STATISTICAL ANALYSIS PLAN

VERSION: 2.0
DATE OF PLAN:

August 10, 2018

BASED ON:

Protocol Amendment 02 dated May 24, 2017

STUDY DRUG: OMS721

PROTOCOL NUMBER: OMS721-GNP-001

STUDY TITLE:

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

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This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

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This document has been reviewed and accepted by:

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1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

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
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
IEC	Independent ethics committee
IgA	Immunoglobulin A
IgA1	Sub-class of the Immunoglobulin A antibody

Abbreviation or Specialist Term	Explanation
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
λz	Elimination rate constant
LLOQ	Lower limit of quantitation
LN	Lupus nephritis
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

2. INTRODUCTION

The statistical analysis plan (SAP) is based on:

- Protocol No. OMS721-GNP-001 Amendment 02, dated May 24, 2017
- ICH guideline E9 (Statistical Principles for Clinical Trials)

The purpose of this document is to provide details on analysis populations and on how the analysis variables will be derived, how missing data will be handled as well as details on statistical methods to be used to analyze the safety and efficacy data of Protocol No. OMS721-GNP-001.

3. STUDY OBJECTIVES

3.1. Primary Objective

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 C3 glomerulopathy, including dense deposit disease, as assessed by adverse events (AEs), vital signs, clinical laboratory tests, and electrocardiograms (ECGs).

3.2. Secondary Objectives

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)
- Pharmacokinetic (PK)
- Pharmacodynamic (PD)

3.3. 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 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 albumin/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)

4. 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 Protocol Amendment 02. 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 12th 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.

Study visits are shown in Section 5.

4.1. Sample Size Justification

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.

5. STUDY DURATION AND VISIT SCHEDULE

5.1. 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[1]	X[1]
Collect 24-hour Urine protein samples		X													X	X
Urine for inflammatory biomarkers	X						X							X		X
Urinalysis [3]	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
Blood Sample Collection: Chemistry, Hematology, Coagulation, Cystatin C[4],	X		X			X	X			X				X	X	X
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. At Follow-Up Visit 2, urine collection supplies are dispensed if the subject is not going into the Retreatment Period. No supplies are dispensed at the last Follow-Up Visit (FU9).
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.

5.2. Cohorts 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

SCR = screening; ECG = electrocardiogram; HIV = human immunodeficiency virus; PD = pharmacodynamics; PK = pharmacokinetics; ADA = anti-drug 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. Samples are not collected at RT3.
8. 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.

6. STUDY ENDPOINTS

The primary endpoints are:

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

The secondary endpoints are:

- 24-hour urine protein change from baseline to 12 weeks
- Urine albumin/creatinine ratio change from baseline to 12 weeks
- Corticosteroid dose needed to maintain stable renal function (Cohort 1)
- PK concentration and PK parameters of OMS721
- PD measure of inhibition of *ex vivo* lectin pathway activation

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 the longest consecutive weeks that 24-hour urine protein < 50% of the baseline for up to 104 weeks (Cohort 3 only)

7. CLINICAL ASSESSMENTS

The study procedures and assessments are presented in Section 10 of the protocol and the schedule of assessments is presented in Section 5.

8. DEFINITIONS AND CONVENTIONS

8.1. Calculations Using Dates

Age at informed consent is calculated as the integer part of (date of informed consent – date of birth)/365.25.

Duration of treatment (days) is defined as (last dose date + 7 – first dose date). If a subject dies within 7 days of the last dose of study treatment, the duration of treatment is calculated as (death date – first dose date + 1).

Study day is defined as:

- Event Date – First Dose Date + 1 if the event date is on or after the first dose date
- Event Date – First Dose Date if the event date is before the first dose date

8.2. Study Visits

8.2.1. Baseline

The analysis value for urine albumin/creatinine ratio is defined as the average of all the values obtained at a timepoint. The planned number of urine albumin/creatinine ratios is three at each scheduled timepoint. The baseline value of the urine albumin/creatinine ratio is defined as the average of the analysis values from the two screening visits. The analysis value for urine protein/creatinine ratio is defined in the same fashion.

