluntarily or involuntarily, the Investigator will notify the Sponsor and the IRB/IEC as required, and provide the reasons for subject withdrawal.

# 9. STUDY DRUG

## 9.1. OMS721

OMS721 is manufactured under current Good Manufacturing Practices (cGMP) for investigational use. OMS721 is a human IgG4 mAb directed against MASP-2. [redacted]

[redacted]

### 9.1.1. Packaging and Labeling

[redacted]

### 9.1.2. Blinding

Cohort 1

No blinding is necessary for Cohort 1 since all subjects receive OMS721.

Cohort 2 and Cohort 3

Subjects in Cohort 2 and Cohort 3 will be randomized in a 1:1 fashion to receive either OMS721 or D5W vehicle control during the first 12 treatment weeks. Randomization for Cohort 3 will be stratified by region: North American and the United Kingdom in one strata and Asia in another strata. Study drug administration will be blinded. Additional treatment courses after the first 12 weeks in Cohort 3 will be open-label OMS721.

Treatment assignment will be blinded to all trial personnel, Omeros and its representatives, with the following exceptions:

- Investigative site pharmacist or designee who responsible for maintaining the blind at the site and will prepare and label the infusion.
- An independent site monitor (Clinical Research Associate), who will only monitor study drug accountability.
- Omeros CMC representative who will manage drug supply
- Omeros clinical data manager overseeing the implementation of the randomization module

In a medical emergency, it may be necessary to identify a subject's assigned treatment before the study has been completed and treatments unblinded. The treatment blind should only be broken if this information is necessary to treat the subject for a medical condition. In this situation, it is important that the treatment blind be maintained for all other subjects. The Omeros Medical Monitor should be contacted immediately if the treatment blind is broken. The date and reason for breaking the blind must be discussed with the Omeros Medical Monitor and recorded in the source documents.

Unblinding a subject's treatment assignment by the Investigator or study site personnel under any other circumstances (except as noted above) will be considered a protocol deviation.

### 9.1.3. Study Drug Dose Preparation

[redacted]

### 9.1.4. Storage and Handling of Study Drug Product

[redacted]

## 9.2. Study Drug Accountability

For Cohorts 2 and 3, the investigator will designate an unblinded pharmacist and/or designee who will be responsible for study drug accountability.

In compliance with U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other applicable regulations, records will be maintained by the investigator and/or pharmacist designee for OMS721 study drug product delivery to the site, the inventory at the site, the use of each vial, and the return of used and unused drug product, including dates and quantities. The investigator and/or pharmacist designee will maintain the investigative site's study drug accountability documentation. The documentation should include which drug product was used After the study has been completed, a copy of the investigator/pharmacy drug accountability records will be provided to the Sponsor. The original drug accountability records will be retained by the site.

## 9.3. Return of Drug Product

At the end of the study, the Sponsor will inform the site as to the disposition of unused drug product. If instructed, unused supplies may be destroyed at the site according to local laws, regulations, and the institution's standard operating procedures.

# 10. STUDY PROCEDURES

The schedule of events is summarized in Section 19 .

## 10.1. Study Schedule

### 10.1.1. Screening Visit 1 (within 28 days of the first dose)

Screening evaluations will occur on two separate occasions within 28 days prior to dosing (Day 1). Before any of the screening evaluations are performed for the specific purpose of this study, the subject must provide informed consent for this study in compliance with regulations and governing IRB/IEC requirements. A subject is considered enrolled into the study once they have provided informed consent and have been assigned a subject number.

The subjects who have begun or completed Screening in Cohort 2 but have not received the first dose must sign an informed consent form and transfer into Cohort 3 prior to randomization. The

duration of the screening period for these subjects is up to 90 days. No screening procedures need to be repeated except a single 24-hour urine protein to be provided within 7 days prior to the first dose of study drug if the subject's screening 24-hour urine protein was provided more than 21 days prior to the first dose of study drug.

During Screening Visit 1, the procedures listed below will be performed and documented to determine subject eligibility prior to treatment assignment.

1. A medical history and demographic information including obtaining a history of whether a patient is anti-PLA-2R antibody positive for subjects with a history of MN.
2. Use of prior and concomitant medications, including corticosteroid dose (if applicable).
3. Vital signs including BP, pulse rate, respiratory rate (RR) and temperature (after at least 5 minutes of rest).
4. A physical examination, including height and weight. Examination of breast, rectal, and genitourinary systems may be deferred unless clinically necessary.
5. A 12-lead ECG (after at least 5 minutes of rest in the supine position).
6. Clinical laboratory tests for hematology, chemistry, coagulation, cystatin C, urinalysis, urine for inflammatory biomarkers, and anti-PLA-2R antibody in subjects with MN. See Section 12.1.1 for complete list required laboratory assessments.
7. Serum pregnancy testing in women of childbearing potential.
8. Serology tests for HIV, hepatitis B, and hepatitis C.
9. The subject will be instructed to collect urine samples for albumin/creatinine and protein/creatinine ratios on any 3 consecutive days prior to their next screening visit (i.e., a total of two three-consecutive-day collections during screening). Dispense appropriate supplies for the urine collection. NOTE: all samples for urine albumin/creatinine and protein/creatinine ratios must be collected at first void in the morning and kept in the refrigerator until the subject returns them.
10. The subject will be instructed to collect urine for 24-hour urine protein excretion and appropriate supplies will be provided. The subject will be instructed to perform the urine collection and return to the clinical site at Screening Visit 2. Subjects must return the urine to the site within 3 days of collection to prevent degradation of the sample.

### 10.1.2. Screening Visit 2 (At least 7 days after Screening Visit 1 and approximately 7 days prior to Treatment Visit 1)

At Screening Visit 2 the following will be performed and documented:

1. Collect urine samples from Screening Visit 1.
2. The subject will be instructed to collect additional urine samples for albumin/creatinine and protein/creatinine ratios on 3 consecutive days prior to Treatment Visit 1. Dispense appropriate supplies for the urine collection. NOTE: all samples for urine albumin/creatinine and protein/creatinine ratios must be collected at first void in the morning and kept in the refrigerator until the subject returns them.

3. Vital signs including BP, pulse rate, RR and temperature (after at least 5 minutes of rest).
4. Review of AEs and concomitant medications.
5. Confirmation of eGFR using the MDRD formula to assess eligibility.
6. Review of inclusion and exclusion criteria for study eligibility.

Note: Site must obtain and process urine samples prior to Treatment Visit 1.

### 10.1.3. Treatment Visit 1 (Day 1, approximately 7 days after Screening Visit 2)

This visit is to confirm eligibility, randomize (Cohort 2 and Cohort 3) subjects, and administer the first dose of study drug. Randomization may occur up to 2 days prior to Treatment Visit 1 if necessary for site logistical reasons provided eligibility has been confirmed. Eligible subjects for Cohort 1 will initiate treatment with OMS721. Eligible subjects for Cohort 2 and Cohort 3 will be randomized by the pharmacist or unblinded drug-designee at the study center. A computer-generated randomization will be created allocating Cohort 2 and Cohort 3 subjects to either OMS721 or vehicle.

