CLINICAL TRIAL PROTOCOL

A Phase Ib/IIa, Open-Label, Multicenter Clinical Trial to Assess Safety and Efficacy of the Human Anti-CD38 Antibody MOR202 in Anti-PLA2R Antibody Positive Membranous Nephropathy (aMN) - M-PLACE

Brief Description of Clinical Trial	Open-Label, Two-Cohort, Multicenter Clinical Trial to assess Safety and Efficacy of MOR202 in anti-PLA2R antibody positive Membranous Nephropathy (aMN)
Clinical Trial Phase:	Ib/IIa
Product Name:	MOR202
Sponsor:	MorphoSys AG
Sponsor's Address:	Semmelweisstrasse 7 D-82152 Planegg GERMANY
Clinical Trial Protocol No.:	MOR202C103
EudraCT No.:	2019-000780-24
IND No.:	142840
Effective Date:	**07-Jul-2020**
Protocol Version:	**Version 7.0**, dated 01-Jul-2020
Previous Versions of the Clinical Trial Protocol:	6.0, 31-Oct-2019 5.0, 26-Jul-2019 4.0, 11-Jul-2019, US only 3.0, 01-Jul-2019, France only 2.0, 29-Mar-2019
Author:	PPD

Sponsor Signatory:

PPD

Principal Investigator's Signature

I have read and understood all pages of this clinical trial protocol. I agree that this protocol contains all the information required to conduct this clinical trial. I agree to conduct the clinical trial as outlined in the clinical trial protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the clinical trial in accordance with ICH GCP guidelines and the principles which have their origin in the Declaration of Helsinki, copies of both documents have been given to me by the sponsor, and I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, the ICH GCP guidelines and the Declaration of Helsinki to enable them to work in accordance with these documents.

Signature: **Date:**

(DD, Mmm, YYYY)

Printed Name:

Address:

<Insert name and qualifications of the Investigator>

Contact Details of Key Trial Personnel

24h-Contact for Medical Emergencies:	Refer to Investigator Site File.
IQVIA Medical Monitor	Refer to Investigator Site File.
Sponsor's Medical Monitor	Refer to Investigator Site File.

SUMMARY OF CHANGES

Amendment 5 (global), 01-Jul-2020, CTP v7.0,

Section	Change	Reason / Comment
Section 1, 7.1, and 7.2	several inclusion (IC) and exclusion criteria (EC) were updated: IC 2: proteinuria determination from 24h urine collection added IC 3, 4,: rephrased IC 5: possibility added to include patients not tolerating ACEI/ARB IC 7: pneumococcus vaccination period extended from 3 to 5 years IC 8 and 9 combined to abolish cohort 1 subgroups, cohort 1 now comprises all patients with antiPLA2R antibodies ≥ 50.0 RU/mL IC 10 and 11 combined and cohort 2 definition revised to enable the participation of subjects refractory to previous therapy without limiting the number of such previous therapies EC 1: updated to enable the participation of subjects with hemoglobin levels below 80 (formerly 90 g/L) EC 5: hypogammaglobulinemia threshold revised to 4 g/L EC 10 and 11 combined due to abolished cohort 1 subgroups (see above), wash out period for previous therapies revised EC 19: hepatitis diagnostics clarified to ensure to exclude subjects with latent hepatitis new EC 21 added: pregnancy new EC 22 added: active infection new EC 23 added: malignancy	Inclusion and exclusion criteria were updated • to expand the patient population • to align with clinical practice, international guidelines, and clinical research standards and further improve the quality of the CTP • for better understanding • EC 5: most commonly accepted threshold, before hypogammaglobulinemia leads to immunocompromised state
Section 1 and 7.2	new EC 6 added to exclude patients with B-cell levels below 5 x 10^6/L	To avoid including patients with prolonged B-cell depletion after previous B-cell depleting therapy (e.g. rituximab)
Section 1, 5, 6.2, 8.3.2, 8.7, 10, 10.1 10.8.1, 12.5	sections updated according to revised in- and exclusion criteria	to assure consistency of the CTP

Section 1 and 5	revised wording for exploratory endpoint on renal function rate deterioration	to assure consistency within study protocol
Section 1	planned total number of clinical trial sites and locations updated	increasing sites and geographic spread to mitigate recruitment challenge due to COVID-19
Section 3.2	definition of progressive disease updated to clarify that only UPCR from 24 h urine collection will be used as criterion	no comment
Section 4.2	information about other clinical trials updated with current information	no comment
Section 8.4	plasmapheresis and immunoadsorption added as prohibited therapies	since they influence outcome parameters
Section 8.2.2 and 10	maximum interval for body weight determination applicable for IMP preparation defined, increased frequency of body weight assessment	to provide more accurate information for dosing and PK analysis
Section 10 and 10.1	Hba1c added a parameter to be tested in central laboratory for subjects with diabetes mellitus type II	to ensure accurate Hba1c is available at screening to check eligibility
Section 10 and 10.1	requirement for kidney ultrasound deleted in schedule of assessments	deleted to align with clinical practice and to simplify CTP
Section 10 and Section 10.1	minimum creatinine amount in collected urine revised in footnote of schedule of assessments, as well as in Section 10.1	recalculated reflecting creatinine excretion of elderly, on low protein diet, or with infrequent physical activity
Section 10.4	added time window for assessment of CBC	to further improve patient safety
Section 10.8.7 and 12.12.1	Additional AESIs added: neutropenia thrombocytopenia major bleeds	to ensure timely reporting of such events
Section 14	Updated list of references, now presented in alphabetical order	no comment
All sections	editorial changes: corrections of inconsistencies/ erroneous wording, moving wording to different positions, adding definitions, consistent use of American spelling, reference to cited literature corrected	no comment

Amendment 4 (global), 31-Oct-2019, CTP v6.0,

Section	Change	Reason / Comment
Sections 1, 6.2 and 7.1	Previous inclusion criteria 10 and 11 revised, inclusion criterion 9 deleted, inclusion criterion 3 expanded.	Criteria changed to enable the participations of subjects historically monitored with different anti-PLA2R assays, subgroups a + b for Cohort 1 with minimum of 10 subjects for 1a introduced
Sections 1, 3, 6.1.2, 6.7, 7.1,7.2, 8.2.2, 8.3.1, 10 and 12	Editorial changes	Corrections of inconsistencies/ erroneous wording, moving wording to different positions, adding definitions
Section 10	Description for one blood sample added to clarify the sampling purpose for future research	Correction to highlight optional sample
Sections 1 and 10	BAFF added as additional biomarker	Enrichment of the research biomarker panel

Amendment 3, 26-Jul-2019, CTP v5.0, European countries, United States of America

Section	Change	Reason / Comment
Table 2 (Schedule of Assessments)	Serum pregnancy test added at Follow Up Visit (FUV), Day 267	Request of German Competent Authority, PEI
Section 10.1	Wording added to address the recommendation of the CTFG related to the pregnancy testing in case of delayed menstrual cycle in women of childbearing potential	Request of German Competent Authority, PEI
Sections 1, 6.2 and 7	Patients in France excluded from enrolment in Cohort 1	Request from French Competent Authority ANSM

Section 7.1	Wording related to the contraception methods in females of childbearing potential revised in Inclusion criterion 14.	Request of US FDA
Sections 1, 5, 7.2, 8.2.2, 8.7 and 10.1	Editorial changes	Corrections of inconsistencies/ erroneous wording

Amendment 2, 11-Jul-2019, CTP v4.0 United States of America

Section	**Change**	**Reason / Comment**
Section 6.3	Added wording "Safety Review Panel" to name the respective safety review board appropriately	Request of US FDA
Section 9.1	Revised wording in order to introduce stricter rules for triggering the safety review by the Safety Review Panel and decisions about pausing recruitment and pausing of MOR202 dosing in all subjects.	Request of US FDA

Amendment 1, 01-Jul-2019, CTP v3.0 France

Section	**Change**	**Reason / Comment**
Section 10.1 Table 2 (Schedule of Assessments)	Wording revised in order to make blood typing mandatory (previously recommended) before treatment with MOR202 in order to mitigate the risk of possible interference of CD38 antibodies with blood bank serologic tests	Request of the French Competent Authority ANSM

1. SYNOPSIS

Title of Clinical Trial	A Phase Ib/IIa, Open-Label, Multicenter Clinical Trial to Assess Safety and Efficacy of the Human Anti-CD38 Antibody MOR202 in antiPLA2R antibody positive Membranous Nephropathy (aMN) - M-PLACE
Investigational Medicinal Product	MOR202 (compound code: MOR03087)
Clinical Trial Protocol Number	MOR202C103
Sponsor	**Sponsor:** MorphoSys AG Semmelweisstraße 7 D-82152 Planegg GERMANY
Clinical Trial Phase	Ib/IIa
Background / Rationale	The purpose of the trial is to assess the safety and efficacy of the human anti-CD38 antibody MOR202 (compound code MOR03087) in patients with anti-PLA2R antibody positive membranous nephropathy (aMN) eligible for immunosuppressive therapy (IST) or who have failed to respond to previous IST. The main treatment rationale is the reduction of membranous nephropathy (MN) specific anti-PLA2R autoantibodies through MOR202 mediated targeted depletion of autoantibody producing plasma cells. Autoantibodies binding to the PLA2R antigen are highly specific to primary MN. They are present in approximately 70% of patients diagnosed with this condition. It is clinically observed that anti-PLA2R antibody titers correlate tightly with disease activity. Taken together with the fact that the disease defining glomerular basement changes contain both PLA2R protein as well as antibody complex deposits, indirect evidence is provided that indeed anti-PLA2R antibodies play a causative role in MN. Patients diagnosed with MN and proteinuria >3.5 g per day initially receive supportive therapy with a combination of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), statins and diuretics as per current clinical standard. If not responding with a significant decrease of proteinuria within months, escalation to IST is indicated with usage of cyclophosphamide, calcineurin inhibitors (CNIs) or mycophenolate mofetil (MMF), even though none of these drugs is approved for use in MN. Recently introduced off-label use therapy with anti-CD20 therapeutic antibody rituximab (RTX) allows for a more targeted IST approach by depleting

	B cell populations involved in producing autoantibodies. However, in MN patients with high anti-PLA2R antibody titers, response rates with RTX seem to be low. One reason could be that a substantial amount of anti-PLA2R antibodies are produced by a mature, long-lived plasma cell pool with a CD20 negative, but CD38 positive immuno-phenotype, potentially limiting the efficacy of an anti-CD20 therapeutic approach. Thus, an anti-CD38 directed specific plasma cell depletion approach employing the monoclonal antibody MOR202 may provide a viable therapeutic option sparing patients of significant toxicity of broader acting immunosuppressive agents, and that is possibly effective in patients with limited benefits from anti-CD20 directed therapy.
Clinical Trial Objectives **(Key Primary and Secondary)**	**PRIMARY OBJECTIVE:** To assess the safety and tolerability of MOR202 treatment in subjects with aMN. **KEY SECONDARY OBJECTIVE:** To assess the effect of MOR202 on serum anti-PLA2R antibodies in subjects with aMN. **SECONDARY OBJECTIVES:** 1. To assess the immunogenicity of MOR202 (anti-MOR202 antibody formation). 2. To assess the pharmacokinetic (PK) profile of MOR202. 3. To assess the safety in subjects with aMN after MOR202 treatment and during the follow-up phase. CCI [redacted]
Clinical Trial Endpoints (Key Primary and Secondary)	**PRIMARY ENDPOINT:** Incidence and severity of treatment-emergent adverse events (TEAEs). **KEY SECONDARY ENDPOINT:** Best immunological response: rate of stringent immunological complete response (sICR), immunological complete response (ICR) and immunological partial response (IPR) based on reduction of serum anti-PLA2R antibody titer.

	SECONDARY ENDPOINTS: 1. Number and antibody titers of subjects tested positive for antiMOR202 antibodies. 2. MOR202 serum concentrations after multiple i.v. administrations. 3. Incidence and severity of adverse events (AEs) in the follow-up phase. **EXPLORATORY ENDPOINTS:** CCI [redacted]
Design and Methodology	Phase Ib/IIa, open-label, two-cohort, multicenter clinical trial to assess safety and efficacy of MOR202 in aMN *Cohorts/Patient Population* Cohort 1 will consist of approximately 20 aMN newly diagnosed or relapsing subjects stable on supportive care treatment with ACEI/ARB

	at screening with proteinuria and medium/high serum titers of anti-PLA2R antibodies, eligible for IST. Cohort 2 will consist of approximately 10 subjects with aMN refractory to IST and requiring other forms of IST. *Intervention* MOR202 monotherapy within a 24-week treatment phase followed by a 28-week observational follow-up phase.
Population	Adult subjects with biopsy proven MN, positive for serum anti-PLA2R antibodies
Key Inclusion Criteria	1. ≥ 18 to ≤ 80 years (at date of signing informed consent form [ICF]). 2. *Urine protein to creatinine ratio (UPCR) of ≥ 3.000 g/g OR proteinuria ≥ 3.500 g/24 h from 24-h urine at screening.* 3. Anti-PLA2R antibody positive MN in need of IST according to the investigator's judgment. The diagnosis of MN should be histologically documented with a diagnostic biopsy; for this purpose, a biopsy at screening or an archival biopsy acquired within 5 years prior to screening is acceptable. 4. *Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min/1.73m² Alternatively eGFR ≥30 and <50 mL/min/1.73m² and interstitial fibrosis and tubular atrophy (IFTA) score < 25% in a renal biopsy* obtained within the last 6 months prior to start of screening (if not available, a biopsy should be performed at screening to obtain the IFTA assessment). 5. Not in spontaneous remission despite proper treatment with ACEIs, ARBs (sufficient dose and treatment duration) as per clinical practice and scientific guidelines. If the Principal Investigator determines that a subject is intolerant to an ACEI or ARB, the reason must be documented and approval obtained from the Medical Monitor prior to enrolment. 6. Systolic blood pressure BP ≤ 150 mmHg and diastolic BP ≤ 100 mmHg after 5 minutes of rest. 7. Subject vaccinated against Pneumococcus within the last 5 years prior to date of signing ICF (subjects may be vaccinated to meet this criterion during screening; interval to first dose of MOR202 must be at least 14 days [MSD SmPC]). 8. Cohort 1 comprises newly diagnosed or relapsed subjects: *Serum anti-PLA2R antibodies ≥ 50.0 RU/mL determined by Euroimmun ELISA at central laboratory.*