For all other study variables, the baseline value is defined as the last non-missing value prior to the first study drug administration.

8.2.2. Day 1

Study Day 1 is defined as the first dose date of study treatment.

8.2.3. Visit Windows Relative to the First Dose of Study Treatment

Table 2: Visit Windows (Days)

Visit	Target Day	Visit Window (Days)[1]
Day -28 (Screening Visit 1)	-28	-28 to -21
Day -14 (Screening Visit 2)	-14	-20 to -1
Day 1 (Treatment Visit 1)	1	1
Day 2 (Treatment Visit 1)[2]	2	2 to 3
Day 4 (Treatment Visit 1)[2]	4	4
Day 8 (Treatment Visit 2)	8	2 to 11
Day D (Treatment Visit T, T>2)	D (15, 22, …, 78)	D – 3 to D + 3
Day 85 (Follow-up Visit 1)	85	82 to 102
Day 120 (Follow-up Visit 2)	120	103 to 148
Day 176 (Follow-up Visit 3)	176	149 to 221
Day 267 (Follow-up Visit 4)	267	222 to 312
Day 358 (Follow-up Visit 5)	358	313 to 403
Day 449 (Follow-up Visit 6)	449	404 to 494

Table 2: Visit Windows (Days) (Continued)

Visit	Target Day	Visit Window (Days)[1]
Day 540 (Follow-up Visit 7)	540	495 to 585
Day 631 (Follow-up Visit 8)	631	586 to 676
Day 722 (Follow-up Visit 9)	722	≥ 677

[1] If there are more than 1 non-missing assessments in the same visit window, the closest one to the target day will be used in the analysis. If there are 2 assessments that are equally spaced from the target day, the latter will be used in the analysis.

[2] Day 2 and Day 4 apply to PK only.

8.3. Analysis Populations

8.3.1. Enrolled Population

The enrolled population includes all subjects who complete the informed consent.

8.3.2. Safety Population

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

8.3.3. Efficacy Population

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.

9. DATA PRESENTATIONS AND DATA MANAGEMENT

9.1. Data Presentations

The plan for tabular presentations and analysis of the data, in general, is divided into five categories:

1. Subject disposition using the enrolled population.
2. Baseline and demographic profile using the safety population.
3. Analyses of the efficacy data using the efficacy population.
4. Safety and tolerability using the safety population.
5. Analyses of PK, PD and ADA.

9.2. Data Management

All statistical analyses will be performed using SAS version 9.4 or later (SAS Institute Inc., Cary, NC).

10. SUBJECT DISPOSITION

The number of subjects treated, completing the protocol specified duration of study drug, discontinuing study drug early, completing the study, and early withdrawal from the study will be summarized by disease group. The reason(s) for early discontinuation of study drug and early withdrawal from the study will be summarized. The number of subjects in Cohort 1 and Cohort 2 who rollover to Cohort 3 will be summarized. A list of subjects failing any eligibility criteria will be provided.

11. BASELINE SUBJECT DATA

11.1. Baseline Demographic and Subject Characteristics

The following demographic and subject characteristics will be summarized by disease group, cohort and treatment: Age at informed consent, gender, ethnicity, race, duration of disease, weight, BMI, positive anti-PLA-2R antibody (MN subjects in Cohort 1 only), baseline 24-hour urine protein, baseline urine albumin/creatinine ratio, baseline dose of prednisone (mg per day, Cohort 1 only), baseline use of immunosuppressive treatment and baseline eGFR.

Concomitant medications used at baseline will be listed.

11.2. Medical History and Physical Examination

A listing of reported medical and surgical history, and physical examination at screening will be provided.

12. EFFICACY ANALYSIS

12.1. General Considerations

All data summaries will be descriptive in nature and efficacy summaries will be presented by disease group, cohort and treatment. 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. Baseline value will be calculated according to Section 8.3.1. All confidence intervals will be constructed at the two-sided 95% confidence level.

The data collected during the re-treatment period for the rollover subjects in Cohort 1 and Cohort 2 will be presented in listings. Because the open-label OMS721 dose is different from the original OMS721 dose and re-treatment is optional, statistical analyses for Cohort 1 and Cohort 2 will include the data collected in the initial treatment period and the initial follow-up period only. Statistical analyses for Cohort 3 will include the subjects who are randomized in Cohort 3 only. All data collected for the randomized subjects in Cohort 3 will be summarized.