Prior to administering the dose of study drug, the following procedures will be performed:

1. Review of AEs and concomitant medications, including corticosteroid dose (if applicable).
2. Vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest).
3. ECG taken (after at least 5 minutes of rest in the supine position).
4. Laboratory samples will be collected for:
    - Hematology, chemistry, coagulation, cystatin C
    - Urinalysis
    - Serum or urine pregnancy test in women of childbearing potential. If the test result is positive then the subject will be excluded from the study
    - Blood samples for future research
    - Serum PK sample
    - Serum PD sample
    - Serum ADA sample
5. For three days prior to Treatment Visit 1, three once daily first void urine samples for albumin/creatinine and protein/creatinine ratios will be collected and brought for analysis at this visit.

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoints: 30 minutes, 1 hour.

2. ECG taken (after at least 5 minutes of rest in the supine position), to be obtained immediately before the 5-minute, post dose PK sample.
3. Serum PK samples at the following timepoints after end of dosing: 5 minutes, 2 hours, and 24 hours (**Day 2**), 72 hours (**Day 4**).
4. Serum PD sample after the end of dosing: 2 hours.
5. The subject may be discharged after arrangements are made for the collection of PK samples on **Days 2 and 4**.

### 10.1.4. Treatment Visits 2, 3, 4 (Days 8, 15, 22; *+/- 2 days*)

Study drug will be administered once per week for a total of 12 weekly doses during the study. The following procedures will be performed at Treatment Visits 2, 3, and 4:

Prior to administering the dose of study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. Laboratory samples will be collected for:
   - Hematology, chemistry, coagulation, cystatin C
   - Urinalysis
   - Urine for inflammatory biomarkers (visit 4 only)
   - Blood samples for future research
   - Serum PK sample
   - Serum PD sample

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoint: 30 minutes.
2. Serum PK samples will be taken at the following timepoint: 30 minutes (visit 2 and visit 3 only).
3. Serum PD samples will be taken at the following timepoint: 30 minutes (visit 2 and visit 3 only).
4. At Treatment Visit 4, provide subjects with supplies to collect first void urine samples for urine albumin/creatinine and protein/creatinine ratios on three mornings prior to Treatment Visit 5.

### 10.1.5. Treatment Visit 5 (Day 29; *+/- 2 days*)

The following procedures will be completed at Treatment Visit 5:

Prior to administering the dose of study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. For three days prior to Treatment Visit 5, three once daily first void urine samples for albumin/creatinine and protein/creatinine ratios will be collected and brought for analysis at this visit.
4. Laboratory samples will be collected for:
    - Serum or urine pregnancy test in women of childbearing potential. If the test result is positive then the subject will be discontinued from study drug administration and followed for outcome of the pregnancy.
    - Serum PK sample
    - Serum PD sample
    - Serum ADA sample

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoint: 30 minutes.
2. Serum PK samples will be taken at the following timepoint: 30 minutes.
3. Serum PD samples will be taken at the following timepoint: 30 minutes.
4. At Treatment Visit 5, Cohort 1 subjects with stable or improving renal function should begin corticosteroid tapering and continue through the ensuing 4-week period to prednisone ≤ 6 mg (or equivalent dose), at the discretion of the Investigator.

### 10.1.6. Treatment Visits 6, 7, 8 (Days 36, 43, 50; *+/- 2 days*)

The following procedures will be performed at Treatment Visits 6, 7, and 8.

Prior to dosing with study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. Laboratory samples will be collected for:
    - Hematology, chemistry, coagulation, cystatin C (visit 8 only)
    - Urinalysis (visit 8 only)

- Blood samples for future research (visit 8 only)
- Serum PK sample
- Serum PD sample

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoint: 30 minutes.
2. At Treatment Visit 8, provide subjects with supplies to collect first void urine samples for urine albumin/creatinine and protein/creatinine ratios on three mornings prior to Treatment Visit 9.
3. In Cohort 1 subjects assess renal function and taper corticosteroid dose accordingly.

### 10.1.7. Treatment Visit 9 (Day 57; *+/- 2 days*)

The following procedures will be completed at Treatment Visit 9:

Prior to dosing with study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. For three days prior to Treatment Visit 9, three once daily first void urine samples for urine albumin/creatinine and protein/creatinine ratios will be collected and brought for analysis at this visit.
4. Laboratory samples will be collected for:
    - Serum or urine pregnancy test in women of childbearing potential. If the test result is positive then the subject will be discontinued from the study and followed for outcome of the pregnancy
    - Serum PK sample
    - Serum PD sample
    - Serum ADA

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoint: 30 minutes.
2. Serum PK samples will be taken at the following timepoint: 30 minutes.
3. Serum PD samples will be taken at the following timepoint: 30 minutes.

### 10.1.8. Treatment Visit 10, 11, 12 (Days 64, 71, 78; *+/- 2 days*)

The following procedures will be performed at Treatment Visits 10, 11, and 12:

Prior to dosing with study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. ECG taken (after at least 5 minutes of rest in the supine position) (visit 12 only).
4. Laboratory samples will be collected for:
    - Serum PK sample
    - Serum PD sample

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoint: 30 minutes.
2. ECG taken (after at least 5 minutes of rest in the supine position), to be obtained immediately post dose (visit 12 only).
3. Serum PK samples will be taken at the following timepoint: 30 minutes (visit 12 only).
4. Serum PD samples will be taken at the following timepoint: 30 minutes (visit 12 only).
5. At Treatment Visit 12, provide subjects with supplies to collect first void urine samples for urine albumin/creatinine and protein/creatinine ratios on three mornings prior to Follow-Up Visit 1.

### 10.1.9. Follow-Up Visit 1 (Day 85; +/- 3 days)

One week after the last dose of study drug, the following procedures and assessments will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. Laboratory samples will be collected for:
    - Hematology, chemistry, coagulation, cystatin C
    - Urinalysis
    - Urine for inflammatory biomarkers
    - Serum or urine pregnancy test in women of childbearing potential. If the test result is positive then the subject will be followed for outcome of the pregnancy

- Serum PK samples
- Serum PD sample
- Serum ADA sample

4. For three days prior to Follow-Up Visit 1, three once daily first void urine samples for urine albumin/creatinine ratios will be collected and brought for analysis at this visit.
5. For Cohort 3 subjects only, subjects will be provided with supplies to collect 24-hour urine samples in the week prior to next Follow-Up Visit. The investigative site will call the subject one week prior to the next follow-up visit to remind the subject to collect the 24-hour urine sample.
6. At Follow-Up Visit 1, subjects will be provided with supplies to collect first void urine samples for urine albumin/creatinine and protein/creatinine ratios on three mornings prior to Follow-Up Visit 2.

### 10.1.10. Follow-Up Visit 2 (Day 120; +/- *3 days*)

Six weeks after the last dose of study drug the following procedures and assessments will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. Laboratory samples will be collected for:
   - Hematology, chemistry, coagulation, cystatin C
   - Serum PK samples
   - Serum PD sample
   - Serum ADA sample
4. For three days prior to Follow-Up Visit 2, three once daily first-void urine sample for urine albumin/creatinine and protein/creatinine ratios will be collected and brought in for analysis at this visit.

Subjects in Cohort 1 and Cohort 2 will complete the study at Follow-up Visit 2 provided they have not rolled into Cohort 3.

Subjects in Cohort 3 will undergo extended follow-up with visits at weeks 26, 39, 52, 65, 78, 91 and 104.