	9. Cohort 2 comprises therapy refractory subjects: a Subject did not achieve immunological remission after prior IST(s) as documented by the investigator AND b Subject is without promising standard therapeutic options as documented by the investigator (i.e. investigator expects efficacy or safety issues with remaining IST options) AND c *Serum anti-PLA2R antibodies ≥ 20.0 RU/mL measured at screening by the Euroimmun ELISA at central laboratory.* Note: France will only enroll patients in Cohort 2. *Parameters in italics are measured in a central laboratory.*
Key Exclusion Criteria	1. *Hemoglobin < 80 g/L.ƒ* 2. *Thrombocytopenia: Platelets < 100.0 x 10⁹/L. ** 3. *Neutropenia: Neutrophils < 1.5 x 10⁹/L.#* 4. *Leukopenia: Leukocytes < 3.0 x 10⁹/L.#* 5. *Hypogammaglobulinemia: Serum immunoglobulins ≤ 4.0 g/L.‡* ƒ Subjects may receive blood transfusions or erythropoietin to meet the criterion. * Subjects may receive thrombopoietin to meet the criterion. # Subjects may receive colony stimulating factors to meet the criterion. ‡ Subjects may receive immunoglobulin substitution to meet the criterion. 6. *B-cells < 5 x 10⁶/L.* 7. Secondary cause of MN (e.g. systemic lupus erythematosus (SLE), medications, malignancies) as determined by the investigator. 8. Concomitant renal disease other than MN (e.g., diabetic renal disease, lupus nephritis, IgA nephropathy).
Sample Size, Planned total number of Clinical Trial Sites and Locations	Approximately 20 subjects in Cohort 1 and approximately 10 subjects in Cohort 2 will be enrolled and receive MOR202. As this is a Phase Ib/IIa trial primarily conducted to explore safety endpoints, no formal statistical hypothesis has been established for the sample size calculation of this trial. It is expected that approximately 10% of the subjects will prematurely discontinue the trial prior to completion of the last treatment cycle (i.e. end of Week 24). Approximately 55 clinical trial sites in the US, Asia Pacific and Europe will participate in the trial.
Investigational and Control Drug(s) (Name, Description)	MOR202 antibody (compound MOR03087). No comparator drug.
Dose, Route of Administration, Treatment Regimen	9 doses of MOR202 will be administered as an intravenous infusion at 16 mg/kg over 6 treatment cycles of 28-days each. Dosing will occur QW in Cycle 1 and Q4W in Cycle 2 to 6.

Supply, Preparation and Administration	MOR202 is supplied as a lyophilized powder for reconstitution in labelled glass vials. MOR202 must be stored at 2-8°C until use. For administration, MOR202 will be reconstituted in water for injection (WFI) and diluted into a commercially available 0.9% (w/v) sodium chloride solution. MOR202 will be administered by slow i.v. infusion. Premedication of subjects with antihistamines and antipyretic drugs is recommended. For the first 3 administrations, glucocorticoid premedication is mandatory.
Visit Schedule and Assessments	Screening: 1 visit Treatment phase: 10 visits, EOT planned after 24 weeks. Follow-up phase: 2 visits, EOS planned 28 weeks after EOT. For details see Figure 1.
Efficacy Assessments	Proteinuria assessed by UPCR in 24-hour urine and spot urine, anti-PLA2R titer, eGFR.
Special Safety Assessments	Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.
Subject Reported Outcomes / QoL	CCI [redacted]
Pharmacokinetics	Serum concentrations of MOR202 at selected time points will be assessed for all subjects treated with MOR202 during the course of the trial.
Immunogenicity	The presence of potential anti-drug antibodies and corresponding titers will be assessed at selected time points for all subjects treated with MOR202 during the course of the trial.
Biomarker Assessments	At selected time points assessments may include: **Peripheral blood** immune cell populations CCI [redacted] **Serum** concentrations of antigen specific antibodies (e.g. anti-tetanus toxoid titer), CCI [redacted] CCI [redacted]

Safety run-in	The safety run-in period consists of the following: The first three subjects dosed in this trial (regardless of cohort) will be treated and observed until Cycle 2, Day 1 (C2D1) or until they demonstrate a toxicity leading to discontinuation of treatment, whichever is earlier. Treatment initiation of further subjects will be paused and re-started after completion of the safety run-in period, unless any grade 4/5 adverse drug reaction (ADR) (i.e. AE at least suspected to be possibly related to MOR202) occurs. If a MOR202 related grade 4/5 ADR occurs, then a safety review must take place and treatment initiation for further patients will be contingent on safety review outcome. Subjects involved in the safety run-in will continue the trial as per protocol. The safety review consists of an evaluation based on the number and type of AEs occurring during the first cycle as well as laboratory values (biochemistry and hematology). It will entail a recommendation either to keep the current dose of MOR202 or to adapt the dose for the remainder of the trial or to terminate the trial because of unacceptable toxicity. The evaluation will be performed within two weeks after completion of the safety run-in phase.
Statistical Methods and Data Analysis	All data in this Phase Ib/IIa trial will be summarized descriptively using appropriate tabular overviews. Summary statistics for continuous variables will include number of subjects, mean, median, Q1, Q3, standard deviation, minimum, and maximum. For categorical variables, frequencies and percentages will be provided. When required for the analysis of a particular variable, the baseline value will be the last recorded value prior to first treatment. For trial endpoints point estimates and 95% confidence limits will be presented. Time-to-event endpoints will be analyzed using the Kaplan-Meier methodology. No formal statistical hypothesis testing will be performed.

2. Table of contents

2.1. List of tables

2.2. List of figures

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

3.1. List of Abbreviations

ACEI	Angiotensin Converting Enzyme Inhibitor
ACTH	Adrenocorticotropic hormone
ADA	Anti drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell-mediated phagocytosis
ADR	Adverse drug reaction
AE	Adverse event, for definition see 10.8.6
AESI	Adverse Event of Special Interest
ALT	Alanine-Aminotransferase
aMN	Anti-PLA2R antibody positive membranous nephropathy
Anti-PLA2R	Anti phospholipase A2 receptor antibodies
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
ARB	Angiotensin II Receptor Blocker
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
AUC	Area under the curve
BAFF	B-Cell Activating Factor
β-hCG	β human Chorionic Gonadotropin
BIR	best overall immunological response
BIRR	best overall immunological response rate
BL	Baseline
BP	Blood pressure
BPR	Best proteinuria response
CBC	Complete blood cell count
CD	Cluster of differentiation
CD20	B-lymphocyte antigen CD20
CD38	B-lymphocyte antigen CD38
C_{max}	Maximum concentration
CI	Confidence Interval
CNI	Calcineurin inhibitor

CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CR	Complete response
CRF	Case Report Form
CRO	Contract research organization
CSA	Cyclosporin A
C_{trough}	Minimum concentration
CTFG	Clinical Trial Facilitation Group
CX	Various fractions of complement, C1q, C5a, ...
CXDY	Cycle X Day Y (eg C1D1 is the 1st day of the 1st cycle)
DEX	Dexamethasone
DMC	Data Monitoring Committee
DTT	Dithiothreitol
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study visit (28 weeks after EOT)
EOT	End of therapy visit (28 days after last dose)
ESA	Erythropoiesis stimulating agent
ESRD	End stage renal disease
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full analysis set
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FiH	First in Human
FSH	Follicle stimulating hormone
FUV	Follow up visit (14 weeks after EOT)
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyltransferase
Hba1c	Glycated hemoglobin

HBcAg	Hepatitis B core antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
IAS	Immunological analysis set
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICR	Immunological complete response
IEC	Independent Ethics Committee
IFN	Interferon
IFT	Immunfluorescence Test
IFTA score	Interstitial fibrosis and tubular atrophy score
Ig	Immunoglobulin
IL	Interleukin
IMP	Investigational medicinal product
IPR	immunological partial response
IRB	Institutional/Independent Review Board
IRR	infusion related reaction
IST	Immunosuppressive therapy
IU	International Units
IUD	Intra Uterine Device
i.v.	intravenously
CCI	[redacted]
LEN	Lenalidomide
LDH	L-Lactate dehydrogenase
mAbs	Monoclonal antibodies
MAC	Membrane attack complex
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter

MM	Multiple myeloma
MMF	Mycophenolat-Mofetil
MN	Membranous nephropathy
mPBPK	minimal physiologically-based PK model
MTD	Maximum tolerated dose
ng	nanogram
NCI CTCAE 5.0	National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0
NK	Natural killer
NMRI	US Naval Medical Research Institute, strain of outbred laboratory mice
NS	Nephrotic syndrome
NYHA	New York Heart Association
OPR	Overall Proteinuria Response
OR	Overall response [complete CR or partial PR response]
ORR	Overall response rate
PBMC	Peripheral blood mononuclear cell
PE	Physical examination
PEI	Paul-Ehrlich Institute
PFS	Progression free survival
PK	Pharmacokinetics
PKAS	Pharmacokinetic Analysis Set
PK/PD	pharmacokinetic/pharmacodynamic
PLA2R	Phospholipase A2 receptor
POM	Pomalidomide
PR	Partial response
Prot-CR	Proteinuria Complete Response
Prot-PR	Proteinuria Partial Response
CCI [redacted]	
QW	Once every week
QTcB	QT interval corrected for heart rate according to Bazett
QTcF	QT interval corrected for heart rate according to Fridericia
Q1	25th Percentile

Q_3	75th Percentile
Q4W	Once every 4 weeks
RTX	Rituximab
RU	Relative Unit
SAE	Serious adverse event, for definition see Section 10.8.6
SAP	Statistical analysis plan
SCR	Screening
Scr	Serum creatinine
sICR	Stringent immunological complete response
SLE	Systemic lupus erythematosus
SmPC	Summary of product characteristics
SOC	Standard of Care
SOP	Standard Operating Procedure
TEAE	Treatment emergent adverse event
TNF	Tumor necrosis factor
TSH	Thyroid stimulating hormone
TTP	Time to progression
$t_{1/2}$	Terminal elimination half-life
UP	Urine protein
UPCR	Urine protein to creatinine ratio
WFI	Water for Injection
WHO	World Health Organization

3.2. List of Definitions specific to nephrology, membranous nephropathy and this clinical trial protocol

Clinically relevant	Practical importance of a treatment effect or abnormality – whether it has a genuine, noticeable effect on daily life of a subject.
End of study	Date of the last visit of the last subject.
End-stage renal disease (ESRD)	For the purpose of this protocol ESRD is defined as decrement in the subject's kidney function to a level at which renal replacement therapy is required to sustain life meeting one of the following criteria: 1. Was on dialysis therapy for more than 30 days continuously. 2. Received a kidney transplant. 3. A physician recommended renal replacement therapy. [dialysis or transplant] and the subject refused therapy. 4. Began dialysis and died < 30 days later. 5. Confirmed eGFR < 10 mL/min/1.73 m^2.
Estimated glomerular filtration rate (eGFR)	eGFR will be calculated as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al 2007, Levey et al 2009): eGFR = $141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] $\times 1.159$ [if black] where: - Scr is serum creatinine in µmol/L, - κ is 61.9 for females and 79.6 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 eGFR as a measure of kidney function
Immunological Responses	Immunological responses are reflected by the reduction of antiPLA2R antibody titers as measured by ELISA. Based on the immunological responses, the following response categories are defined for this protocol (the baseline value is the last measurement obtained prior to treatment start):
- Immunological partial response (IPR)	Reduction of anti-PLA2R antibody titers by at least 50% compared to baseline
- Immunological complete response (ICR)	Reduction of anti-PLA2R antibody titers to less than 14.0 RU/mL

- Stringent immunological complete response (sICR)	ICR and a negative result in anti-PLA2R immunofluorescence test
Progressive disease	Decrease of eGFR by more than 30% of baseline eGFR, or increase in UPCR determined from 24 h urine collection by more than 50% from baseline value and less than 10% decline of anti-PLA2R antibody titers compared to baseline.
Proteinuria	Proteinuria will be assessed by UPCR from 24 h urine throughout this clinical trial.
Proteinuria Responses	Proteinuria responses are reflected by the reduction of proteinuria as measured by UPCR. Based on the proteinuria responses, the following response categories are defined by this protocol (baseline proteinuria value is defined as the mean of the values determined at screening and prior to Cycle 1 Day 1 pre-dose [UPCR from 24 h urine]):
- Proteinuria complete response (Prot-CR)	Reduction of proteinuria to less than 0.5 g/g, serum albumin within the reference range and stable eGFR (at least 80% of baseline).
- Proteinuria partial response (Prot-PR)	Reduction by at least 50% of UPCR at a given visit compared to baseline, proteinuria below 3.0 g/g and stable eGFR (at least 80% of baseline), but not meeting Prot-CR.
- Overall proteinuria response (OPR)	The sum of Prot-CR and Prot-PR
Treatment emergent adverse event (TEAE)	TEAEs are defined as any adverse event reported within the following time interval: start of first administration of trial drug until date of last administration of MOR202 + 28 days
Toxicity and symptoms for adverse event reporting and medical history are graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0 (NCI-CTCAE 5.0) throughout this Clinical Trial Protocol unless otherwise stated. A copy will be provided in the Investigator Site File.	

4. INTRODUCTION

The purpose of the trial is to assess safety and efficacy of the human anti-CD38 antibody MOR202 (compound MOR03087) in subjects with anti-PLA2R antibody positive membranous nephropathy (aMN) eligible for immunosuppressive therapy (IST) or who have failed to respond to previous IST.

Membranous nephropathy (MN) is the leading cause of nephrotic syndrome (NS) in adults (Medawar et al 1990). About 80% of MN cases are idiopathic, 20% are related to other diseases or exposures (Couser et al 2017). The overall global incidence is estimated at 1.2 per 100,000 per year (Mc Grogan et al 2011).

Although up to 30% of patients experience spontaneous remissions, and although the disease usually progresses slowly, approximately 30% to 40% of patients eventually develop end-stage renal disease (ESRD) (Ruggenenti et al 2003, Troyanov et al 2004). Patients with MN remaining nephrotic are at increased risk for thromboembolic (Wagoner et al 1983) and cardiovascular events (Lee et al 2016). Currently, there is no approved standard treatment for MN and there is no predictive test available that identifies patients who will undergo spontaneous remission. The current treatment regimen mainly comprises off-label use of various non-immunosuppressive and immunosuppressive drugs (Couser et al 2017, Bomback et al 2018).

Commonly, patients presenting with proteinuria and an established (histological) diagnosis of MN receive supportive, non-immunosuppressive therapy. Typically, this consists of a combination of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), statins and diuretics. Evidence of a direct therapeutic effect of ACEIs and/or ARBs either immunologically or on proteinuria directly is lacking, particularly in light of the aforementioned underlying rate of spontaneous remissions.