12.2. Testing Statistical Assumptions Including Comparability at Baseline

The efficacy objective of this study is to estimate the effect of OMS721. Baseline characteristics will not be compared among the disease groups and study treatment.

12.3. Statement of the Null and Alternate Hypotheses

The efficacy objective of this study is to estimate the effect of OMS721. Formal statistical tests will not be performed.

12.4. Subgroup Analyses

All analyses will be performed by disease group, cohort and treatment. Due to the small sample size of the study, subgroup analysis is not planned.

12.5. Multiple Comparisons and Multiplicity

Not applicable.

12.6. Analysis of 24-hour Urine Protein

Change from baseline in 24-hour urine protein and change from baseline in natural log transformed 24-hour urine protein will be summarized descriptively for each visit by disease, cohort and treatment. Ninety-five percent confidence intervals (CIs) for the mean change in both the original value and the log-transformed value will be provided for each visit using t-distribution. For Cohort 2 and Cohort 3, the mean difference between OMS721 and vehicle and its 95% CI will also be provided for each visit using t-distribution.

12.7. Analysis of Urine Albumin/Creatinine Ratio and Urine Protein/Creatinine Ratio

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

$$\text{Baseline urine albumin/creatinine ratio} = (R_1 + R_2)/2,$$

R_1 and R_2 are the average values at screening visits 1 and 2, respectively. The baseline urine protein/creatinine ratio is defined in the same fashion.

Change from baseline and change in natural log transformed analysis value of urine albumin/creatinine ratio and urine protein/creatinine ratio at each scheduled visit will be summarized descriptively for each disease group, cohort and treatment. Nine-five percent CIs for the mean change in both the original value and the log transformed value at each scheduled visit will be provided using t-distribution. For Cohort 2 and Cohort 3, the mean difference between OMS721 and vehicle and its 95% CI will also be provided for each visit using t-distribution.

12.8. Analysis of eGFR

eGFR will be calculated using the 4 equations in Table 3. Change in eGFR from baseline at each scheduled visit will be summarized descriptively for each disease group, cohort and treatment. Nine-five percent CIs for the mean change from baseline will also be provided using t-distribution. For Cohort 2 and Cohort 3, the mean difference between OMS721 and vehicle and its 95% CI will also be provided for each visit using t-distribution.