### 10.1.11. Cohort 3 Extended Follow-Up Visits (Weeks 26, 39, 52, 65, 78, 91, and 104; +/- *2 weeks)*

At each extended follow-up visit the following procedures will be performed:

1. AEs and concomitant medications will be recorded.

2. Laboratory samples will be collected for:
    - Hematology, chemistry, cystatin C
    - Urinalysis
    - Urinary 24-hour protein
    - Urine for inflammatory biomarkers
    - Serum ADA sample
3. Subjects will be provided with supplies to collect 24-hour urine samples in the week prior to next Follow-Up Visit. The investigative site will call the subject one week prior to the next follow-up visit to remind the subject to collect the 24-hour urine sample. Subjects will not be provided with collection supplies at the last Follow-Up Visit.

Cohort 3 subjects who have 24-hour urine protein > 1000 mg anytime between weeks 18-91 or 24-hour urine protein ≥ 50% of baseline during the follow-up period may elect, with the agreement of the Investigator, to receive open-label OMS721 370 mg IV for 12 weeks. Additional 12-week OMS721 treatment courses may be administered as often as subjects have 24-hour urine protein > 1000 mg or 24-hour urine protein ≥ 50% of baseline during weeks 18-91. The visit schedule for each series of additional OMS721 treatment is provided below. If a subject receives re-treatment, the subject's re-treatment visit schedule will be followed until the re-treatment follow-up is completed (see below for re-treatment schedule). At that time, the subject's next visit will be at the first regularly scheduled follow-up visit following the initial OMS721 treatment course.

### 10.1.12. Cohort 3 Re-Treatment Visit 1 RT1 (*+/- 2 days*)

Prior to re-treatment visit 1, subject eligibility for re-treatment must be confirmed. OMS721 will be administered to all subjects undergoing re-treatment.

Prior to administering the dose of study drug the following procedures will be performed:

1. Review of AEs and concomitant medications.
2. Vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest).
3. ECG taken (after at least 5 minutes of rest in the supine position)
4. Laboratory samples will be collected for:
    - Hematology, chemistry, coagulation, cystatin C
    - Urinalysis
    - Urine for inflammatory biomarkers
    - Serum or urine pregnancy test in women of childbearing potential. If the test result is positive then the subject will be excluded from further treatment, but continue follow-up
    - Blood samples for future research
    - Serum PK sample

- Serum PD sample
- Serum ADA sample

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoints: 30 minutes, 1 hour.
2. ECG taken (after at least 5 minutes of rest in the supine position), to be obtained immediately post dose).
3. Serum PK samples at the following timepoints after end of dosing: 5 minutes, 2 hours, and 24 hours (**Day 2**), 72 hours (**Day 4**).
4. Serum PD sample after the end of dosing: 2 hours.
5. The subject may be discharged after arrangements are made for the collection of PK samples on **Days 2 and 4**.

### 10.1.13. Cohort 3 Re-Treatment Visits RT2 – RT12 (*+/- 2 days*)

Study drug will be administered once per week for a total of 12 weekly doses during the study. The following procedures will be performed:

Prior to administering the dose of study drug, the following procedures will be performed:

1. Vital signs including BP, pulse rate, RR and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications will be recorded.
3. ECG taken (after at least 5 minutes of rest in the supine position) (re-treatment visit 12 only).
4. Laboratory samples will be collected for:
    - Hematology, chemistry, coagulation, cystatin C (re-treatment visit 2, re-treatment visit 5, and re-treatment visit 9)
    - Urinalysis (re-treatment visit 2 and re-treatment visit 9)
    - Urine for inflammatory biomarkers (re-treatment visit 2 and re-treatment visit 9)
    - Blood samples for future research (re-treatment visit 2, re-treatment visit 5, and re-treatment visit 9)
    - Serum PK sample (re-treatment visit 2, re-treatment visit 5, re-treatment visit 9, and re-treatment visit 12)
    - Serum PD sample (re-treatment visit 2, re-treatment visit 5, re-treatment visit 9, and re-treatment visit 12)
    - Serum ADA sample (re-treatment visit 5 and re-treatment visit 9)

- Serum or urine pregnancy test in women of childbearing potential. If the test result is positive then the subject will be excluded from further treatment, but continue follow-up (re-treatment visit 5 and re-treatment visit 9)

Study drug will be administered by IV infusion over 30 minutes.

After dosing with study drug, the following procedures will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest) at the following timepoint: 30 minutes.
2. ECG taken (after at least 5 minutes of rest in the supine position), to be obtained immediately post dose (re-treatment visit 12 only).
3. Serum PK samples will be taken at the following timepoints at the end of dosing: 5 minutes and 2 hours (re-treatment visit 12 only)
4. Serum PD samples will be taken at the following timepoints at the end of dosing: 2 hours (re-treatment visit 12 only)
5. At Re-Treatment Visits 4, 8, and 12, provide subjects with supplies to collect first void urine samples for urine albumin/creatinine and protein/creatinine ratios on three mornings prior to Re-Treatment Visits 5, 9, and Re-Treatment Follow-Up Visit.

### 10.1.14. Cohort 3 Re-Treatment Follow-Up Visit RTFU(*+/- 3 days*)

One week after the last dose of study drug, the following procedures and assessments will be performed:

1. Vital signs will be taken including BP, pulse rate, RR, and temperature (after at least 5 minutes of rest).
2. AEs and concomitant medications, including corticosteroid dose (if applicable) will be recorded.
3. Laboratory samples will be collected for:
   - Hematology, chemistry, coagulation, cystatin C
   - Blood samples for future research
   - Urinalysis
   - Urine for inflammatory biomarkers
   - Serum or urine pregnancy test in women of childbearing potential. If the test result is positive then the subject will be followed for outcome of the pregnancy
   - Serum PK samples
   - Serum PD sample
   - Serum ADA sample
4. For three days prior to Re-Treatment Follow-Up Visit, three once daily first void urine samples for urine albumin/creatinine ratios will be collected and brought for analysis at this visit.

5. A 24-hour urine collection for urine protein will be initiated and appropriate supplies will be provided. The subject will be instructed to perform the urine collection and return the urine to the site within 3 days of collection to prevent degradation of the sample.

### 10.1.15. Early Withdrawal from the Study

All subjects will be encouraged to complete all evaluations. However, subjects who prematurely discontinue the study will have the assessments for Follow-Up Visit 1 (or Re-Treatment Follow-up Visit 1, if applicable) performed, and will be followed for 30 days if there is a serious adverse event (SAE), if possible.

### 10.1.16. Unscheduled Visits

Unscheduled visits and assessments for subject safety should be documented and recorded.

### 10.1.17. Timing of Study Procedures

Procedures with a specified time frame will be considered per protocol if they are performed within the following windows: vital signs on dosing days ± 5 minutes in the first hour of start of dosing and ± 10 minutes thereafter; PK and PD draws on the day of dosing ± 5 minute; PK draws Days 2 and 4 ± 2 hours. If multiple procedures are specified at one timepoint they should be performed in the following order: blood draw and then vital signs, with the blood draw at the exact specified time.