Should supportive therapy not lead to reduction of proteinuria within months, treatment is escalated by employing IST with the most common IST regimens being cyclophosphamide combined with steroids, calcineurin inhibitors (CNIs: cyclosporine [CSA] or tacrolimus), mycophenolate-mofetil (MMF) or rituximab (RTX). To a lesser extent, adrenocorticotropic hormone (ACTH) has been used. Treatment effects of these combinations appear to be similar: remission of proteinuria can be expected in about 50 to 60% of patients in the first year and 70 to 80% at 2 to 3 years (Couser et al 2017).

Out of all patients with primary MN not receiving IST, 30% to 40% progress to ESRD in 10 years after disease onset. IST reduces the progression rate to 10% or less (Bomback et al 2018). Relapses in proteinuria are seen in about 25% of patients previously treated with IST. The cases are usually re-treated with a different IST combinations (Couser et al 2017, Bomback et al 2018).

Autoantibodies binding to the PLA2R antigen are highly specific to primary MN. They are present in approximately 70% of patients diagnosed with this condition (Beck et al 2009). It is clinically observed that anti-PLA2R antibody titers correlate tightly with disease activity (Bomback et al 2018). Taken together with the fact that the disease defining glomerular basement changes contain both PLA2R protein as well as antibody complex deposits, indirect evidence is provided that indeed anti-PLA2R antibodies play a causative role in MN. This in consequence currently leads to a change of previously established therapy algorithms, i.e. to an IST guided by anti-PLA2R titers in patients where these antibodies are detectable. Nowadays, patients with elevated

circulating levels of anti-PLA2R antibodies and proteinuria >3.5 g per day are candidates for early IST (Couser et al 2017, Bomback et al 2018, Vriese et al 2017).

The above described ISTs exhibit considerable toxicity: 25% of patients treated with cyclophosphamide demonstrate adverse events (AEs) such as infections, infertility, hematologic toxicity and malignancy later in life (Couser et al 2017). Disadvantages of CNIs include long-term nephrotoxicity, the need to closely monitor drug levels and the increased risk for hypertension and diabetes. Relapse rates with CNIs seem to be higher than with cyclophosphamide [40 to 50 % versus 25%] (Cattran and Brenchley 2017, Tran et al 2015, van de Logt et al 2016).

Therapy with RTX, an anti-CD20 therapeutic antibody, allows for a more targeted IST approach by depleting B cell populations involved in producing autoantibodies. RTX response rates seem to be similar to alkylating agents and CNIs, whereas side effects seem to be less than for other drugs used in IST (Ruggenenti et al 2012, Fervenza et al 2017, Fervenza et al 2015). A prospective randomized trial testing RTX versus Cyclosporin A found RTX to be non-inferior (Fervenza et al 2017).

Interestingly, CD20 is not expressed on mature antibody producing plasma cells, the main source of endogenous immunoglobulins. Indeed, a variable but essential amount of the circulating antiPLA2R antibodies may be produced by a mature, long-lived plasma cell pool with a CD20 negative but CD38 positive immunophenotype. Residual long-lived plasma cells could be a possible explanation for RTX non-responders as well as data indicating a trend towards lower response rate of RTX in MN for subjects with high anti-PLA2R antibody titers (Ruggenenti et al 2012, van de Logt et al 2018).

Thus, an anti-CD38 directed specific plasma cell depletion by MOR202 may provide a viable emerging therapeutic option sparing patients of significant toxicity of broader acting immunosuppressive agents, possibly effective in patients with limited benefit of an anti-CD20 directed therapy.

4.1. Background - nonclinical studies

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[redacted]

4.1.3. Toxicology

Based on the high sequence identity between marmoset monkey and human CD38 protein, the comparable binding affinity and expression levels of CD38 on blood cells as well as the similar activity to induce ADCC by PBMCs, the marmoset monkey was selected as the relevant species for the non-clinical safety assessment of MOR202.

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[redacted]

CCI [redacted]

4.2. Background - clinical studies

To date, MOR202 has been administered in the first-in-human (FIH) study MOR202C101 in 91 subjects with MM. This study is a combined dose escalation and dose confirmation study with a maximum dose of 16 mg/kg administered i.v. once weekly (including a loading dose on Cycle 1, Day 4). MOR202 was applied either as a single agent or in combination with dexamethasone (DEX), lenalidomide (LEN)/DEX or pomalidomide (POM)/DEX. The overall treatment duration was based on clinical response with a continuous treatment for up to 3 years. The maximum tolerated dose (MTD) was not reached in this trial and the recommended dose was defined at 16 mg/kg once weekly (i.e. the highest dose tested). As of 30-Nov-2019, 21 subjects were treated at this dose level for more than 6 months (13 subjects for more than 12 months and 9 subjects for more than 24 months) (Jarutat 2018, Raab et al 2020). CCI [redacted]

4.2.1. Clinical pharmacokinetics and immunogenicity

The PK of MOR202 administered i.v. to MM patients has been well characterized by a 2-compartment population PK model. The volume of distribution was found to be increased at lower MOR202 doses most likely reflecting the impact of target-mediated drug disposition (TMDD) effects. So far, anti-drug antibody (ADA) samples from 85 MM subjects with a treatment duration up to a maximum of 3 years have been analyzed. No ADA has been detected to date.

4.2.2. Clinical safety

The most commonly reported treatment-emergent adverse events (TEAEs) in the FIH study (MOR202C101) in MM were hematological AEs, such as lymphocytopenia, leukocytopenia, thrombocytopenia, and anemia.

The combination drugs for MM used in the FIH study are intrinsically myelosuppressive when administered as single agents. Anti-CD38 monoclonal antibodies (mAbs) may further deteriorate cytopenias induced by such background therapy. Cytopenic effects are well known and manageable via treatment with colony stimulating factors and blood transfusions.

CCI [redacted]

Non-hematological TEAEs related to MOR202 reported in more than 5% of subjects overall in the FIH study were fatigue, infusion-related reactions, respiratory and urinary tract infections, diarrhea, nausea, hypokalemia, C-reactive protein increased, cough, constipation, hypophosphatemia, pyrexia, nasopharyngitis, and oral herpes.

Please refer to the Investigator Brochure for MOR202 for further details.

4.2.3. Clinical efficacy

In the MM studies, MOR202 has demonstrated clinical activity comparable to other CD38 targeting agents in MM in terms of overall response rates (Raab et al 2020). CCI [redacted]

4.2.4. Other anti-CD38 antibodies

Daratumumab and isatuximab have been approved for the therapy of different types of MM. TAK-079 is currently in mid stage clinical development for MM, systemic lupus erythematosus (SLE), myasthenia gravis and immune thrombocytopenic purpura.

There is no information available, whether these compounds were tested in patients with MN.

5. CLINICAL TRIAL PURPOSE AND OBJECTIVES

The purpose of the trial is to assess the safety and efficacy of the human anti-CD38 antibody MOR202 in subjects with aMN in two cohorts with subjects:

- Presenting with medium/high anti-PLA2R titer either newly diagnosed or after relapse and eligible for IST (Cohort 1) or
- With aMN refractory to IST (Cohort 2).

	Objective	Endpoint
Primary	To assess the safety and tolerability of MOR202 treatment in subjects with aMN.	Incidence and severity of TEAEs.
Key Secondary	To assess the effect of MOR202 on serum antiPLA2R antibodies in subjects with aMN.	Best immunological response: rate of sICR, ICR and IPR based on reduction of serum anti-PLA2R antibody titer.
Secondary	To assess the immunogenicity of MOR202 (anti-MOR202 antibody formation) in subjects with aMN.	Number and antibody titers of subjects tested positive for anti-MOR202 antibodies.
	To assess the PK profile of MOR202 in subjects with aMN.	MOR202 serum concentrations after multiple i.v. administrations.
	To assess the safety in subjects with aMN after MOR202 treatment and during the follow-up phase.	Incidence and severity of AEs in the follow-up phase.
Exploratory	CCI [redacted]	

	CCI	
	Additional exploratory analyses may be performed to characterize further potential pharmacodynamic biomarkers under MOR202 treatment.	CCI • Changes in peripheral blood immune cell populations. CCI

6. CLINICAL TRIAL DESIGN

6.1. Rationale

6.1.1. Rationale for this Clinical Trial

This trial primarily seeks to assess the safety and tolerability of MOR202 therapy in aMN subjects. As a key further objective, the immunological response under MOR202 therapy will be assessed. Reduction in proteinuria as an early clinical efficacy parameter will be measured as well.

The monoclonal anti-CD38 antibody MOR202 selectively binds to the CD38 antigen and thereby depletes antibody producing cells such as plasmablasts and plasma cells mainly via ADCC and ADCP.

Plasma cells and plasmablasts are the source of pathogenic anti-PLA2R antibodies. Published evidence shows a tight correlation of the clinical course of MN with PLA2R autoantibody titers: high titers and sustained or re-emerging positivity of anti-PLA2R antibody titers during therapy have been demonstrated as negative predictors for outcome. Here, MOR202's mode of action provides a compelling rationale for hard-to-treat aMN subjects, i.e. those presenting with high autoantibody titers, or subjects with insufficient immunological response to prior therapy.

6.1.2. Dosing Rationale

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6.2. Overall Clinical Trial Design and Investigational Plan

This phase Ib/IIa multicenter trial enrolls subjects with anti-PLA2R antibody positive membranous nephropathy (aMN) indicated for IST into two cohorts:

Cohort 1 will consist of approximately 20 aMN newly diagnosed or relapsing subjects stable on supportive care treatment with ACEI/ARB at screening with proteinuria and medium/high serum titers of anti-PLA2R antibodies eligible for IST. **(Note: Patients in France will not be enrolled in Cohort 1.)**

Cohort 2 will consist of approximately 10 subjects with aMN refractory to IST and requiring other forms of IST.

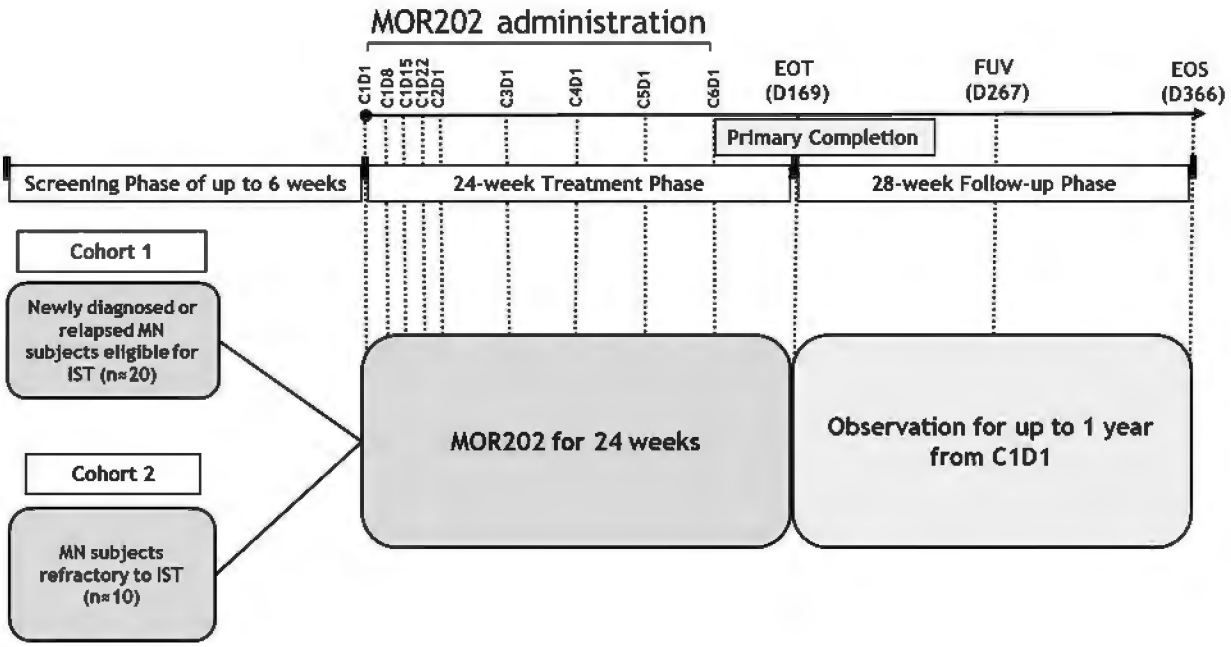
For detailed description of the subjects in Cohort 1 and 2 and the respective in- and exclusion criteria refer to Section 7.1 and Section 7.2.

The trial design includes a Safety Run-in, which in the initial stage of the trial intends to limit drug exposure to the first three subjects (see Section 6.3). The remainder of planned subjects may only start treatment contingent on a positive outcome of the safety observations in these initial three subjects.

All trial subjects, including the safety run-in subjects, will follow the clinical trial schedule (Figure 1) consisting of a

- Screening Phase
- Treatment Phase
- Follow-up Phase

Figure 1 Clinical Trial Schedule



6.3. Safety Run-in

As this is the first time that MOR202 is tested in subjects with aMN, a safety-run-in is planned.

The safety run-in period consists of the following:

The first three subjects dosed in this trial (regardless of cohort) will be treated and observed until C2D1 or until they have demonstrated a toxicity leading to discontinuation of treatment, whichever is earlier. In order to ensure sufficient exposure of three safety run-in subjects to MOR202, subjects will be replaced if within their first treatment cycle (C1) they

- Missed more than two doses of MOR202, or
- Discontinued treatment for reasons other than toxicities.

The safety run-in continues until three subjects are treated with sufficient exposure to MOR202. Replaced subjects may remain on trial and continue trial treatment as per protocol.

After the safety run-in, further subjects may start treatment unless any grade 4/5 ADR (related to MOR202) has occurred. If a grade 4/5 ADR occurs during the safety run-in, then a safety review must take place and start of treatment for further subjects will be contingent on the safety review outcome. The safety review will consist of an evaluation based on the number and type of all AEs occurring during the first cycle and laboratory values (biochemistry and hematology) and will be

performed by representatives of the participating investigators and the sponsor (Safety Review Panel) as defined in a respective charter. The safety review will be held after C2D1 of the third subject.

The outcome of this safety review will also provide a confirmation on the dose and dosing schedule for MOR202 or recommendation for an adapted dose and/or dosing schedule to be used in the following part of the trial or recommendation for termination of the trial because of unacceptable toxicity. Safety run-in subjects will continue the trial as per protocol during the safety review. Afterwards, their MOR202 dose may be altered as well.

6.4. Screening Phase

See Section 10.1 and Section 10.2.

6.5. Treatment Phase

All subjects enrolled in the trial will be treated for 24 weeks across six 28-day treatment cycles.

In total, 9 doses of MOR202 will be administered on the following treatment days: Cycle 1 Day 1, 8, 15 and 22, and on Day 1 of Cycle 2 to 6 (for details see Figure 1 and Table 2).