Table 3: eGFR Equations

Formula	SCr or SCyst Range[1]	Equation (mL/min/1.73 m^2)
MDRD		$175 \times SCr\ (mg/dL)^{-1.154} \times age^{-0.203} \times [0.742 \text{ if female}] \times (1.212 \text{ if African American})$
CKD-EPI-SCr		$141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ [if female] x 1.159 [if black] where κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1
Female	SCr ≤ 0.7 mg/dL	$144 \times (Scr/0.7)^{-0.329} \times 0.993^{age} \times 1.159$ [if black]
	SCr > 0.7 mg/dL	$144 \times (Scr/0.7)^{-1.209} \times 0.993^{age} \times 1.159$ [if black]
Male	SCr ≤ 0.9 mg/dL	$141 \times (Scr/0.9)^{-0.411} \times 0.993^{age} \times 1.159$ [if black]
	SCr > 0.9 mg/dL	$141 \times (Scr/0.9)^{-1.209} \times 0.993^{age\ x} 1.159$ [if black]
CKD-EPI-Cyst	SCyst ≤ 0.8 mg/L	$133 \times (Scyst/0.8)^{-0.499} \times 0.996^{age}$ [x0.932 if female] x 1.159 [if black]
	SCyst >0.8 mg/L	$133 \times (Scys/0.8)^{-1.328} \times 0.996^{age}$ [x0.932 if female] x 1.159 [if black]
CKD-EPI SCr–Cyst		
Female	SCr ≤ 0.7 mg/dL and SCyst ≤ 0.8 mg/dL	$130 \times (Scr/0.7)^{-0.248} \times (Scyst/0.8)^{-0.375} \times 0.995^{age}$ [× 1.08 if black]
	SCr ≤ 0.7 mg/dL and SCyst > 0.8 mg/dL	$130 \times (Scr/0.7)^{-0.248} \times (Scyst/0.8)^{-0.711} \times 0.995^{age}$ [× 1.08 if black]
	SCr>0.7 mg/dL and SCyst ≤ 0.8 mg/dL	$130 \times (Scr/0.7)^{-0.601} \times (Scyst/0.8)^{-0.375} \times 0.995^{age}$ [× 1.08 if black]
	SCr >0.7 mg/dL and SCyst > 0.8 mg/dL	$130 \times (Scr/0.7)^{-0.601} \times (Scyst/0.8)^{-0.711} \times 0.995^{age}$ [× 1.08 if black]
Male	SCr ≤0.9 mg/dL and SCyst ≤ 0.8 mg/dL	$135 \times (Scr/0.9)^{-0.207} \times (Scyst/0.8)^{-0.375} \times 0.995^{age}$ [× 1.08 if black]
	SCr≤0.9 mg/dL and SCyst > 0.8 mg/dL	$135 \times (Scr/0.9)^{-0.207} \times (Scyst/0.8)^{-0.711} \times 0.995^{age}$ [× 1.08 if black]
	SCr >0.9 mg/dL and SCyst ≤ 0.8 mg/dL	$135 \times (Scr/0.9)^{-0.601} \times (Scyst/0.8)^{-0.375} \times 0.995^{age}$ [× 1.08 if black]
	SCr >0.9 mg/dL and SCyst > 0.8 mg/dL	$135 \times (Scr/0.9)^{-0.601} \times (Scyst/0.8)^{-0.711} \times 0.995^{age}$ [× 1.08 if black]
1 Scr is serum creatinine in mg/dL; Scyst is serum cystatin in mg/L.		

12.9. Analysis of Other Efficacy Endpoints

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

Change in serum creatinine from baseline to each scheduled visit will be summarized for each disease group, cohort and treatment. Nine-five percent CIs for the mean change from baseline will also be provided using t-distribution.

Duration of therapeutic response will be summarized descriptively by disease, cohort and treatment.

13. SAFETY AND TOLERABILITY

13.1. Overall Summary of Safety

An overall summary of treatment-emergent adverse events, which is defined as the AEs occurring or worsening after the start of study treatment, will be provided by disease group, cohort and treatment. All AEs will be coded by MedDRA. The following items will be included in the overall summary:

- Subject incidence of treatment-emergent AEs
- Subject incidence of treatment-related AEs (defined as probable or possible related to study drug)
- Subject incidence of treatment-emergent AEs by maximum CTCAE grade
- Subject incidence of treatment-emergent serious AEs (SAEs)
- Subject incidence of treatment-emergent AEs leading to discontinuation of study drug
- Subject incidence of treatment-emergent AEs leading to discontinuation of study
- Subject incidence of treatment-emergent fatal AEs
- Total number of unique treatment-emergent AE MedDRA preferred terms
- Median number of unique treatment-emergent AE MedDRA preferred terms per subject
- Total number of unique treatment-emergent SAE MedDRA preferred terms
- Median number of unique treatment-emergent SAE MedDRA preferred terms per subject

13.2. Adverse Event Preferred Term and Body/Organ System Summary Tables

Subject incidence of the following AEs will be provided by disease group, cohort and treatment:

- pre-treatment AEs by MedDRA SOC and preferred term (pre-treatment AEs are those AEs that occurred prior to the start of study treatment)

- treatment-emergent AEs by MedDRA SOC, and preferred term
- treatment-emergent AEs by MedDRA preferred term
- treatment-related AEs by MedDRA SOC, and preferred term
- treatment-emergent AEs by MedDRA preferred term, and maximum CTCAE grade
- AEs leading to study drug discontinuation by MedDRA SOC, and preferred term
- AEs leading to study discontinuation by MedDRA SOC, and preferred term
- treatment-emergent SAEs by MedDRA SOC, and preferred term
- treatment-related SAEs by MedDRA SOC, and preferred term
- AEs leading to death by MedDRA SOC, and preferred term