### 10.1.18. Timing of Study Visits

All Treatment Visits will be within ± 2 days of the scheduled day. All Follow-Up Visits will be within ± 3 days of the scheduled day. Cohort 3 Extended Follow-up Visits 4-10 will be within ± 2 weeks. If study drug cannot be administered within the visit window ± 2 days, the Investigator should contact the Sponsor Medical Monitor to discuss the course of action and disposition of the subject.

## 10.2. Concomitant Therapy

Belimumab, eculizumab, and rituximab are not to be used during the study. For subjects in Cohort 2 and Cohort 3, treatment with corticosteroids is prohibited during the study except inhaled corticosteroids and short-term use of corticosteroids that are not being used for the management of IgAN. All other medications for the health and well-being of the subject are permitted and are to be recorded.

## 10.3. Treatment Compliance

The study drug is to be administered by study personnel. Administration dates and times must be recorded in the CRFs. If any portion of a dose of study drug is not administered, an explanation must be provided in the source document and on the CRF.

### 10.3.1. Definition of Departures from Protocol

The following definitions will apply to the reporting of emergency and non-emergency departures from the protocol:

**Protocol Deviation:** Any non-adherence to study procedures or schedules, as specified by the protocol.

# 11. ASSESSMENT OF EFFICACY

## 11.1. Efficacy Measures

- Change from baseline in proteinuria assessed by 24-hour urine protein excretion
- Change from baseline in urine albumin/creatinine ratio by disease
- Corticosteroid dose required to maintain stable renal function by disease in Cohort 1 subjects
- Change from baseline in serum creatinine by disease
- Change from baseline in eGFR calculated using the following equations by disease state: MDRD equation, CKD-EPI using serum creatinine, CKD-EPI using cystatin C, and CKD-EPI using creatinine – cystatin C
- Urine protein/creatinine ratio change from baseline by disease
- Urine inflammatory markers by disease
- Duration of therapeutic response, if observed, defined as the number of consecutive weeks that 24-hour urine protein < 50% of baseline for up to 104 weeks (Cohort 3 only)

## 11.2. Pharmacokinetic/Pharmacodynamic/Immunogenicity Measures

- OMS721 PK
- OMS721 PD
- Analysis of ADA. Sample collection and processing procedures will be provided in the study laboratory manual
- Serial blood samples will be collected according to the Schedule of Events (Section 19) for future research, which may include analyses of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), protein, or cells. The samples are collected in the event that emerging data from this study or published data from other research suggest that specific analyses may be informative with respect to prognosis, pharmacological response, clinical response, or toxicities

# 12. ASSESSMENT OF SAFETY

Investigators are responsible for monitoring the safety of subjects who have entered this study and for alerting the Sponsor to any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The Investigator is responsible for appropriate medical care of subjects during the study.

## 12.1. Safety Parameters

Safety will be evaluated by assessing AEs, clinical laboratory tests, vital signs, and ECG. Only clinically significant (per Investigator opinion) changes in vital signs or laboratory tests accompanied by clinical symptoms or those that require medical intervention will be reported as AEs.

### 12.1.1. Laboratory Tests

For evaluation of safety laboratory assessments, a central or local laboratory will be used for all of the sites. The name and address of the clinical laboratory are included in the Investigator file.

The following laboratory assessments will be performed in this study:

- Chemistry tests include glucose, urea nitrogen, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, calcium, sodium, potassium, chloride, and bicarbonate
- Hematology tests include white blood cell count with automated differential (neutrophils, segmented neutrophils, lymphocytes, monocytes, eosinophils and basophils), red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, and platelet count
- Coagulation tests include prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR)
- Pregnancy test (serum and urine)
- Urinalysis tests include color, specific gravity, pH, glucose, protein, bilirubin, urobilinogen, blood, ketone, nitrite, leukocyte esterase and microscopic if required (red blood cells, white blood cells and bacteria)

### 12.1.2. Other Safety Measures

- Vital signs include temperature, pulse rate, systolic and diastolic BP, and RR
- ECG parameters include pulse rate, PR interval, QRS interval, QT interval, and QTc interval calculated by Fridericia's formula (QTcF), along with a clinical interpretation by the Investigator

## 12.2. Definition of Adverse Events

### 12.2.1. Definition of Adverse Events

The following definitions from the International Conference on Harmonisation (ICH) Guideline E2A will apply to the reporting of AEs and adverse drug reactions (ADR):

**Adverse Event:** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

**Adverse Drug Reaction:** All noxious and unintended responses to a medicinal product related to any dose.

**Unexpected Adverse Drug Reaction:** An adverse drug reaction, the nature or severity of which is not consistent with the IB.

**Serious Adverse Event:** Any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
  - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

Serious adverse events also include important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### 12.2.2. Definitions of Severity

AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0.

Note that "seriousness" and "severity" are distinct concepts. "Serious" is a term applied to an AE that meets specific requirements (refer to Section 12.2.1). "Severity" refers to the AE intensity classification.

### 12.2.3. Relationship to Study Drug

The Investigator (a study physician) will determine the assessment of the causal relationship of the AE to the study drug.

The relationship of AEs to study drug is categorized as probable, possible, unlikely, or not related. An alternative etiology must be provided for all AEs for which the relationship to study drug is considered "possible," "unlikely," or "not related."

Definitions of each of these terms are below:

**Probable:** The AE has a timely relationship to administration of the study drug and there is no apparent, potential alternate etiology.

**Possible:** The AE has a timely relationship to administration of the study drug and there is an apparent, potential alternate etiology.

**Unlikely:** The AE is likely related to an etiology other than administration of study drug.

**Not Related:** The AE is related to an etiology other than the study drug.

An AE with causal relationship not initially determined will require follow-up to assign causality.

### 12.2.4. Assessment of the Clinical Outcome of Adverse Events

The Investigator (a study physician) will determine the clinical outcome of the AE as follows:

**Recovered Completely:** The subject has fully recovered from the event with no residual effects observable.

**Recovered with Sequelae:** Effects of the event are constant. The likelihood of these effects changing (improving or worsening) is low.

**Not Yet Recovered:** Effects of the event are still present and changing. The event is not considered recovered completely or recovered with sequelae.

**Unknown; Lost to Follow-up:** Not known, not observed, not recorded, or refused to provide information.

**Died:** The event was the primary cause or not the primary cause of death (may or may not be the immediate cause of death).

## 12.3. Reporting Adverse Events

### 12.3.1. Adverse Event Reporting

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. AEs may be reported by the subject, discovered by the Investigator and Investigator's staff, or detected through physical examination, laboratory test, or other means.

AEs include:

- Any unfavorable and unintended sign, medical diagnosis, or symptom that occurs between the time the first administration of study drug and the study duration required by the protocol

- Any new undesirable medical experience or an unfavorable and unintended change of an existing condition that occurs between the time the first administration of study drug and the study duration required by the protocol, whether or not considered related to study drug
- Abnormal laboratory findings considered by the Investigator to be clinically significant, i.e., those that are unusual for the population being studied or individual subject

Whenever possible, the Investigator should group signs or symptoms that constitute a single diagnosis into a single event term. For example, cough, rhinitis, and sneezing might be grouped together as *upper respiratory tract infection*.

In cases where the Investigator notices an unanticipated benefit to the subject, study site personnel should enter *unanticipated benefit* with the actual event term (for example, the complete actual term would be *unanticipated benefit-sleeping longer*).