The Treatment Phase ends with the EOT visit, scheduled between 28 and 42 days after the last administration of MOR202. For details see Section 10.4.

6.6. Follow-up Phase

The follow-up phase consists of 28 weeks of post-treatment follow-up starting from the EOT visit. It consists of two visits at an interval of 14 weeks each.

The follow-up phase ends with the EOS visit, scheduled 28 weeks after the EOT visit. For details see Section 10.5.

6.7. Clinical Trial Duration

The duration of this trial is planned to be approximately 2 years from first subject signing the informed consent form (ICF) until trial completion.

Subjects will be on the clinical trial from signing of ICF until the EOS visit (i.e. a planned maximum time period of 58 weeks: up to 6-week screening phase, 24-week treatment phase and 28-week follow-up phase).

6.8. Risks and Benefits to Subjects

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[redacted]

Similar safety findings were also observed in the FiH trial MOR202C101 (see Section 4.2 and Section 6.1.2). In this trial administering MOR202 to MM subjects the most frequent MOR202 related treatment emergent adverse events (TEAEs) were thrombocytopenia, neutropenia, lymphopenia, and infections. No ADAs were detected in this trial until the primary completion date (samples analyzed from 85 subjects treated for up to 29 months at a maximum) (Jarutat 2018).

It is expected that the potential risks as described above will be adequately controlled by the design of this trial (e.g. by the inclusion and exclusion criteria) as well as by frequent monitoring for potential ADRs. Since a major pharmacological effect of MOR202 is depletion of plasma cells and plasmablasts, the risk for a potentially reduced function of the adaptive immune system was further addressed. This comprises monitoring and potential substitution of total serum immunoglobulin as well as vaccination before trial start (see Section 7.1 and Section 7.2).

MOR202 offers a novel mechanism of action that may have the potential to emerge as an important treatment option for aMN patients compared to current (off-label) treatment options. Particularly with calcineurin inhibitors (CNIs) being intrinsically nephrotoxic and cyclophosphamide as an alkylating cytotoxic drug being associated with known hematotoxicity, risk of ovarian insufficiency and secondary malignancy, new therapeutic options are needed for the treatment of MN. Recent literature suggests that RTX, although more favorable in the safety profile compared to the aforementioned drugs, might have decreased activity in high anti-PLA2R antibody titer subjects (Ruggenenti et al 2015). This patient population is specifically addressed by Cohort 1 of this trial.

Non response to an immunosuppressive regimen may be caused by survival of long-lived plasma cells producing anti-PLA2R antibodies. These cells demonstrate a high expression of MOR202's target CD38. This patient population is specifically addressed by Cohort 2 of this trial.

In this context and taking into account the existing clinical experience with MOR202, the overall risk/benefit ratio for the trial subjects is regarded as acceptable.

7. SELECTION OF SUBJECTS

All subjects must sign the ICF and must meet the following selection criteria at screening to participate in the trial.

7.1. Inclusion Criteria

Since deviations from inclusion criteria can have a negative impact on subject safety or the scientific integrity and regulatory acceptability of the clinical trial, the Sponsor will not provide waivers to them *(parameters in italics will be tested at screening; parameters not in italics will be determined locally)*:

Cohort 1 and 2:

1. ≥ 18 to ≤ 80 years (at date of signing ICF).
2. *Urine protein to creatinine ratio (UPCR) of ≥ 3.000 g/g OR proteinuria ≥ 3.500 g/24 h from 24 h urine at screening.*
3. Anti-PLA2R antibody positive MN in need of IST according to the investigator's judgment. The diagnosis of MN should be histologically documented with a diagnostic biopsy; for this purpose, a biopsy at screening or an archival biopsy acquired within 5 years prior to screening is acceptable.
4. *Estimated glomerular filtration rate (eGFR) ≥ 50 mL/min/1.73 m². Alternatively eGFR ≥ 30 and < 50 mL/min/1.73m² and interstitial fibrosis and tubular atrophy (IFTA) score < 25% in a renal biopsy obtained within the last 6 months prior to start of screening* (if not available, a biopsy should be performed at screening to obtain the IFTA assessment).

5. Not in spontaneous remission despite proper treatment with ACEIs, ARBs (sufficient dose and treatment duration) as per clinical practice and scientific guidelines. If the Principal Investigator determines that a subject is intolerant to an ACEI or ARB, the reason must be documented and approval obtained from the Medical Monitor prior to enrolment.
6. Systolic blood pressure (BP) ≤ 150 mmHg and diastolic BP ≤ 100 mmHg after 5 minutes of rest.
7. Subject vaccinated against Pneumococcus within the last 5 years prior to date of signing ICF (subjects may be vaccinated to meet this criterion during screening; interval to first dose of MOR202 must be at least 14 days [MSD SmPC]).
8. Cohort 1 comprises newly diagnosed or relapsed subjects: *Serum anti-PLA2R antibodies ≥ 50.0 RU/mL determined at screening by Euroimmun ELISA at central laboratory.*
9. Cohort 2 comprises therapy refractory subjects:
    a. Subject did not achieve immunological remission after prior IST(s) as documented by the investigator AND
    b. Subject is without promising standard therapeutic options as documented by the investigator (i.e. investigator expects efficacy or safety issues with remaining IST options) AND
    c. *Serum anti-PLA2R antibodies ≥ 20.0 RU/mL measured at screening by the Euroimmun ELISA at central laboratory.*

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[redacted]

Note: France will only enroll patients in Cohort 2.

7.2. Exclusion Criteria

Since deviations from exclusion criteria can have a negative impact on subject safety or the scientific integrity and regulatory acceptability of the clinical trial, the sponsor will not provide waivers to them. Subjects must be excluded from participating in this clinical trial if they meet any of the following criteria at screening *(parameters in italics will be tested at screening;* parameters not in italics will be determined locally):

1. *Hemoglobin ≤ 80 g/L†*
2. *Thrombocytopenia: Platelets ≤ 100.0 × 10^9/L**
3. *Neutropenia: Neutrophils ≤ 1.5 × 10^9/L#*
4. *Leukopenia: Leukocytes ≤ 3.0 × 10^9/L#*
5. *Hypogammaglobulinemia defined as serum immunoglobulin ≤ 4.0 g/L‡*

† Subjects may receive blood transfusions or erythropoietin to meet the criterion.
* Subjects may receive thrombopoietin to meet the criterion.
# Subjects may receive colony stimulating factors to meet the criterion.
‡ Subjects may receive immunoglobulin substitution to meet the criterion.

6. *B-cells ≤ 5 × 10^6/L.*
7. Secondary cause of MN (e.g. SLE, medications, malignancies) as determined by the investigator.
8. Concomitant renal disease other than MN (e.g., diabetic renal disease, lupus nephritis, IgA nephropathy).

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[redacted]

8. TREATMENT OF SUBJECTS

8.1. Prior Therapy

The following prior therapy will be recorded in the eCRF:

- All prior medications/non-drug procedures given for MN.
- All prior immunosuppressive medications.
- All other medication and other therapy (including non-drug procedure) taken by/administered to the subject within 30 days prior to signature of ICF.

The entry must include the dose, regimen, route of administration, indication, and dates of use (start, end).

8.2. Investigational Medicinal Product (IMP)

Each Investigator is responsible for ensuring that deliveries of IMP(s) and other clinical trial materials from the sponsor are completely and correctly received, recorded, handled and stored safely and properly in accordance with all applicable regulatory guidelines, and used in accordance with this clinical trial protocol.

The IMP must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the IMP will be limited to the Investigator or designee. The IMP must be dispensed or administered only to subjects enrolled in the clinical trial and in accordance with the protocol. After the clinical trial and overall drug accountability, all unused IMP must be returned to the sponsor or destroyed on site following the Drug Handling Manual.

8.2.1. MOR202

MOR202 antibody (i.e. compound MOR03087, this protocol refers to as MOR202) will be supplied by the sponsor as a lyophilized powder for reconstitution in labelled glass vials. MOR202 must be stored at 2-8°C until use.

MOR202 will be labelled according to applicable regulatory requirements. All chemical, physical and pharmaceutical characteristics are summarized in the Investigator's Brochure.

8.2.2. Preparation and application of MOR202 including prophylaxis of infusion reactions

MOR202 will be administered i.v. at a dose of 16 mg/kg. Preferably, body weight data will be collected in the morning of the dosing day. In case this is not possible, the MOR202 dose must be based on a weight determined within 14 days prior to dosing.

For administration, CCI [redacted] The individual MOR202 infusion will be prepared under aseptic conditions and administered at the trial site according to the directions of the Drug Handling Manual.

CCI [redacted]

8.3. Concomitant Therapy

Subjects are allowed to continue medications that they are taking at baseline, particularly, supportive therapy for MN and therapy initiated at screening such as immunoglobulin substitution or erythropoiesis stimulating agent (ESA) therapy. Subjects are allowed to receive concomitant medications that are medically indicated as standard of care for the treatment of symptoms and intercurrent illnesses, unless they fall under prohibited medications. Subjects may also receive therapy to mitigate side effects of the trial medication as clinically indicated, as well as best supportive care as per institutional guidelines. This may include medications such as diuretics, anti-lipid-medication, anti-hypertensive (e.g. ACEI), anticoagulation, antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, or antibiotics. The Investigator should instruct the subject not to take any additional medications (including over-the-counter products) during the trial without prior consultation.

Investigators should document all medication and other therapy (including non-drug procedure) taken by/administered to the subject during the entire course of the trial including the screening and the follow-up phase. The entry must include the dose, regimen, route of administration, indication, and dates of use (start, end).

8.3.1 Management of Infusion Related Reactions (IRRs)

If a subject presents with a grade 1 or 2 infusion reaction:

- The infusion should be stopped immediately.
- The subject should receive appropriate further treatment with an antihistamine, paracetamol (acetaminophen), and glucocorticoids as clinically indicated.

- Once the symptoms have been resolved or reduced to "mild" according to the investigator's assessment, the infusion can be continued at an infusion rate of 50% of the initial rate. If, after 1 hour, the subject is symptom-free and vital signs are stable, the infusion rate may be increased every 30 minutes by approximately 25% of the reduced rate as tolerated.
- If a subject who developed a grade 1 or 2 IRR will receive further infusions, then premedication with glucocorticoids either as mandated by this protocol or by local guidelines should be given before start of any subsequent MOR202 infusion. The infusion rate should be slowed down and the duration of infusion should exceed that of the last prior infusion by at least 30 minutes.

If a subject exhibits a grade 3 IRR:

- The infusion should be stopped immediately.
- The subject must receive appropriate treatment with an antihistamine, paracetamol (acetaminophen), and glucocorticoids and, as necessary, further medications (i.e. epinephrine, bronchodilator).
- Only after the resolution of all symptoms to ≤ grade 1, and after having received appropriate prophylactic medication(s) as described above, the infusion may be resumed at an infusion rate of 25% of the initial rate. If, after 1 hour, the subject's symptoms do not return and vital signs are stable, the infusion rate may be increased to a maximum of 50% of the initial rate.
- If, after the resumption of the infusion, symptoms return (irrespective of grade), the infusion must be discontinued for that visit date and the infusion tubing should be disconnected. Based on the investigator's decision, the subject may receive further MOR202 at the next scheduled visit provided clinically appropriate precautions were taken.
- If a subject who developed a grade 3 IRR will receive further infusions, then premedication with glucocorticoids either as mandated by this protocol or by local guidelines should be given before start of any subsequent MOR202 infusion. The infusion rate should be slowed down and the duration of infusion should exceed that of the last prior infusion by at least 30 minutes.

If a subject presents with a grade 4 IRR:

- The infusion must be discontinued immediately and the infusion tubing should be disconnected.
- The subject must receive appropriate treatment with an antihistamine, paracetamol (acetaminophen), and glucocorticoids and, if necessary, further medications (i.e. epinephrine, bronchodilator).
- The subject must not receive any further MOR202 infusion and must discontinue trial treatment, subject may enter the follow-up phase.

8.3.2 Infection Prophylaxis

The immunoglobulin level will be monitored throughout the trial. If this level drops below 4 g/L, initiating substitution therapy with a polyvalent immunoglobulin according to local institutional guidelines is advised. Generally, a trough level of at least 5 g/L shall be targeted, with a substitution of 0.2 g per kg body weight every 3 to 4 weeks.

Furthermore, investigators may follow institutional guidelines on infection prophylaxis for subjects regarded to be at high risk of infection.

8.4. Prohibited Therapy: Immunosuppressive therapies (IST)

The use of ISTs other than MOR202 is prohibited during the entire trial. This includes, but is not limited to ACTH, chemotherapies, immunotherapy, biological response modifiers, mAbs with or without conjugation, CNIs (e.g. cyclosporine, tacrolimus), plasmapheresis and immuno-adsorption. MOR202 treatment of subjects in need of immunosuppressive therapies must be discontinued and the subject must be discontinued from the trial (see Section 8.8.5).

Subjects in need of systemic corticosteroid therapy other than for prophylaxis and treatment of IRR for more than 7 days may continue being treated with MOR202, but will be excluded from the Per Protocol Analysis Set and the Immunological Analysis Set (IAS).

8.5. Treatment Adherence

Subjects will receive MOR202 under the direct supervision of site personnel. Each administration volume or dose will be checked.

The vial/outer package code and volume or dose per administration will be recorded in each subject's eCRF as well as in the source data. At each visit after initiation of treatment, site staff will record adherence of subjects to their assigned regimen.

Non-adherence is defined as administering ≤ 70% or > CCI of a MOR202 dose.

Any MOR202 dose missed without a medical reason is considered a non-adherence.

8.6. Overdose

In this clinical trial, an overdose of MOR202 is defined as a dose exceeding CCI of the planned dose.

In clinical trial MOR202C101, four incidents of doses exceeding the calculated dose were noted, all of these doses exceeded the planned dose by no more than 10.5% and affected subjects remained asymptomatic.

In case of overdose, infusion should be discontinued immediately and subjects should be closely monitored for signs or symptoms of AEs for 24 hours, and appropriate symptomatic treatment instituted immediately if needed. No specific antidote is available. Overdose with clinical symptoms will be reported as AE (non-serious or serious) in accordance to Section 10.8.10.

8.7. Treatment management of subjects with toxicity

For the first dosing of MOR202, subjects should exhibit hemoglobin, leucocyte, neutrophil and platelet counts meeting the eligibility criteria. They should not have an active infection ≥ grade 2.