13.3. Study Treatment Adherence and Extent of Exposure

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

The total dose volume (mL) received, the total intended dose volume (mL) and the number of doses received will be summarized for scheduled visits and unscheduled visits by disease group, cohort and treatment. Intended dose volume at each dose administration for Cohort 1 and Cohort 2 is calculated as

$$4 \text{ mg/kg} \times \text{Weight (kg)} \div \text{Drug concentration}.$$

If the weight is greater than 100 kg, the intended dose volume will be calculated using 100 kg. This study uses two drug concentrations, 100 mg/mL and 185 mg/mL.

In addition, relative dose intensity (%), defined as the total dose volume received as a percentage of the total intended dose volume will be summarized for scheduled visits and unscheduled visits by disease group. Listing of dosing information will also be provided.

13.4. Concomitant and Other Medications

Subject incidence of concomitant medications will be provided by WHODrug preferred term, disease group, cohort and treatment.

13.5. Routine Laboratory Data

Summary statistics for actual values and for change from baseline will be tabulated as appropriate for laboratory results by scheduled visit, disease group, cohort and treatment. Subjects with laboratory values outside of the normal reference range at any post-baseline safety assessment will be listed by disease group, cohort and treatment.

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

13.6. Vital Signs

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

13.7. Physical Examination

Physical examination will be listed.

13.8. 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 group, cohort and treatment. 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 group, cohort and treatment.

14. PHARMACOKINETIC ANALYSES

PK parameters for OMS721 will be calculated using non-compartmental analysis. Only concentrations greater than or equal to the validated lower limit of quantitation (LLOQ) will be used in the PK analyses. Actual blood sampling times will be used in all PK analyses. Per protocol times will be used to calculate mean concentrations for graphical displays. The maximum concentration (C_{max}) and time to maximum concentration (T_{max}) will be taken directly from the individual's data. The elimination rate constant, λ_z, will be calculated as the negative of the slope of the terminal log-linear segment of the time-concentration curve. The range of data to be used for each subject and treatment will be determined by visual inspection of a semi-logarithmic plot of concentration versus time and will be comprised of at least three data points along the elimination phase. Elimination half-life ($t_{½}$) will be calculated according to the following equation:

$$t½ = \frac{0.693}{\lambda z}$$

The area under the curve (AUC) of the final sample with a concentration ≥ LLOQ [AUC(0-t)] will be calculated using the linear trapezoidal method and extrapolated to infinity [AUC(inf)] using:

$$AUC(\text{inf}) = AUC(0-t) + \frac{C_{tf}}{\lambda z}$$

where C_{tf} is the final concentration ≥ LLOQ.

Clearance (CL) will be calculated by *Dose/AUC*. Volume of distribution will be calculated by *Dose/λz x AUC*.

Concentrations and derived PK parameters will be summarized using descriptive statistics. Graphs of individual subject and mean concentrations, by disease group and cohort, will be presented on linear and semi-logarithmic axes.

15. 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 treatment at each scheduled time point.

16. PHARMCOKINETIC-PHARMACODYNAMIC ANALYSES

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

17. IMMUNOGENICITY ANALYSES

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

18. INTERIM ANALYSES

Two interim analyses are planned for Cohort 3. An interim analysis will be performed when all randomized subjects in the non-exclusive Asian group have completed the 6-week follow-up period after the initial 12 weeks of study treatment, or have discontinued the study. Similarly, an interim analysis for the exclusive Asian group will also be performed when the Asian subjects have the 6-week follow-up period after the initial 12 weeks of study treatment, or have discontinued the study.

19. REFERENCES

None

20. APPENDIX

20.1. Data Display Specifications

Table shells are documented separately.

21. PROTOCOL AND SAP AMENDMENTS AND DEVIATIONS FROM THE PROTOCOL

21.1. Changes from Protocol

The duration of therapeutic response is clarified to be the number of the longest consecutive weeks that 24-hour urine protein < 50% of the baseline for up to 104 weeks (Cohort 3 only).

21.2. Changes from SAP

The changes to the SAP are based on Protocol Amendment 02.