AEs will be collected from the time informed consent is obtained until the last Follow-Up visit. All AEs will be documented in the source records and will be recorded in the CRFs as appropriate. All AEs, whether observed by the Investigator or reported by the subject, and whether or not thought to be related to the study drug, will be recorded on the appropriate CRF. In describing AEs on the CRF, standard, medically accepted terminology will be used.

The description of each AE will identify the date of onset, duration, severity (see Section 12.2.2 for Definitions of Severity), any action taken (including any diagnostic procedures or laboratory tests performed and all treatments which were administered), the outcome of the event, and relationship to the study drug.

Any medical condition that is present at the time that the subject is screened should be considered as baseline and not recorded as an AE. However, if the medical condition increases in frequency or severity during or following administration of the study drug, it will be recorded as an AE on the appropriate CRF.

### 12.3.2. Serious Adverse Event Reporting

All SAEs will be:

- Recorded on the appropriate SAE form
- Followed through resolution or stability by the Investigator
- Reviewed by the Investigator

The investigative site is required to report any SAE directly to the Sponsor's pharmacovigilance designee on the SAE form within 24 hours of becoming aware of the event, whether or not the SAE is deemed drug-related (see Section 1.2 for contact information).

The Investigator will complete an Expedited or Serious Adverse Event Form within the following timelines:

- All deaths and immediately life threatening events, whether related or unrelated, will be recorded on the Expedited or Serious Adverse Event Form and faxed/electronically communicated within 24 hours of site awareness

- Serious adverse events other than death and immediately life threatening events, that meet expedited reporting criteria, regardless of relationship, will be recorded on the SAE form and faxed/electronically communicated by the site within 72 hours of becoming aware of the event

Other supporting documentation of the event may be requested by the pharmacovigilance contractor and should be provided as soon as possible.

A distinction is drawn between serious and severe events. A severe event is a major experience of its type. A severe event does not necessarily need to be serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke, but it would be considered an SAE.

Death is an outcome of an event and not an event per se (sudden death or death of unexplainable causes can be reported, but follow-up will be required until cause of death is determined).

### 12.3.3. Reporting of Serious Adverse Events to Regulatory Agencies

The Sponsor or Sponsor's designee will submit the SAEs requiring expedited reporting to regulatory agencies. The IRB/IEC will be notified of SAEs in accordance with federal, national and local laws and regulations.

### 12.3.4. Pregnancy and Overdose Reporting

Cases of pregnancy must be reported for tracking purposes. If a subject becomes pregnant during the study, the Sponsor's Pharmacovigilance designee must be notified by fax or email within 24 hours of site awareness and the subject discontinued from study drug. Additional instructions for reporting of the pregnancy and outcome will be provided by the Sponsor at the time of notification. Pregnancies of partners of male subjects will also be followed provided the subject's partner provides informed consent for follow-up of the pregnancy.

Occurrences of overdose should be reported to the Sponsor for tracking purposes. Overdose is defined as any dosing above the protocol-defined dosing instructions. Additional instructions for reporting overdose information will be provided by Omeros at the time of notification.

## 12.4. Type and Duration of the Follow-Up of Subjects After Adverse Events

All reportable AEs will be followed until satisfactory resolution or until the Investigator deems the event to be chronic or the subject to be stable.

If an SAE persists at the last study visit or the time of early termination after study treatment, it will be marked as "ongoing" and "not yet recovered" in the CRF and will be followed by the Investigator until such time that it is deemed to be resolved or at a stable condition. Follow-up data for such SAEs will be collected in the source documents and reported appropriately.

# 13. STATISTICS

## 13.1. Determination of Sample Size

The primary objective of the study is to assess safety and tolerability of OMS721. The sample size has been empirically determined. The study is not powered for statistical comparisons. Descriptive data summaries will be provided.

This is an exploratory study and the Cohort 1 sample size is considered clinically relevant to explore the effect of OMS721 in steroid-dependent IgAN, lupus nephritis, primary MN, and C3 glomerulopathy including dense deposit disease.

The sample size for Cohort 2 (subjects with IgA nephropathy who are not receiving corticosteroids) is considered clinically relevant to explore the effect of OMS721 in this population.

The sample size for Cohort 3 (subjects with IgA nephropathy who are not receiving corticosteroids) is considered clinically relevant to explore the duration of therapeutic response and the effect of additional courses of OMS721 treatment. The sample size for the Asian population residing in Asia in Cohort 3 is considered clinically relevant to explore the effect of OMS721 in this population.

## 13.2. Statistical and Analytical Methods

The statistical and analytical methods are summarized in this section. A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. Any changes to the statistical methods will be described in the clinical study report.

### 13.2.1. General Considerations

All data summaries will be descriptive in nature and summaries will be by disease and cohort, additionally safety information will be summarized overall for all subjects. Summary statistics for continuous variables will include number of subjects, mean, median, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be provided. When required for the statistical analysis of a particular variable, the baseline value will be the last recorded value prior to the administration of the first dose of study treatment. The exception is the urine albumin/creatinine and protein/creatinine ratios (Section 13.2.5).

Statistical analyses will group subjects according to their assigned cohort, except for the rollover subjects who will constitute their own cohort.

#### 13.2.1.1. Handling of Missing Data

Analyses will be based on observed data without imputation.

#### 13.2.1.2. Analysis Populations

The safety population includes all subjects who receive any amount of study drug.

The efficacy population includes all subjects who receive any amount of study drug, and have a baseline and at least one post-baseline 24-hour urine protein.

### 13.2.2. Subject Disposition

An accounting of study subjects by disposition will be tabulated by disease and cohort. Subjects who discontinue study drug prematurely or withdraw from the study will be summarized and listed, with reason for early termination/withdrawal.

### 13.2.3. Subject Characteristics

Demographic and other baseline characteristics and concomitant medications will be listed. Demographics and disease characteristics will be summarized by disease and cohort.

### 13.2.4. Treatment Compliance

Because all dosing will be under direct supervision of study personnel, treatment compliance will not be analyzed. Dosing information will be listed.

### 13.2.5. Efficacy Analyses

The analysis values for urine albumin/creatinine ratio and urine protein/creatinine ratio are defined as the average of all the values obtained for a timepoint. The planned number of these tests is three of each at each scheduled timepoint. The baseline value for each of these tests is defined as the average of the analysis values at the two screening visits.

Change from baseline in the 24-hour urine protein, average urine albumin/creatinine ratio and average urine protein/creatinine ratio at each visit will be summarized descriptively by disease and cohort. Ninety-five percent confidence intervals for the mean change in 24-hour urine protein, urine albumin/creatinine ratio and protein/creatinine ratio at each scheduled visit will be provided using t-distribution. In addition, change from baseline in the natural log transformed average for each of these tests will be summarized in the same fashion.

eGFR will be calculated using the following equations from baseline to each scheduled visit by disease and cohort: MDRD equation, CKD-EPI using serum creatinine, CKD-EPI using cystatin C, and CKD-EPI using creatinine – cystatin C.

Change from baseline to each scheduled visit in corticosteroid dose in Cohort 1, based on milligrams of prednisone (or equivalent dose), will be summarized for each disease group as applicable.

Change in serum creatinine from baseline to each scheduled visit will be summarized for each disease and cohort.

All efficacy endpoints will be descriptively summarized by visit, disease and cohort.