For subsequent doses, in case a subject shows laboratory values as listed below, further treatment of the subject has to be interrupted:

- Hemoglobin level < 60 g/L (grade 3): interruption until resolved to ≥ 80 g/L.
- Platelet count < 75.0 x 10^9/L (grade 2): interruption until resolved to ≥ 100.0 x 10^9/L.
- Neutrophil count < 1.000 x 10^9/L (grade 3): interruption until resolved to ≥ 1.500 x 10^9/L.

If the subject exhibits any other clinically relevant adverse drug reaction ≥ grade 3, MOR202 administration has to be interrupted until the toxicity has resolved to grade 2 or better.

8.8. Subject Discontinuation of IMP and Subject Withdrawal

8.8.1. Discontinuation due to toxicity

MOR202 treatment must be permanently discontinued, if:

- Needing platelet transfusion.
- Not recovering to ≤ grade 2 from ≥ grade 3 ADRs related to MOR202 within 21 days despite adequate treatment of the ADR.
- Experiencing grade 4 IRR.

Subjects discontinuing MOR202 treatment will have their EOT visit (earliest after 28 days after last dose of MOR202) and enter the follow-up phase.

8.8.2. Discontinuation due to other reasons

MOR202 treatment must be permanently discontinued for subjects:

- With progressive disease as defined in Section 3.2
- Wishing to discontinue MOR202 treatment
- With pregnancy

Investigator(s) have the right to discontinue subjects from MOR202 treatment in the event of illness, AEs, or other reasons putting a risk to the health or well-being of the subject, or in case of lack of subject's co-operation.

The reason for discontinuing MOR202 treatment must be noted in the eCRF.

Subjects discontinuing MOR202 treatment will have their EOT visit (earliest after 28 days after last dose of MOR202) and enter the follow-up phase.

8.8.3. Discontinuation due to efficacy - stringent immunological complete remission

Furthermore, treatment may be discontinued for subjects with stringent immunological complete remission (sICR) confirmed by repeat measurement at least 25 days apart. These subjects will follow their planned schedule, but will not be treated at the following CxD1 visits, unless a subject turns positive again during the treatment phase.

8.8.4. Withdrawal due to Subject Decision

Each subject is free to withdraw from the clinical trial at any time. All efforts will be made to complete and report the observations up to the time of withdrawal as thoroughly as possible. A complete final evaluation at the time of the subject's withdrawal should be made (all assessments scheduled for EOT/EOS visit depending on time of withdrawal). An explanation why the subject

is withdrawing from the clinical trial should be provided. If withdrawn in the treatment phase, these subjects will not enter the follow-up phase.

8.8.5. Withdrawal due to Use of Prohibited Therapy [Immunosuppressive Therapy]

Subjects starting on prohibited IST other than MOR202 will be withdrawn from the clinical trial. If withdrawn in the treatment phase, these subjects will immediately be scheduled for their EOT visit (at least 28 days after the last MOR202 dose) and will not enter the follow-up phase.

8.9. Subject replacement

After safety run-in, withdrawn or discontinued subjects will not be replaced.

8.10. IMP Accountability

The assigned pharmacist or other designated individual at the site will maintain up-to-date records:

- Of IMP delivered to the site
- The dispensation to and use by each subject
- And the return of unused IMP to the sponsor or disposal

9. TRIAL PAUSING OR TERMINATION

9.1. Safety Review Triggers and Decision Making

After completion of the safety run-in, toxicities leading to discontinuation will be continuously monitored. Recruitment into the MOR202C103 clinical trial will be paused in the following situation until a safety review by the Safety Review Panel consisting of representatives of the participating investigators and the sponsor (as defined in Section 6.3) is performed:

- If at any time treatment with MOR202 had to be discontinued due to the reasons listed in Section 8.8.1 in at least 2 subjects treated.

The safety review will consist of an evaluation based on the number and type of AEs and laboratory values (biochemistry and hematology) and will be performed by representatives of the participating investigators and the sponsor as defined in a respective charter. Based on the assessment, the Safety Review Panel (see Section 6.3) will decide on further steps, e.g. pause of dosing in all subjects, introduction of any required protocol changes or trial termination due to unacceptable toxicity.

Additional safety review may be triggered at any time if any of the following occur:

- Thrombocytopenia ≥ grade 3 in at least 4 subjects
- IRR ≥ grade 3 in at least 4 subjects
- A single patient is not recovering to ≤ grade 2 from ≥ grade 3 ADRs related to MOR202 within 21 days despite adequate treatment of the ADR.

The Safety Review Panel will convene, perform a safety review and make recommendations as outlined above.

9.2. Clinical Trial (Site) Termination

The sponsor can terminate this clinical trial for any reason at any time.

10. CLINICAL TRIAL ASSESSMENTS

The Schedule of Assessments is presented in Table 2. All examinations or assessments to be performed at a specific visit are indicated with an X. Results obtained from these assessments need to be documented in the hospital record of the subject unless they are generated in a central laboratory.

Visits maybe postponed due to AEs as described above (see Section 8.7), but in all other situations conducting visits as scheduled is important.

Each treatment cycle (C) consist of 28 days (D). Allowed visit windows are

- ± 2 days for C1D8 to C2D1,
- ± 7 days for C3D1 to C6D1,
- + 14 days for EOT visit, and
- ± 14 days for FUV and EOS visit.

Further excursions from the timing of assessments will be considered protocol deviations and should be recorded in the source documents along with the reason.

The date of the next visit will always be recalculated based on the actual date of the previous IMP administration.

Subjects missing a treatment visit within the specified visit window for reasons other than toxicity will get the next dose at the next scheduled visit and thus receive less than the planned 9 MOR202 applications.

Table 2 Schedule of Assessments

Clinical Trial Schedule of Assessments	SCR	BL C1D1	C1D8	C1D15	C1D22	C2D1	C3D1	C4D1	C5D1	C6D1	EOT	FUV	EOS
Day[6] Tests/assessments	-42 to -1	1	8 ±2 days	15 ±2 days	22 ±2 days	29 ±2 days	57 ±7 days	85 ±7 days	113 ±7 days	141 ±7 days	169 +14 days	267 ±14 days	366 ±14 days
Informed consent	X												
Medical history/ demography/ disease therapy history/ allergies and hypersensitivities	X												
Inclusion/exclusion	X												
Recording of prior/concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	X[3]									X		
Kidney biopsy	X[4]												X[5]

Clinical Trial Schedule of Assessments	SCR	BL C1D1	C1D8	C1D15	C1D22	C2D1	C3D1	C4D1	C5D1	C6D1	EOT	FUV	EOS
Day6 Tests/assessments	-42 to -1	1	8 ±2 days	15 ±2 days	22 ±2 days	29 ±2 days	57 ±7 days	85 ±7 days	113 ±7 days	141 ±7 days	169 +14 days	267 ±14 days	366 ±14 days
Blood typing and screening for irregular antibodies at local blood bank	X6												
Full physical examination (Limited)	X	L	L	L	L	L	L	L	L	L	X	L	X
Height	X												
Body weight	X	X2	X2	X2	X2	X2	X2	X2	X2	X2	X	X	X
Vital signs	X	X2	X2	X2	X2	X2	X2	X2	X2	X2	X	X	X
Adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X
CCI													
Serum pregnancy (in FCBP)	X										X	X	X
Urine pregnancy (in FCBP)		X2	X2	X2	X2	X2	X2	X2	X2	X2			
Pregnancy and risk counselling	X												
Hepatitis B/C, HIV Serology/Virology	X												
Urine analysis	X	X2				X2		X2		X2	X		X
24 h urine collection for UPCR ratio, Na+	X	X2						X2			X	X	X
Single urine sample: UPCR ratio#	X	X2						X2	X2	X2	X	X	X
Anti-PLA2R antibodies	X	X2	X2	X2	X2	X2	X2	X2	X2	X2	X	X	X
CBC with differential blood	X	X2	X2	X2	X2	X2	X2	X2	X2	X2	X	X	X
Serum Biochemistry, Immunoglobulins	X	X2	X2	X2	X2	X2	X2	X2	X2	X2	X	X	X
Hba1c	X9												
Coagulation		X2		X				X			X		
Lipid panel	X					X					X		
On site hematology		X2	X2	X2	X2	X2	X2	X2	X2	X2			

Clinical Trial Schedule of Assessments	SCR	BL C1D1	C1D 8	C1D 15	C1D 22	C2D 1	C3D 1	C4D 1	C5D1	C6D1	EOT	FUV	EOS
Day[6] Tests/assessments	-42 to -1	1	8 ±2 days	15 ±2 days	22 ±2 days	29 ±2 days	57 ±7 days	85 ±7 days	113 ±7 days	141 ±7 days	169 +14 days	267 ±14 days	366 ±14 days
MOR 202 infusion with pre-infusion medication		X	X	X	X	X	X	X	X	X			
PK sampling MGR202 (serum)		X1	X1	X1	X1	X1	X2	X2	X2	X2	X	X	X
PK sampling MGR202 (urine) (spot check) [4]		X2	X2	X2		X2	X2	X2	X2	X2	X	X	X
ADA sampling		X2					X2		X2	X2	X	X	X
Biomarker sampling (blood)	X8	X2	X2	X2		X2		X2			X	X	X
Biomarker sampling (serum)[2]		X1	X1	X1		X2		X2			X	X	X
Biomarker sampling (urine) (spot check)[3][4]		X2	X2	X2		X2		X2			X	X	X
CCI [redacted]													

X1: predose and 30 min after end of infusion;
X2: predose, MOR202 may not be applied without baseline UPCR value from 24 h urine collection,
X3: postdose;
X4: mandatory for all subjects if not done within the last 5 years before start of screening, mandatory for subjects with eGFR < 50ml/min/1.73m2 or with diabetes mellitus type 2 if not done within the last 6 months before start of screening, optional for all other patients;
X5 optional for subjects who had a kidney biopsy at screening,
X6: see Section 10.1 of clinical trial protocol,
X7: predose during treatment phase, only for subjects who provided optional consent for future research,
X8: Only B-cell, T-cell, and natural killer (NK) cell counts,
X9: only in subjects with diabetes mellitus type II

SCR: screening, BL: baseline; EOT: end of treatment; FUV: follow-up visit, EOS: end of study

[1]Immune cell counts CCI [redacted]

[2]Antigen specific immunoglobulin levels CCI [redacted]

CCI [redacted]

[6]The date of the next visit will always be recalculated based on the actual date of the previous IMP administration. Thus, the actual number of days from baseline visit (C1D1) for an individual subject might differ from the standard scheme as shown in the Schedule of Assessments in the protocol.

For screening, subjects will be given supplies for collection of a 24-hour urine sample at screening and will return with the collected sample within the screening phase. For other visits, the sample will be collected 24 hours immediately prior to the visit. Subjects who forget to collect this sample prior to the visit, start a 24-hour urine sample at the same visit day and return it the next working day. If the collected urine does not contain at least 5 mg creatinine/kg/day for females and 6 mg creatinine/kg/day for males, urine collection needs to be repeated.

Clinical Trial Schedule of Assessments	SC R	BL C1D1	C1D 8	C1D 15	C1D 22	C2D 1	C3D 1	C4D 1	C5D1	C6D1	EOT	FUV	EOS
Day6	-42 to -1	1	8 ±2 days	15 ±2 days	22 ±2 days	29 ±2 days	57 ±7 days	85 ±7 days	113 ±7 days	141 ±7 days	169 +14 days	267 ±14 days	366 ±14 days
Tests/assessments													
Limited PEs must include vital signs and general appearance and may be focused on clinical symptoms observed. If clinically indicated, a full PE must be performed at any trial visit.													
Parameters in italics are measured in a central laboratory.													

10.1. Screening Phase

All subjects must meet all inclusion criteria and none of the exclusion criteria listed in Section 7.1 and Section 7.2. Signed and dated informed consent must be obtained from all subjects prior to their entering the clinical trial.

The Screening Phase begins on the date when the ICF is signed; it will last for up to 42 days and is followed by treatment start (Cycle 1 Day 1, C1D1).

The assessments to be performed at screening are:

Documentation of

- Informed consent
- Medical history including results of biopsies and disease therapy history
- Laboratory values including
  - proteinuria
  - all available historic anti-PLA2R titers and IFT results
- Demography (age, gender, race)
- Prior and concomitant medications
- Allergies and hypersensitivities

Assessment of

- In- and exclusion criteria
- Physical examination
- Electrocardiogram (ECG)
- Vital signs (blood pressure, heart rate, body temperature)
- Weight (in kg without decimals with 1st decimal rounding in case of higher precision scales; e.g. 67.4 rounded to 67; 67.5 rounded up to 68)
- Height (in centimeter without decimals)

Laboratory

- Complete blood count with differential white blood cell count (CBC)
- B-cell count
- HbA1c
- Serum biochemistry including immunoglobulins

- Hepatitis B/C, HIV Serology/Virology (incl. PCR confirmation)
- Lipid panel
- Urine analysis
- eGFR
- Liver function tests (AST, ALT, gamma-GT, bilirubin)
- 24 hour urine for urine protein, creatinine, and sodium

An abnormal laboratory value may be reanalyzed during the screening phase.

Substitution with immunoglobulins before or during screening is permitted. Data on immunoglobulin administration should be entered in the eCRF as concomitant medication.

24 hour urine:

For screening, subjects will be given supplies for collection of 24-hour urine and will return the collected sample within the visit window. For visits C4D1, EOT, FUV, and EOS the sample will be collected prior to the visit. Subjects who forget to collect this sample prior to the visit, start a 24-hour urine sample at the visit day and return it the next working day after completion. If the collected urine does not contain at least 5 mg creatinine/kg/day for females and 6 mg creatinine/kg/day for males, urine collection needs to be repeated immediately without undue delay.

Kidney biopsy

- Mandatory:
  - For all subjects if not done within the last 5 years before start of screening.
  - For subjects with eGFR < 50 mL/min/1.73m^2 if not done within the last 6 months before start of screening.
  - For subjects with diabetes mellitus type 2 if not done within the last 6 months before start of screening.
- Optional:
  - For all other subjects.

The histological assessment of a fresh kidney biopsy obtained under this clinical trial protocol should include a confirmation of the diagnosis of MN as well as the grade of any existing interstitial fibrosis. Biopsies will further be subject to biomarker studies as outlined in the exploratory objectives, theses analyses will be retrospective in nature.

Females of child bearing potential (FCBP, for definition see above Section 7.1) will be tested for pregnancy (serum or urine analysis at different visits). Of note, in each case of delayed menstrual period (over one month between menstruations during the study) confirmation of absence of pregnancy with pregnancy test (urine or serum on discretion of investigator) is strongly recommended. This recommendation also applies to FCBP with infrequent or irregular menstrual cycles.

FCBPs and non-vasectomized males will be counselled for pregnancy risks.