### 13.2.6. Pharmacokinetic Analyses

PK parameters for OMS721 will be calculated according to a pharmacokinetic analysis plan.

### 13.2.7. Pharmacodynamic Analyses

The extent of *ex vivo* lectin pathway activation will be calculated relative to the subject's baseline (pre-dose) result. The lectin pathway activity of post-dose samples is expressed as % inhibition relative to baseline. The lectin pathway activity will be summarized by disease, cohort, and time.

### 13.2.8. Pharmacokinetic-Pharmacodynamic Analyses

OMS721 concentration and lectin pathway activity will be plotted to explore their relationship.

### 13.2.9. Immunogenicity Analyses

The presence of ADA and the presence of NAb will be summarized by disease, cohort, and time.

### 13.2.10. Safety Analyses

#### 13.2.10.1. Extent of Exposure

Study drug administration and duration of treatment will be summarized and listed by disease, cohort, and overall.

#### 13.2.10.2. Adverse Events

The incidence of all reported AEs and treatment-related AEs will be tabulated by disease, cohort, and overall. AEs will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. A treatment-emergent AE (TEAE) is defined as an event that first occurs or worsens in intensity after the administration of study drug.

An overview of TEAEs, TEAEs related to study procedures, SAEs, deaths, and TEAEs leading to discontinuation of study drug and withdrawal from the study will be presented by system organ class, preferred term, disease and cohort.

AEs judged to be related to protocol procedures or study conduct by the Investigator will be listed.

#### 13.2.10.3. Serious Adverse Events

SAEs will be listed and summarized in the same manner as all AEs. Events with a fatal outcome will be listed.

#### 13.2.10.4. Clinical Laboratory Results

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by scheduled visit, disease and cohort. Subjects with laboratory

values outside of the normal reference range at any post-baseline safety assessment will be listed by visit, disease and cohort.

Shifts from baseline laboratory values (normal/abnormal) will be tabulated by disease and cohort.

#### 13.2.10.5. Vital Signs

Summary statistics for actual values and change from baseline will be tabulated for vital signs by disease, cohort and scheduled visit.

### 13.2.11. Electrocardiogram

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and QTcF interval) at each time recorded as well as the change from baseline will be summarized with descriptive statistics by disease, cohort and visit. These parameters will be determined electronically by the ECG machine at the clinical site. QTcF will be calculated using Fridericia's formula.

The overall ECG assessment will be reported as "Normal," or "Abnormal – not clinically significant," or "Abnormal – clinically significant" with respect to relevant abnormalities by the Investigator. A shift table comparing the ECG assessment over the treatment period to baseline will be presented by disease and cohort.

# 14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The Investigator will maintain appropriate medical and research records for this study in accordance with the ethics committee (EC), regulatory, and ICH requirements for the protection of confidentiality of subjects. The Investigator and his/her study center(s) will permit authorized representatives of the Sponsor, the governing EC, competent authority, FDA, EMA, and/or other regulatory agencies to examine clinical records for the purposes of monitoring the study, including verifying the accuracy and completeness of data, evaluating study safety, assessing protocol and regulatory adherence, and quality assurance reviews, audits, and inspections.

## 14.1. Study Monitoring

The Investigator and his/her study center(s) agree to allow the Sponsor or the Sponsor's designees to have direct access to the source data/documents (as noted above) during the monitoring visits. The monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of CRFs, to resolve any inconsistencies in the study records, as well as assuring that all protocol requirements, applicable regulations, and Investigator's obligations are being fulfilled.

The study monitor will record the date of each visit together with a summary of the status and progress of the study. Proposed actions will be confirmed with the Investigator.

## 14.2. Audits and Inspections

The study center will allow representatives of Omeros to periodically audit, at mutually convenient times, during and after the study all CRFs and corresponding source documents for each subject. CRFs will be reviewed by the Sponsor or the Sponsor's designees for adherence to protocol, completeness, and acceptability. Portions of the subject's medical and hospital records pertinent to the study will be reviewed at the study center to assure accuracy. It is important that the Investigator and/or other staff are available at these visits. If contacted by a regulatory agency for an inspection, please call the Sponsor's study monitor immediately. Contact information for the Sponsor's study monitor is included in the investigator study file.

# 15. QUALITY CONTROL AND QUALITY ASSURANCE

Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Data management will implement quality control procedures and generate data quality checks. Any missing data or data anomalies will be communicated to the site(s) or other involved party (e.g., laboratory) for clarification/resolution. The site will be obligated to resolve the finding in a timely manner. Data cleaning and quality control measures are outlined in the Data Management Plan for the study.

## 15.1. Monitoring

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- Provide instructional material to the study sites, as appropriate
- Provide start-up training and continuing training (if applicable) to the Investigators and study personnel on the protocol, the completion of the CRFs, and study procedures
- Make periodic monitoring visits to the investigational site
- Be available for consultation and stay in contact with the investigational site personnel by mail, telephone, electronic mail, and/or fax
- Monitor the subject data recorded in the CRF against source documents at the investigational site
- Review and evaluate CRF data and use standard computer criteria to detect anomalies in data collection, which will be forwarded to the Investigator for resolution

## 15.2. Auditing

The study may be audited by the Sponsor or its representatives at any time.

# 16. ETHICS

## 16.1. Ethics Review

Each participating institution must provide for the review and approval of this protocol, the associated informed consent documents, and any patient-directed materials by a properly constituted IEC or IRB. Any amendments to the protocol, consent, or patient-directed materials must also be approved prior to implementation. The Investigator will provide Omeros or its designee with documentation of the IRB/IEC approval of the protocol, informed consent document, and patient-directed materials before the study may begin at the investigative site(s).

In addition, the Investigator or designee will submit for review to the investigative site's IRB/IEC:

- Clinical IB and updates
- Required safety and SAE reports
- Deviations from the protocol and applicable FDA regulations (as required by the IRB/IEC)
- Any additional submissions (e.g., continuing review reports or new information) required by the site's IRB/IEC

The IRB/IEC will provide initial and continuing review. The continuing review will be performed at least once per year.

The Investigator or designee must provide the Sponsor or its designee all IRB/IEC related submission decisions, approvals, and/or acknowledgement of receipts, as appropriate.

## 16.2. Ethical Conduct of the Study

### 16.2.1. Regulatory Considerations

This study will be conducted in compliance with the ICH Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance (1996), GCP, Health Insurance Portability and Accountability Act (HIPAA), 21 CFR Part 11, and any additional national, state, and local rules and regulations.

After reading the protocol, the Investigator will sign the Investigator Agreement and return it to Omeros or its designee.

### 16.2.2. Investigator Information

The contact information and qualifications of the Principal Investigator and Sub-Investigators and name and address of the research facilities are included in the investigator file.

### 16.2.3. Protocol Amendments and Study Termination

Any Investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by Omeros prior to seeking approval from the IRB/IEC, and prior to implementing. The Investigator is responsible for enrolling

subjects who have met protocol eligibility criteria. Protocol violations must be reported to Omeros and to the local IRB/IEC in accordance with IRB/IEC policies.

The Sponsor may terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

### 16.2.4. Participant Confidentiality

All reports and communications relating to subjects in the study will identify each subject only by the subject's initials and/or subject number.

### 16.2.5. Clinical Trial Agreement

Payments by the Sponsor or its designee to Investigators and institutions conducting the trial, requirements for Investigators' insurance, the publication policy for clinical trial data, and other requirements are specified in the Clinical Trial Agreement.

## 16.3. Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continuing throughout the individual's study participation. Any procedures specifically for the study cannot be started until the informed consent form is signed by the subject and the person conducting the consent. Discussion of risks and possible benefits of this therapy will be provided to the subjects. Consent forms describing in detail the study agent(s)/intervention(s), study procedures and risks are given to the subject and written documentation of informed consent is required prior to starting the study agent/intervention. Consent forms will be IRB/IEC approved and the subject will be asked to read and review the document. Upon reviewing the document, the Investigator will explain the research study to the subject and answer any questions that may arise. The subjects should have sufficient opportunity to discuss the study and process the information in the consent process prior to agreeing to participate. The subjects may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

In addition, subjects will provide written permission for use and disclosure of protected health information collected in connection with participation in this study through an authorization that satisfies the HIPAA Privacy Rule (see 45 CFR 164.508). The authorization will be provided to subjects in accordance with IRB/IEC procedures. The authorization may either be combined with the informed consent or provided as a separate document.

## 16.4. Investigator Reports

During the conduct of the study and at its completion, the Investigator will report to the IRB/IEC as required by the applicable IRB/IEC requirement and regulations. In addition, the Investigator will report to the Sponsor in accordance with regulation 21 CFR 312.64.

# 17. DATA HANDLING AND RECORDKEEPING

## 17.1. Data Management Responsibilities

All source documents and laboratory reports must be reviewed by the Investigator's site staff to ensure that documents are accurate and complete. AEs must be graded, assessed for severity and causality and reviewed by the Investigator or designee.

Data collection is the responsibility of the clinical study staff at the site under the supervision of the Investigator. During the study, the Investigator must maintain complete and accurate documentation for the study.

## 17.2. Data Capture Methods

Case Report Forms are used to transmit the information collected in the performance of this study to Omeros and FDA. Data will be collected using the Medidata Rave EDC system. Data are captured electronically and stored by the vendor during the study. At the end of the study, the Investigator will be provided with an electronic file of all of the CRFs for their subjects.

The Investigator and study personnel will ensure that proper data for the clinical study are collected and accurately documented in the appropriate sections of the CRFs. The Investigator will review each CRF for completeness and accuracy and sign and date the CRFs, where indicated. In addition, it will be the Investigator's responsibility to provide signatures where requested indicating concurrence with data in the CRF.

CRFs will be reviewed by monitors from Omeros or its representative for adherence to protocol, completeness, and acceptability. Portions of the subject's medical and hospital records pertinent to the study will be reviewed at the study center to assure accuracy.

## 17.3. Source Documents

Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP, regulatory, and institutional requirements for the protection of confidentiality of participants.

Source data are all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Examples of these original documents and data records include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and participant files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. FDA regulations require that the Investigator prepares and maintains adequate and accurate records for each subject treated with study drug.

## 17.4. Retention of Records

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the Investigator until notified by the Sponsor in writing that retention is no longer necessary.

CRFs are used to transmit the information collected in the performance of this study to Omeros and regulatory agencies. For paper studies, the original CRFs will be retained by the Sponsor, and the Investigator will retain copies of the CRFs with the other records for this study. The Investigator will be provided with an electronic file of all of the CRFs for their subjects after the database has been locked.

The Sponsor will archive the EDC data, including associated queries and audit trail.

FDA regulations require that the Investigator prepares and maintains adequate and accurate records for each subject treated with study drug. Source documents such as hospital, clinic or office charts, laboratory reports, ECGs, operative reports, anesthesia records, consultation reports, history and physical examination reports, study worksheets, and the signed informed consent will be included in the Investigator's files with the subject's study records.

Records containing subject medical information must be handled in accordance with the requirements of the HIPAA Privacy Rule (US) or applicable privacy regulations in the relevant countries and consistent with the terms of the subject authorization contained in the informed consent document for the study (the authorization). Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the authorization. Furthermore, documents to be transferred to the Sponsor should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of subject identities.

No study document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

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Full-text references are available upon request.

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# 19. APPENDICES

## 19.1. MDRD Equation

MDRD Equation when calculating creatinine clearance if the lab uses an Isotope-Dilution Mass Spectrometry (IDMS) method for serum creatinine determination:

eGFR (mL/min/1.73 m2) = $175 \times (SCr)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times (1.212$ if African American)

Note: SCr = Serum Creatinine measurement should be mg/dL.

## 19.2. Study Schedule of Events – Cohorts 1, 2, and 3 First 12 Week Treatment Period

| Period | Screening | | Treatment (12 Weeks) | | | | | | | | | | | Follow-Up (6 Weeks) | | Cohort 3 Extended Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | SCR 1 | SCR 2 | T1 | | | T2, T3 | T4 | T5 | T6, T7 | T8 | T9 | T10, T11 | T12 | FU 1 | FU 2 | FU 3-FU 9 |
| Day | -28 | -14 | 1 | 2 | 4 | 8,15 | 22 | 29 | 36, 43 | 50 | 57 | 64,71 | 78 | 85 | 120 | 176, 267, 358, 449, 540, 631, 722 |
| | | (+/- 7) | | | | (+/- 2) | | | | | | | | (+/- 3) | | (+/- 14) |
| Week | -4 | -1 | 1 | | | 2-3 | 4 | 5 | 6-7 | 8 | 9 | 10-11 | 12 | 13 | 18 | 26,39,52,65,78, 91,104 |
| Informed Consent, Medical History, & Physical Examination | X | | | | | | | | | | | | | | | |
| Review of Inclusion/Exclusion Criteria | X | X | X | | | | | | | | | | | | | |
| Randomization (where applicable) | | | X | | | | | | | | | | | | | |
| Assessment of renal function and tapering of corticosteroid dose (where applicable) | | | | | | | | X | X | X | | | | | | |
| Vital Signs | X | X | | | | | | | | | | | | X | X | |
| Vital Signs pre-dose | | | X | | | X | X | X | X | X | X | X | X | | | |
| Vital Signs post dose: 30 min | | | X | | | X | X | X | X | X | X | X | X | | | |
| Vital Signs post dose: 1 hr | | | X | | | | | | | | | | | | | |
| ECG | X | | | | | | | | | | | | | | | |
| ECG pre-dose | | | X | | | | | | | | | | X | | | |
| ECG post dose | | | X[7] | | | | | | | | | | X | | | |
| Dispense urine collection kit[1] | X | X | | | | | X | | | X | | | X | X | | |
| Collect Urine Samples from urine collection kit[2] | | X | X | | | | | X | | | X | | | X | X | |
| Dispense supplies for 24-hour Urine protein collection[1] | X | | | | | | | | | | | | | X | | X |
| Collect 24-hour Urine protein samples | | X | | | | | | | | | | | | | X | |
| Urine for inflammatory biomarkers | X | | | | | | X | | | | | | | X | | X |
| Urinalysis [3] | X | | X | | | X | X | | | X | | | | X | | X |
| Blood Sample Collection: Chemistry, Hematology, Coagulation, Cystatin C[4,] | X | | X | | | X | X | | | X | | | | X | X | X |