The assessments performed during screening may substitute as baseline data if for any reason baseline values from the baseline period (Section 10.3 and Table 2) are missing.

On a single occasion during screening, it is permitted to repeat the central laboratory assessments of serum chemistry and hematology if out-of-range laboratory results might have been caused by a transient, medically plausible event, e.g. dehydration. The repeat procedure and the rationale behind must be documented in the source data. Such repeated assessment will not be counted as "re screening" for that subject.

For all screening failure subjects data on demographics and inclusion/exclusion criteria will be documented in the eCRF. Serious adverse events will be reported in accordance with Section 10.8.10.

For subjects requiring blood transfusions the presence of high levels of therapeutic anti-CD38 antibodies in host serum like MOR202 most likely interferes with blood bank serologic tests, particularly the indirect Coombs test (Oostendorp et al 2015, Weinig 2017 [MOR202L069]).

Therefore, subjects must be typed and screened for the eventual presence of irregular antibodies before the first administration of MOR202. Phenotyping may be considered prior to starting MOR202 treatment as per local practice. Red blood cell genotyping is not impacted by CD38 antibodies and may be performed at any time.

In the event of a planned transfusion blood transfusion centers should be notified of the interference with indirect antiglobulin tests.

If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.

Further technical guidance to mitigate this interference is published in the AABB bulletin #16-02 (AABB), e.g. a baseline typing and screening for irregular antibodies before starting MOR202 treatment and/or the use of dithiothreitol (DTT)-treated cells for antibody detection (screening) and identification during MOR202 treatment as well as at least 6 months after the last MOR202 administration (Chapuy et al 2016, Chapuy et al 2015).

10.1.1. Screening Failures

Subjects who sign an informed consent but fail to start treatment for any reason will be considered a screen failure. Minimum data requirements for the eCRF are: the reason for not starting treatment, demographic information, and SAEs.

10.2. Re-screening Procedures

Subjects can be re-screened at the discretion of the investigator under certain circumstances. Rescreening is restricted to one attempt per subject and can only be performed if one of the following criteria is met:

- The subject has already consented and met all of the inclusion and none of the exclusion criteria and his or her enrollment was delayed due to an unexpected change in the subject's personal situation (e.g., family issues).
- The subject previously failed to be eligible due to a circumstance (e.g., planned surgery, pathological laboratory test result) that has resolved.
- The subject previously failed screening but has become eligible for the trial based on a change in the inclusion and exclusion criteria as a result of a protocol amendment.

- The subject was successfully screened but could not start treatment within the screening phase.

The following procedures apply:

- The subject must sign and date a new ICF as part of the rescreening procedure.
- The subject will receive a new unique identification number via the interactive response technology.
- A new electronic case report form (eCRF) should be completed.
- The subject will be documented as rescreened in the source documents.
- All screening procedures must be completed again.

A rescreened subject can be enrolled, if all of the inclusion criteria are met and none of the exclusion criteria are met.

10.3. Baseline – Cycle 1 Day 1 immediate pre-dose assessments

Before administration of MOR202, any missing data from screening shall be obtained. For assessments refer to the Schedule of Assessments (Table 2). MOR202 may not be applied without baseline UPCR value from 24 h urine collection.

Subjects who forget to collect a 24-hour urine sample prior to the baseline visit must not be dosed. The subject must complete a 24-hour urine sample on the day of the rescheduled baseline visit before dosing.

10.4. Treatment Phase

In the first treatment cycle MOR202 will be administered at 16 mg/kg once weekly (i.e. 4 doses for cycle 1 in total). In treatment cycle 2-6 MOR202 will be administered at 16 mg/kg once every 4 weeks on the first day of each cycle (i.e. C2D1, C3D1, ...; 5 doses for Cycle 2 to 6 in total). For assessments refer to the Schedule of Assessments (Table 2).

Before each dose of MOR202, the complete blood count (CBC) needs to be determined at the local laboratory. The time window from blood draw to MOR 202 application should not exceed 48 hours. The values need to be recorded in the eCRF.

10.5. Follow-up Phase

Safety measurements will be performed in the Follow-Up Phase which spans from the EOT Visit until the EOS Visit: **EOT takes place 28 days after the last administration of MOR202.** The visit window is + 14 days, thus up to 42 days after the last administration of MOR202. After the EOT visit subjects will be followed up for further 28 weeks at two visits with an interval of 14 weeks each: FUV and EOS. For assessments refer to the Schedule of Assessments (Table 2).

10.6. Early Discontinuation and Withdrawal

See Section 8.8.

10.7. Efficacy Assessments

CCI

[redacted]

For details refer to the Schedule of Assessments (Table 2).

10.8. Safety Assessments

Safety monitoring for all subjects enrolled will include laboratory safety assessments (e.g., hematology, serum biochemistry, urinalysis and coagulation) and clinical evaluations (e.g., physical examinations, vital signs, 12-lead ECG) as detailed in the Schedule of Assessments (Table 2).

Laboratory and AE toxicities will be graded according to NCI-CTCAE, version 5.0. Subjects who experience any toxicity should be followed until the toxicity has stabilized, the toxicity has returned to the baseline level, or a new treatment has commenced.

10.8.1. Clinical Safety Laboratory Evaluation

Blood and urine samples for safety assessment will be obtained for various parameters as displayed in Table 3 as described in the Schedule of Assessments (Table 2). The collection time will be documented in the eCRF.

Table 3 Clinical safety laboratory parameters

Evaluation	Analysis
On site hematology (EDTA blood)	CBC with differential count Erythrocyte sedimentation rate
Hematology *(EDTA blood)*	*CBC with differential count* *B-cell count*
Serum biochemistry *(serum sample)*	*ALT, total albumin, alkaline phosphatase, amylase, AST, bicarbonate, bilirubin (total), urea, total calcium, chloride, creatinine, creatinine kinase, GGT, glucose, LDH, lipase, phosphate, potassium, protein (total), sodium, uric acid, magnesium, β_2-microglobulin, C-reactive protein, immunoglobulins, Hba1c in subjects with diabetes mellitus type II*
Coagulation parameters *(sodium citrate blood)*	*Activated partial thromboplastin time, prothrombin time, international normalization ratio, D-dimers*

Serology parameters (serum sample)	*HIV-1/2 antibodies;* *HCV antibody (if positive HCV RNA PCR)* *HBs antigen (qualitative), HBs antibody, HBc antibody (if isolated positive, HBV DNA PCR)*
Pregnancy test (serum sample)	*FCBP only: serum ß-HCG*
Pregnancy test (urine)	FCBP only: ß-HCG urine, Test assay should have a minimum sensitivity of 25 IU/mL (urine sticks will be provided centrally).
Urinalysis	Appearance, color, urine bilirubin, glucose, hemoglobin, ketones, pH, protein, specific gravity, urobilinogen. Microscopy will only be performed if clinically indicated.
Parameters in italics are measured in a central laboratory.	

The values of the central laboratory will be transferred electronically to the eCRF with the corresponding normal ranges.

The investigator needs to specify for any abnormal laboratory findings whether clinically relevant or not. If the finding is considered clinically relevant, it constitutes an AE and should be recorded as such in the eCRF. Additional diagnostic tests are at the discretion of the investigator.

10.8.2. Vital Signs

Vital signs will be measured as described in the Schedule of Assessments (Table 2). Vital sign parameters include measurements of heart rate, body temperature, and systolic/diastolic BP. BP and heart rate are measured after a period of 5 minutes of rest. The subject should take the same position each time heart rate and blood pressure are measured. BP should be measured from the arm contra-lateral to the site of IMP administration whenever possible.

10.8.3. Electrocardiograms

A standard 12-lead ECG will be obtained as described in the Schedule of Assessments (Table 2). All ECG recordings will be read at the site according to local practice.

10.8.4. Physical Examination

Physical examination (PE) will be performed according to the Schedule of Assessments (Table 2). A full PE will be performed at the screening, EOT and EOS visit.

Full PE should include at least vital signs, general appearance, skin, head, eyes, ears, nose, throat including Waldeyer lymphatic structures, lungs, breasts and axillae, lymph nodes, cardiovascular system, back and spine, abdomen (if applicable including spleen size below the costal margin), extremities, infusion site, and a basic neurological examination (if any neurological abnormalities are noted, a full neurological examination will be performed).

Limited PEs must include at least vital signs and general appearance and should be focused on clinical symptoms observed. If clinically indicated, a full PE must be performed at any trial visit.

10.8.5. Adverse Events (AEs)

Site personnel must remain vigilant for the occurrence of AEs. It is their responsibility to detect, document and report (S)AEs.

An AE is defined as any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to that product.

Generally, the diagnosis instead of the individual symptoms should be reported as the AE term. If a diagnosis has been reported as an AE, it is not necessary to report each individual sign and symptom of that AE as a separate AE. For example, if a febrile neutropenia is reported as an AE, there is no need to report neutrophil count decrease and fever above 38°C, or other related signs, symptoms, or laboratory values as separate AEs. However, if such events occur in isolation, and febrile neutropenia is not diagnosed, then each event should be reported as an AE.

Death should be considered an outcome and not a distinct event. The event or condition that caused the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported.

AEs include any clinically significant deterioration of a subject's medical status after signing of the ICF. Also an increase in the frequency or intensity of a pre-existing episodic event or conditions and events resulting from protocol mandated procedure (e.g. invasive procedures) fall under the definition of AE.

The following events **do not** meet the AE definition:

- Medical procedures will not be reported as AE. The underlying condition being the reason to perform the medical procedure will be reported as AE.
- Events without an untoward medical occurrence (e.g. planned surgery with hospitalization for conditions already existing at screening).
- Progression of underlying disease will not be reported as AE.
- Pre-existing diseases or pre-existing medical conditions known or detected before ICF signature and not increasing in severity.

All serious and non-serious AEs must be followed up for a final outcome until the end of the follow-up phase. Subjects prematurely withdrawn from the clinical trial will be followed up at least until 28 days after last IMP treatment. A final outcome of "unknown" is not considered acceptable. A final outcome of "not yet resolved" is acceptable.

The subjects will be closely observed and questioned for any kind of AE during the clinical trial procedures and at follow-up appointments throughout the clinical trial period with non-leading questioning (e.g. "How do you feel?"). The subjects will be instructed to immediately report any symptoms and signs to the site personnel (i.e. between formal observations).

10.8.6. Serious Adverse Events (SAEs)

An SAE is defined as any AE that:

- Results in death
- Is life threatening (immediate risk)
- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization signifies that the subject was an inpatient for at least one overnight stay) unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with deterioration of symptoms related to aMN.
  - Elective or pre-planned treatment for a pre-existing condition that is unrelated to aMN and has not worsened since signing of the ICF.
  - Social reason and respite care in the absence of any deterioration in the subject's general condition.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is another important medical event. Based upon appropriate medical judgment, the event may jeopardize the subject and may require medical intervention to prevent one of the outcomes listed above (e.g. emergency treatment at home).

NOTE: The term "life threatening" refers to an event in which the subject was, in the view of the reporting investigator, at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe. Medical judgment should be exercised in deciding whether an AE is serious in other situations: Important AEs that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the previous definitions should also be considered serious.

10.8.7. Adverse Events of Special Interest (AESI)

AEs of special interest (AESI) in this clinical trial should be reported along with their respective symptoms (e.g. hives, chills, and fever for infusion reaction) using the trial specific SAE report form.

AESIs include:

- Infusion related reactions to MOR202 ≥ grade 3
- Cytokine release syndrome
- Allergic reactions to MOR202
- Infections ≥ grade 3
- Neutropenia ≥ grade 3 (< 1.0 x 10^9/L)
- Thrombocytopenia ≥ grade 3 (< 50.0 x 10^9/L)
- Major bleeds (defined as critical organ bleed or hemoglobin decrease of more than 20 g/L within 24 h)

10.8.8. Pregnancy

All pregnancies detected during the clinical trial will be reported in the trial specific pregnancy form and will be followed up until delivery or abortion.

Each pregnancy of a clinical trial subject or a female partner of a male clinical trial subject must be reported within 24 hours.

Female clinical trial subjects who become pregnant must be withdrawn from treatment.

Pregnancy in a subject or female partner of a male clinical trial subject who has received trial medication is not considered an AE unless the pregnancy results in complications in mother or child. AEs meeting seriousness criteria have to be reported as SAE of mother or child respectively. For example, if the child is born with a birth defect, this should be reported as a SAE of the child.

The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects or congenital abnormalities or maternal and newborn complications. Every infant has to be followed up for 3 months after delivery.

10.8.9. Assessment of AEs, SAEs and AESIs

As far as possible, each AE should be evaluated to determine the following:

- Relationship to trial drug (suspected/not suspected).
- Duration (start and end date or if continuing at EOS).
- Intensity: The intensity of all AEs will be graded as mild, moderate, or severe using the following definitions:
    - o Mild: Tolerable
    - o Moderate: Interferes with normal activity
    - o Severe: Incapacitating (causes inability to perform usual activity or work).
- Toxicity grade (severity): The toxicity grade of AEs will be graded according to the NCI-CTCAE version 5.0 of November 27, 2017 using the following definitions:
    - o Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
    - o Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)
    - o Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
    - o Grade 4: Life-threatening consequences; urgent intervention indicated.
    - o Grade 5: Death related to AE.
- Seriousness
- Outcome

- Action taken (no action taken; trial drug temporarily interrupted; trial drug permanently discontinued due to this AE; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization).

10.8.10. Reporting of AEs, SAEs and AESIs

All AEs and SAEs will be collected from the signing of the ICF until the EOS visit. For screening failure patients only SAEs will be collected.

All SAEs and AESI must be reported to IQVIA Pharmacovigilance within 24 hours of investigator awareness. The investigator will submit any updated (follow-up) SAE data within 24 hours of investigator awareness.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including AEs resulting in death, at any time after a participant has been discontinued from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify IQVIA Pharmacovigilance.

All AEs, including SAEs will be reported in eCRF. SAEs and AESIs will automatically be transmitted to IQVIA Pharmacovigilance via the eCRF. If the eCRF is not available, a paper SAE Report Form should be sent to IQVIA Pharmacovigilance via email or fax or the Investigator should call the IQVIA SAE hotline within 24 hours of being made aware of the SAE/AESI. When the eCRF system becomes available again, the SAE/AESI information must be entered as soon as possible of the system becoming available. Refer for contact information to the site reference manual for contact details.

The sponsor or designee will report all SAEs to local health authorities, Independent Ethics Committees (IECs) or Institutional/Independent Review Boards (IRBs) and investigators as required by local regulations.