| Period | Screening | | Treatment (12 Weeks) | | | | | | | | | | | Follow-Up (6 Weeks) | | Cohort 3 Extended Follow Up |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Visit | SCR 1 | SCR 2 | T1 | | | T2, T3 | T4 | T5 | T6, T7 | T8 | T9 | T10, T11 | T12 | FU 1 | FU 2 | FU 3-FU 9 |
| Day | -28 | -14 | 1 | 2 | 4 | 8,15 | 22 | 29 | 36, 43 | 50 | 57 | 64,71 | 78 | 85 | 120 | 176, 267, 358, 449, 540, 631, 722 |
| | | (+/- 7) | | | | (+/- 2) | | | | | | | | (+/- 3) | | (+/- 14) |
| Week | -4 | -1 | 1 | | | 2-3 | 4 | 5 | 6-7 | 8 | 9 | 10-11 | 12 | 13 | 18 | 26,39,52,65,78, 91,104 |
| Anti- PLA2R[5] | X | | | | | | | | | | | | | | | |
| Calculation of eGFR using the MDRD formula | | X | | | | | | | | | | | | | | |
| Serology for HIV, hepatitis B and hepatitis C | X | | | | | | | | | | | | | | | |
| Pregnancy Test – females of child bearing potential[6] | X | | X | | | | | X | | | X | | | X | | |
| Study Drug Administration | | | X | | | X | X | X | X | X | X | X | X | | | |
| Research Sampling | | | X | | | X | X | | | X | | | | | | |
| PK Sampling | | | | | | | | | | | | | | X | X | |
| PK Sampling pre-dose | | | X | | | X | X | X | X | X | X | X | X | | | |
| PK Sampling post dose: 5 minutes and 2 hours | | | X | | | | | | | | | | | | | |
| PK Sampling post dose: 30 min | | | | | | X | | X | | | X | | X | | | |
| PK Sampling post dose: 24 hours | | | | X | | | | | | | | | | | | |
| PK Sampling post dose: 72 hours | | | | | X | | | | | | | | | | | |
| PD Sampling | | | | | | | | | | | | | | X | X | |
| PD Sampling pre-dose | | | X | | | X | X | X | X | X | X | X | X | | | |
| PD Sampling post dose: 30 min | | | | | | X | | X | | | X | | X | | | |
| PD Sampling post dose: 2 hours | | | X | | | | | | | | | | | | | |
| ADA Sampling | | | | | | | | | | | | | | X | X | X |
| ADA Sampling pre dose | | | X | | | | | X | | | X | | | | | |
| Adverse Events | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/therapies | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

SCR = screening; ECG = electrocardiogram; HIV = human immunodeficiency virus; PD = pharmacodynamics; PK = pharmacokinetics; ADA = anti-drug antibody; NAb = Neutralizing antibody

1. Instruct the subject on how to collect and provide supplies.
2. Collect first void urine on each of three mornings, 1st void urine samples.
3. Urinalysis tests include color, specific gravity, pH, glucose, protein, bilirubin, urobilinogen, blood, ketone, nitrite, leukocyte esterase and microscopic if required (red blood cells, white blood cells and bacteria).
4. The following laboratory assessments will be performed in this study:
    - Chemistry tests include glucose, urea nitrogen, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, ALT, AST, calcium, sodium, potassium, chloride, and bicarbonate
    - Hematology tests include white blood cell count with automated differential (neutrophils, segmented neutrophils, lymphocytes, monocytes, eosinophils and basophils), red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, red cell distribution width, and platelet count
    - Coagulation tests include PT, PTT and INR
5. Anti-PLA2R is only to be performed for subjects with membranous nephropathy.
6. Pregnancy test must be via serum for Screening Visit 1. May be urine or serum for all other visits.
7. ECG collected post-dose before 5-minute PK sample.

Note: Procedures with a specified time frame will be considered per protocol if they are performed within the following windows: vital signs on dosing days ± 5 minutes in the first hour of start of dosing and ±10 minutes thereafter; PK and PD draws on the day of dosing ± 5 minute; PK draws Days 2 and 4 ± 2 hours. If multiple procedures are specified at one timepoint they should be performed in the following order: blood draw and then vital signs, with the blood draw at the exact specified time.

## 19.3. Study Schedule of Events – Cohort 3 Re-Treatment

| **Period** | **Treatment (12 Weeks)** | | | | | | | | | | | **Follow-Up (1 Week)** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit** | RT1 | | | RT2, RT3 | RT4 | RT5 | RT6, RT7 | RT8 | RT9 | RT10, RT11 | RT12 | RT FU |
| **Day** | 1 | 2 | 4 | 8,15 | 22 | 29 | 36,43 | 50 | 57 | 64,71 | 78 | 85 |
| | | | | (+/- 2) | | | | | | | | (+/- 3) |
| **Week** | 1 | | | 2-3 | 4 | 5 | 6-7 | 8 | 9 | 10-11 | 12 | 13 |
| Confirm Eligibility and Informed Consent | X | | | | | | | | | | | |
| Vital Signs | | | | | | | | | | | | X |
| Vital Signs pre-dose | X | | | X | X | X | X | X | X | X | X | |
| Vital Signs post dose: 30 min | | | | X | X | X | X | X | X | X | X | |
| Vital Signs post dose: 30 min, 1 hr | X | | | | | | | | | | | |
| ECG pre-dose | X | | | | | | | | | | X | |
| ECG post dose | X[8] | | | | | | | | | | X | |
| Dispense urine collection kit[1] | | | | | X | | | X | | | X | |
| Collect Urine Samples from urine collection kit[2] | | | | | | X | | | X | | | X |
| 24 Urine protein collection[1] | | | | | | | | | | | | X |
| Urine for inflammatory biomarkers[7] | X | | | X | | | | | X | | | X |
| Urinalysis [3,7] | X | | | X | | | | | X | | | X |
| Blood Sample Collection: Chemistry, Hematology, Coagulation, Cystatin C[4,7] | X | | | X | | X | | | X | | | X |
| Calculation of eGFR using the MDRD formula | | | | | | | | | | | | |
| Pregnancy Test – females of child bearing potential[6] | X | | | | | X | | | X | | | X |
| Study Drug Administration | X | | | X | X | X | X | X | X | X | X | |
| Research Sampling[7] | X | | | X | | X | | | X | | | X |
| PK Sampling | | | | | | | | | | | | X |
| PK Sampling pre-dose[7] | X | | | X | | X | | | X | | X | |
| PK Sampling post dose: 5 minutes and 2 hours | X | | | | | | | | | | X | |
| PK Sampling post dose: 24 hours | | X | | | | | | | | | | |
| PK Sampling post dose: 72 hours | | | X | | | | | | | | | |
| PD Sampling | | | | | | | | | | | | X |
| PD Sampling pre-dose[7] | X | | | X | | X | | | X | | X | |
| PD Sampling post dose: 2 hours | X | | | | | | | | | | X | |
| ADA Sampling pre dose | X | | | | | X | | | X | | | X |
| Adverse Events | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medications/therapies | X | X | X | X | X | X | X | X | X | X | X | X |

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6. Pregnancy test must be via serum for Screening Visit 1. May be urine or serum for all other visits.
7. Samples are not collected at Visit 3
8. ECG collected post-dose before 5-minute PK sample.

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