10.9. Pharmacokinetics and Immunogenicity

Blood samples for pharmacokinetics (PK; MOR202) and Immunogenicity (ADA; antiMOR202) should be collected on the visits specified in the Schedule of Assessments (Table 2).

The details of blood sample handling and shipment instructions will be provided in a separate laboratory manual.

The actual dates and times of PK and ADA blood sampling will be recorded in the eCRF.

10.10. Pharmacodynamic Biomarkers

Blood and urine samples for biomarkers should be collected on the visits specified in the Schedule of Assessments (Table 2).

The details of sample handling and shipment instructions will be provided in a separate laboratory manual.

The actual dates and times of biomarker sampling will be recorded in the eCRF.

Due to the exploratory nature of some assays, the sponsor may decide at any point during the trial to terminate these assessments, in which case the sites will be informed accordingly.

11. DATA HANDLING AND QUALITY ASSURANCE

11.1. Completing and Signing Case Report Forms

Trained clinical trial site personnel will enter the data into the eCRF. For any missing data a reason should be given. Any errors should be corrected within the electronic system and source documents. The audit trail will record all changes made, the date and time of the correction, and the person correcting the error.

11.2. Clinical Monitoring

The Sponsor or designee will monitor the clinical trial conduct at the clinical trial sites to ensure data quality (accurate and complete data collection), and protection of subjects' safety and rights.

11.3. Audit and Inspection

The sponsor or regulatory authorities may audit the investigational site. The sponsor's or IQVIA's Quality Assurance Unit, independent of the Clinical Research and Development Department, is responsible for auditing the trial.

The investigator(s) must accept that regulatory authorities conduct an inspection to verify compliance of the trial with GCP.

11.4. Clinical Data Management

The sponsor or designee will be responsible for processing and quality control of the data. The handling of data, including data quality control, will comply with all applicable regulatory guidelines. Adverse events and concomitant medication terms will be coded with the current MedDRA version and WHO medication dictionary. At the end of the trial all MedDRA codes will be updated to the newest versions.

11.5. Archiving

All trial documentation at the sites and Sponsor site will be archived in accordance with International Council for Harmonization (ICH) E6-Good Clinical Practice (GCP) and the sponsor's quality standards and SOPs.

12. STATISTICAL METHODS AND PLANNED ANALYSIS

The data will be analyzed by the sponsor and/or designated CRO. Any data analysis carried out independently by the investigator should be submitted to the sponsor before publication or presentation.

It is planned that the data from participating centers in this protocol will be combined, so that an adequate number of subjects will be available for analysis.

12.1. Timing of Analysis

12.1.1. Primary Completion Analysis

The primary completion analysis will be performed after the last subject completes Cycle 6 of treatment, i.e. after the EOT visit, or 28 days after the last subject received the last dose of MOR202.

If the enrolment for one of the cohorts needs significantly longer, the primary completion analysis may be performed by cohort, otherwise at the same time for both cohorts.

Primary, key secondary and selected exploratory endpoints will be analyzed at the time of primary completion. Details will be provided in the Statistical Analysis Plan (SAP).

12.1.2. Final Analysis

After the last subject completed the last visit, a final analysis will be performed.

Additional safety and follow-up analyses may be performed by the Sponsor as and when deemed necessary.

12.2. Population for Analysis

Subjects who were screened but never started MOR202 treatment will be listed. Screening failures will not be included in any of the summary tables.

12.2.1. Full Analysis Set (FAS)

All subjects who received at least one dose of MOR202. Efficacy and safety analyses will be performed on FAS.

12.2.2. Per Protocol Set

Subjects included in FAS without any important protocol deviation that could impact efficacy endpoints.

12.2.3. Pharmacokinetic Analysis Set (PKAS)

All subjects with evaluable MOR202 serum concentration data.

12.2.4. Immunogenicity Analysis Set (IAS)

All subjects with at least one MOR202 ADA sample.

12.3. General Statistical Considerations

Tabulations of summary statistics, graphical presentations, and statistical analyses will be performed using SAS® software version 9.3 or higher.

Continuous, quantitative variable summaries will include the number of subjects (N) (with nonmissing values/valid cases), mean, standard deviation, minimum, 25th quartile (Q1), median, 75th quartile (Q3) and maximum, except for PK metrics, where additional statistics may be used.

Categorical, qualitative variable summaries will include the frequency and percentage of subjects/entries in the particular category.

Definition of baseline value: the last pre-administration observation will be used as the baseline value for calculating post-administration changes from baseline.

All data obtained via the eCRF and entered into the database will be provided in separate data listings showing individual subject values. A SAP detailing the statistical analyses will be finalized prior to first subject first visit.

12.4. Subject Disposition, Demographics and other Baseline Characteristics

A table will be provided with the following information:

- Number of subjects included in each analysis set.
- Number of subjects screened, enrolled, received at least one dose of trial treatment, discontinued treatment within first 24 weeks, discontinued trial during the 28-week follow-up phase after treatment phase and finished complete follow-up and had their scheduled last-visit.
- Number of subjects withdrawn from the clinical trial and the reason for withdrawal.

Demographic information will be summarized using descriptive statistics for the FAS. Gender and race will be summarized by counts and percentages.

Medical history will be summarized by counts and percentages using MedDRA system organ class (SOC) and preferred term classifications. Concomitant medications will be recorded and coded using the WHO Drug Dictionary enhanced and grouped by anatomical therapeutic chemical (ATC) classes. Tabulations with counts/percentages will show the number of medications/percentage used in each class.

The medical history related to MN will be summarized displaying the

- Duration of disease since initial diagnosis,
- Number and type of prior therapies, and
- Best response during or following previous therapy.

12.5. Sample Size

Three evaluable subjects will be enrolled in the safety run-in phase. These subjects can belong to either Cohort 1 or Cohort 2.

Once the Safety run-in is completed successfully, additional subjects will be enrolled in Cohort 1 and Cohort 2 in parallel. Approximately 20 subjects will be enrolled in Cohort 1 and approximately 10 subjects will be enrolled in Cohort 2.

With a sample size of 20 subjects in Cohort 1, there is an 88% probability to observe at least one occurrence of a particular AE if the natural incidence of this AE in Cohort 1 is 10%.

Cohort 2 includes subjects with aMN refractory to IST. Thus it is expected that incidence of AEs will be higher in Cohort 2 than in Cohort 1. With a sample size of 10 subjects in Cohort 2, there is an 80% probability to observe at least one occurrence of a particular AE if the incidence of this AE is 15%.

12.6. Procedures for Missing, Unused and Spurious Data

Missing values will not be substituted by estimated values, but treated as missing in the statistical evaluation. All data from all subjects dosed in the clinical trial will be included in all listings, plots, summary tables, and statistical analyses when appropriate.

If a subject in the safety run-in phase discontinues the trial for any reason other than treatment related toxicity, this subject will be replaced.

In the event of a significant volume of missing data, sensitivity analyses for efficacy and biomarker endpoints may be performed using the principle of multiple imputation.

12.7. Procedures for Reporting Deviations from Original Statistical Plan

Details of the analyses to be performed on data from this trial will be provided in a separate SAP.

Any deviations from the statistical analysis outlined in this protocol and reasons for the deviations listed will be described in the clinical trial report.

12.8. Primary Objective Analysis

The primary objective of this trial is to assess the safety and tolerability of MOR202 in subjects with aMN during the treatment phase. For details of the safety analysis see Section 12.12.

12.9. Key Secondary Objective Analysis

The key secondary objective is to assess the effect of MOR202 on serum anti-PLA2R antibodies in subjects with aMN.

The key secondary endpoint for this objective is best overall immunological response (BIR).

BIR is defined when a subject is classified as having a IPR, ICR or sICR based on the definitions provided in Section 3.2 of this protocol achieved at any time during the trial.

The best overall immunological response rate (BIRR) is defined as the proportion of subjects with best overall immunological response. BIRR along with its 95% CIs (Clopper-Pearson) will be presented by cohort.

In addition, for each visit available, the number (counts and percentages) of subjects in each of the following categories will be presented in a table: IPR, ICR or sICR. Missing response evaluations will also be presented.

For primary completion analyses, the above analyses will be performed based on the visits during the safety run-in phase and treatment phase.

For final analyses, the above analyses will be performed based on all the visits during the trial.

This analyses will be performed on FAS. Further details will be specified in the SAP.

12.10. Secondary Objective Analysis

12.10.1. Immunogenicity of MOR202

Immunogenicity of MOR202 (anti-MOR202 antibody formation) in subjects with aMN will be assessed by presenting ADA status (positive/negative), ADA titer (when ADA status was positive), and potential drug interference in the assay (yes/no when ADA status was negative). The results will be summarized descriptively for each cohort and visit.

This analysis will be performed on the IAS.

12.10.2. Pharmacokinetic (PK) profile of MOR202

For subjects in the PKAS, individual serum concentrations of MOR202 will be listed.

Descriptive statistics will be calculated by day for serum concentrations and for the listed PK parameters. Mean (± standard error) serum concentrations of MOR202 vs. time will be plotted using both linear and semi-logarithmic scales.

The following PK parameters, where appropriate, will be determined for MOR202 serum concentrations by non-compartmental analysis using individual concentration-time profiles:

- $t_{1/2}$: terminal elimination half-life (h)

MOR202 serum levels may be further analyzed performing population PK analyses, which will be reported separately.

Further details will be specified in the SAP.

12.10.3. Safety in subjects with aMN during the follow-up Phase

The incidence and severity of AEs during the post-treatment follow-up phase until the EOS will be presented. For details see Section 12.12.

12.11. Exploratory Objective Analysis

12.11.1. Efficacy Analysis

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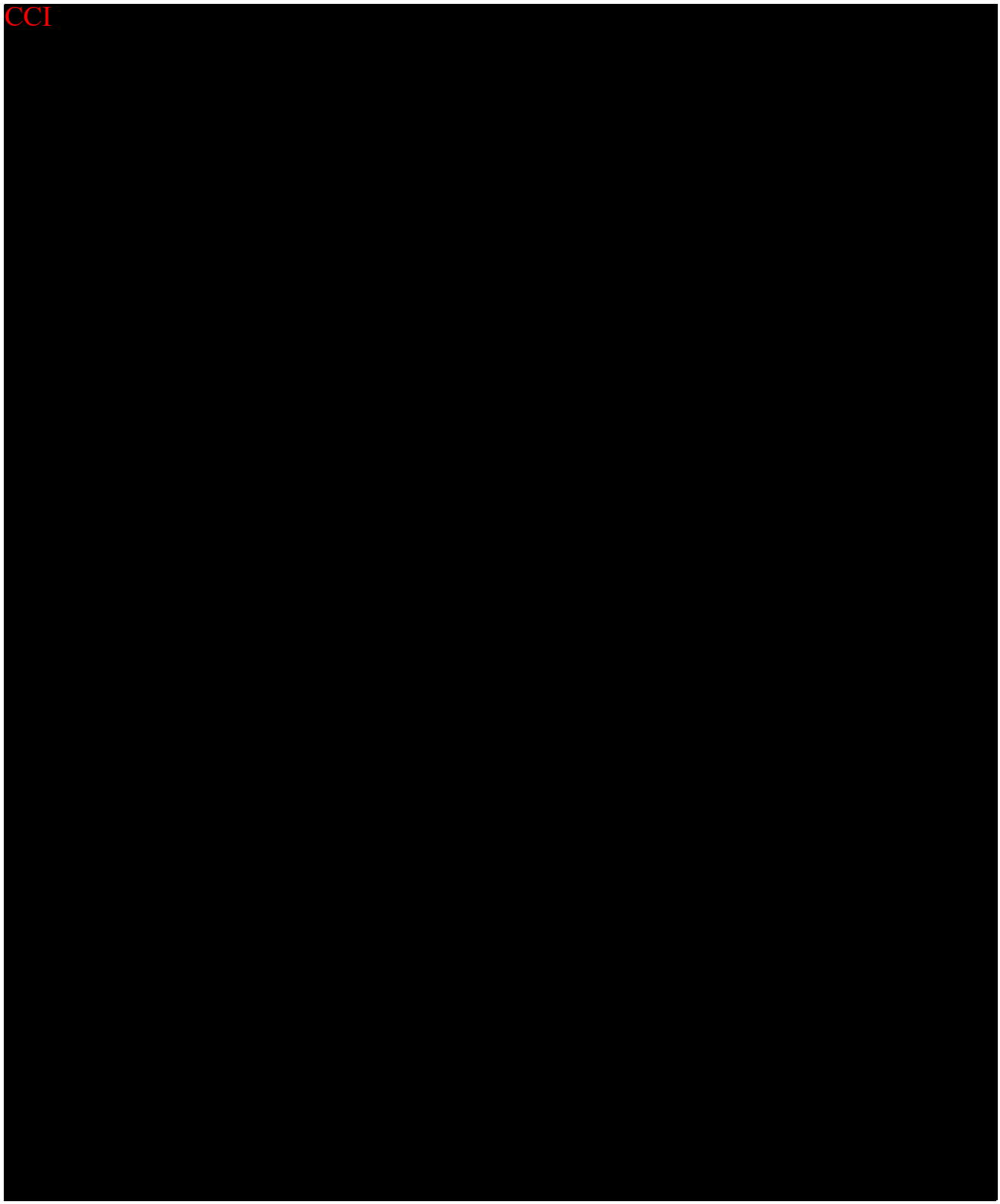

12.11.2. CCI

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12.11.3. CCI [redacted]

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12.11.4. Pharmacodynamic Biomarkers

Additional PD biomarkers may be identified by assessing the effect of MOR202 on the following biomarkers:

i. Peripheral blood immune cell populations.

CCI [redacted]

These biomarkers will be assessed and characterized using descriptive statistics of the following:

- Absolute levels by visit.
- Absolute and relative change from baseline to each visit until EOS.
- Post EOT samples only: Absolute and relative change from EOT visit to each subsequent visits until EOS.

These analyses will be performed on FAS by cohort. Further details will be specified in the SAP.

12.12. Safety Analysis

The primary and one of the secondary objectives of this trial is to assess the safety and tolerability of MOR202 in subjects with aMN.

Primary Objective:

Incidence and severity of TEAEs.

Secondary Objective:

To assess the safety of subjects with aMN after MOR202 treatment and during the follow-up phase.

12.12.1. Adverse Events

All AEs which start after the first dose of trial medication until 28 days after last treatment will be considered as TEAEs. Adverse events that start during the trial but before the time of the first dose

of MOR202 (e.g. screening phase) will be classified as non-treatment emergent adverse events and will be presented in a separate AE listing.

Adverse events will be coded according to Medical Dictionary for Regulatory Activities (MedDRA), system organ class (SOC) and preferred term. Incidence and frequency of all AEs will be summarized by SOC, preferred term, relationship to treatment, severity and seriousness.

An AE summary table will be presented showing the number of events, number of subjects and the percentage of subjects in each cohort and overall having:

- All TEAEs
- TEAEs by maximum severity
- SAEs
- Drug-related TEAEs
- Drug-related TEAEs in each severity/toxicity grading
- TEAEs that led to treatment discontinuation
- IRRs by grade

Adverse events of special interest (AESI) in this trial are:

- Infusion related reactions to MOR202 ≥ grade 3
- Cytokine release syndrome
- Allergic reactions to MOR202
- Infections ≥ grade 3
- Neutropenia ≥ grade 3 (< 1.0 x 10^9/L)
- Thrombocytopenia ≥ grade 3 (< 50.0 x 10^9/L)
- Major bleeds (defined as critical organ bleed or hemoglobin decrease of more than 20 g/L within 24 h)

The sponsor will describe AESI, in addition to those reported as SAEs. AESI tabulations will be analogous to the tabulation of TEAEs.

As part of one of the secondary endpoint, the sponsor will analyze the incidences and severity of AEs of MOR202 during the follow-up phase until EOS. Post-treatment AE tabulations will be analogous to the tabulation of TEAEs.

The sponsor will discuss other significant AEs as appropriate, e.g. laboratory abnormalities that qualify as AEs (other than those meeting the definition for serious) and any events that led to an intervention (including premature discontinuation of IMP, increase of dose interval, or significant additional concomitant therapy) in addition to those reported as SAEs.

12.12.2. New Abnormalities

The sponsor will internally evaluate each clinical laboratory result, vital sign result, and ECG result to assess if it reflects a new abnormality, and for numeric data, to assess if it reflects a significant worsening from baseline or an outlying result or extreme value. These terms are defined for clinical laboratory results, vital sign results, and ECG results as follows:

- A new abnormality will be any abnormal post baseline result for a subject whose baseline value was within normal limits.

- A significant worsening will be any numeric clinical laboratory result, vital sign result, or ECG interval measurement that represents a change from baseline by >25% of the baseline value, in the direction away from normal (i.e., in the direction that is clinically significant).
- An outlying result for any numeric laboratory result, vital sign result, or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:

  < 25th Percentile (Q1) - 1.5 * (interquartile range) OR
  > 75th Percentile (Q3) + 1.5 * (interquartile range).
- An extreme value for any numeric laboratory result, vital sign result, or ECG interval measurement will be any post-administration change from baseline that meets either of the following criteria:

  < 25th Percentile (Q1) – 3 * (interquartile range) OR
  > 75th Percentile (Q3) + 3 * (interquartile range).

Subjects who demonstrate new abnormal results will be noted in data listings and reviewed by the sponsor. All results showing a significant worsening will be noted in data listings and reviewed by the sponsor. Outlying results or extreme values will be identified and reviewed in the context of the subject's other abnormal results.

12.12.3. Clinical Laboratory Evaluation

The analysis of central laboratory parameters for each treatment arm will be presented, separated into blood parameters (e.g., hematology, serum chemistry, coagulation) and urine parameters (urinalysis). All data collected in the course of the trial will be listed.

The analyses will be performed on FAS. Further details will be specified in the SAP.

12.12.4. Vital Signs

Descriptive summaries of actual values and changes from baseline will be calculated for vital signs. These summaries will be presented for the FAS at all time points. Each abnormal value will be flagged to show whether it is a value below or above the normal limit.

12.12.5. Electrocardiograms

Summary ECG assessment (categories: 'normal'; 'abnormal', 'clinically significant'; 'abnormal', 'not clinically significant') will be tabulated by time point using frequency tabulations.

Each result of the 12-lead ECG (PR, QRS, RR and QT interval values) will be flagged to show whether it is a value below or above the normal limit.

Summary statistics for all time points will be displayed for QT and both QTc correction methods. The Bazett's correction method for QTc (Bazett 1920) will be applied as follows:

$$\text{Bazett's Correction (QTcB)} = QT/RR^{1/2}$$

The Fridericia correction method for QTc (Fridericia 1920) will be applied as follows:

$$\text{Fridericia's Correction (QTcF)} = QT/RR^{1/3}$$

where relative rate (RR) = 60/heart rate

Also, the number and percentage of subjects with QTc values above the normal limit (≥ 450 ms, ≥ 480 ms, ≥ 500 ms) and the number and percentage of subjects who experienced a change ≥ 30 ms or a change ≥ 60 ms will be presented by time point.

13. SPECIAL REQUIREMENTS AND PROCEDURES

13.1. Regulatory and Ethical Considerations

This trial was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice (ICH-GCP), with applicable local regulations and with the ethical principles laid down in the Declaration of Helsinki.

Before starting this trial, the clinical trial protocol will be submitted to the IEC/IRB and/or regulatory authorities (in accordance with local regulations) for evaluation. The trial will not start before the IEC/IRB and/or regulatory authorities give written approval or a favorable opinion as required. Any amendments to the protocol will require IEC/IRB and/or regulatory authority approval as required before implementation, except for changes necessary to eliminate an immediate hazard to subjects.

13.2. Publication of Trial Protocol and Results

Information on the protocol will be posted in a publicly accessible database such as clinicaltrials.gov and/or the EU Clinical Trials Register. In addition, the results of this trial will be submitted for publication and/or posted in a publicly accessible database in accordance with local regulations.

13.3. Investigator's Responsibilities

13.3.1. Overall Responsibilities

Before initiating a trial, the investigator/institution must ensure approval/favorable opinion is obtained from the IEC/IRB for the protocol, written ICF, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with the protocol, ICH-GCP, applicable local regulations and the ethical principles laid down in the Declaration of Helsinki.

The investigator is responsible to provide oversight of the conduct of the study at their site. Investigators will apply due diligence to avoid protocol deviations. If the investigator feels a protocol amendment is necessary to improve the conduct of the study, such an amendment is required to be agreed upon by the sponsor and approved by the IEC/IRB and/or regulatory authorities as required prior to implementation. Notwithstanding the need for approval of protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this trial, even if this action represents a deviation from the protocol. In such cases, the sponsor must be notified of this action, as well as the IEC/IRB and/or regulatory authorities as required.

13.3.2. Subject Informed Consent

The investigator or his/her representative is responsible for explaining the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study. Subjects must be informed that their participation is voluntary. Subjects or their legally

authorized representative will be required to sign the ICF prior to any study-specific procedures being performed. The original ICF must be kept as part of the study records at the site, and a copy must be provided to the subjects or their legally authorized representative. Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study. The process of obtaining informed consent must be documented in the subject's source documents.

13.3.3. Direct Access to Source Data/Documents

The investigator must give access to all relevant data and records to monitors, auditors, other designated agents of the sponsor, IEC/IRB, and regulatory authorities as required. Personal medical information will always be treated as confidential. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

13.3.4. Confidentiality

Subjects will be assigned a unique identifier by the sponsor. The investigator must ensure that any subject's data that are transferred to the sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.

13.4. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators and sub-investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

13.5. Publication Policy

Any presentation or publication of data from this trial will be intended as a joint publication by the investigator(s)/appropriate trial site personnel and appropriate sponsor personnel. Authorship will follow the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts Submitted to Biomedical Journals and will be defined prior to the first publication.

For multicenter studies, it is mandatory that the first publication be based on data from all centers, and that the data are analyzed and submitted as stipulated in the protocol by a statistician assigned by the sponsor.

Thus, no investigator or institution may publish any results of the trial conducted at their site, before such a first multicenter publication is made which covers the data from all sites. The authors have the final responsibility for the decision to submit their manuscript and shall be given full access to the data resulting from the trial.

The coordinating investigator and/or authors shall coordinate any intended publication of trial results with the sponsor, to enable the sponsor to ensure that results are presented in a responsible and coherent manner.

The sponsor reserves the right to review all manuscripts and abstracts at least 60 days before their submission for publication or presentation. This is not intended to restrict or hinder publication or presentation, but is to allow the sponsor to protect the confidentiality of information and to provide comments that may not yet be available to the investigator.

At the sponsor's request, any confidential information (other than trial results) will be deleted and all reasonable comments made by the sponsor will be incorporated prior to the submission for publication or presentation. In the rare event that such publication would affect the patentability of any invention to which the sponsor has rights, the sponsor has the right to request an additional delay to the proposed publication of no more than 90 days so as to allow the sponsor to protect its intellectual property rights.

The results of the trial may be used by the sponsor for the purposes of national and international registration, publication, and information for medical professionals. If necessary, the authorities will be notified of the investigators' names, addresses, qualifications, and extent of involvement.

14. REFERENCES

External references

- AABB. AB#16-02 Mitigating the Anti-CD38 Interference with Serologic Testing.
- Bazett HC. An analysis of the time relationships or time-relations of electrocardiograms. Heart 1920; 7:353-80.
- Beck LH, Bonegio RGB, Lambeau G, Beck DM, Powell DW, Cummins TD et al. M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. N Engl J Med 2009; 361(1):11-21.
- Bomback AS, Fervenza FC. Membranous Nephropathy: Approaches to Treatment. Am J Nephrol 2018; 47 Suppl 1:30-42.
- Cao Y, Jusko WJ. Incorporating target-mediated drug disposition in a minimal physiologically-based pharmacokinetic model for monoclonal antibodies. J Pharmacokinet Pharmacodyn 2014; 41(4):375-87.
- Cattran DC, Brenchley PE. Membranous nephropathy: integrating basic science into improved clinical management. Kidney Int 2017; 91(3):566-74.
- Chapuy CI, Aguad MD, Nicholson RT, AuBuchon JP, Cohn CS, Delaney M et al. International validation of a dithiothreitol (DTT)-based method to resolve the daratumumab interference with blood compatibility testing. Transfusion 2016; 56(12):2964-72.
- Chapuy CI, Nicholson RT, Aguad MD, Chapuy B, Laubach JP, Richardson PG et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion 2015; 55(6 Pt 2):1545-54.
- Couser WG. Primary Membranous Nephropathy. Clin J Am Soc Nephrol 2017; 12(6):983-97.
- Fervenza F. A Multi-Center Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR). New Orleans; 2017. (Kidney Week) [cited 2018 Nov 29]. Available from: URL: https://www.asn-online.org/education/kidneyweek/2017/programabstract.aspx?controlId=2831149.

- Fervenza FC, Canetta PA, Barbour SJ, Lafayette RA, Rovin BH, Aslam N et al. A Multicenter Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR). Nephron 2015; 130(3):159-68.
- Fridericia LS. Die Systolendauer im Elektrokardiogramm bei normalen Menschen und bei Herzkranken. [The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. Acta Medica Scandinavica 1920; 53:469-86.
- Jarutat T. Preliminary Efficacy of the Human Anti-CD38 Antibody MOR03087 as Monotherapy and in Combination with Standard Therapy in Subjects with Relapsed or Refractory Multiple Myeloma; A Phase I/IIa, Open-Label, Multicenter, Dose-Escalation Study to Evaluate the Safety and Study: MOR202C101 EudraCT Number: 2009-015942-50; 2018.
- Lee T, Derebail VK, Kshirsagar AV, Chung Y, Fine JP, Mahoney S et al. Patients with primary membranous nephropathy are at high risk of cardiovascular events. Kidney Int 2016; 89(5):1111-8.
- Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. Clin Chem 2007; 53(4):766-72.
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009; 150(9):604-12.
- McGrogan A, Franssen CFM, Vries CS de. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrol Dial Transplant 2011; 26(2):414-30.
- Medawar W, Green A, Campbell E, Carmody M, Donohoe J, Doyle G et al. Clinical and histopathologic findings in adults with the nephrotic syndrome. Ir J Med Sci 1990; 159(5):137-40.
- Merck Sharp and Dohme Ltd (UK). Pneumococcal polysaccharide Vaccine: SmPC Summary of Product Characteristics.
- Niederalt C, Kuepfer L, Solodenko J, Eissing T, Siegmund H-U, Block M et al. A generic whole body physiologically based pharmacokinetic model for therapeutic proteins in PK-Sim. J Pharmacokinet Pharmacodyn 2018; 45(2):235-57.
- Oostendorp M, van Lammerts Bueren JJ, Doshi P, Khan I, Ahmadi T, Parren PWHI et al. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. Transfusion 2015; 55(6 Pt 2):1555-62.
- Raab, Marc S.; Engelhardt, M; Blank, A; Goldschmidt, H; Agis, H; Blau, IW et al. (2020): MOR202, a novel anti-CD38 monoclonal antibody, in patients with relapsed or refractory multiple myeloma: a first-in-human, multicentre, phase 1–2a trial. In The Lancet Haematology. DOI: 10.1016/S2352-3026(19)30249-2
- Ruggenenti P, Cravedi P, Chianca A, Perna A, Ruggiero B, Gaspari F et al. Rituximab in idiopathic membranous nephropathy. J Am Soc Nephrol 2012; 23(8):1416-25.

- Ruggenenti P, Debiec H, Ruggiero B, Chianca A, Pellé T, Gaspari F et al. Anti-Phospholipase A2 Receptor Antibody Titer Predicts Post-Rituximab Outcome of Membranous Nephropathy. J Am Soc Nephrol 2015; 26(10):2545–58.
- Ruggenenti P, Chiurchiu C, Brusegan V, Abbate M, Perna A, Filippi C et al. Rituximab in idiopathic membranous nephropathy: a one-year prospective study. J Am Soc Nephrol 2003; 14(7):1851–7.
- Tran TH, J Hughes G, Greenfeld C, Pham JT. Overview of current and alternative therapies for idiopathic membranous nephropathy. Pharmacotherapy 2015; 35(4):396–411.
- Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC. Idiopathic membranous nephropathy: definition and relevance of a partial remission. Kidney Int 2004; 66(3):1199–205.
- van de Logt A-E, Hofstra JM, Wetzels JF. Pharmacological treatment of primary membranous nephropathy in 2016. Expert Rev Clin Pharmacol 2016; 9(11):1463–78.
- van de Logt A-E, Dahan K, Rousseau A, van der Molen R, Debiec H, Ronco P et al. Immunological remission in PLA2R-antibody-associated membranous nephropathy: cyclophosphamide versus rituximab. Kidney Int 2018; 93(4):1016–7.
- Vriese AS de, Glassock RJ, Nath KA, Sethi S, Fervenza FC. A Proposal for a Serology-Based Approach to Membranous Nephropathy. J Am Soc Nephrol 2017; 28(2):421–30.
- Wagoner RD, Stanson AW, Holley KE, Winter CS. Renal vein thrombosis in idiopathic membranous glomerulopathy and nephrotic syndrome: Incidence and significance. Kidney Int 1983; 23(2):368–74.

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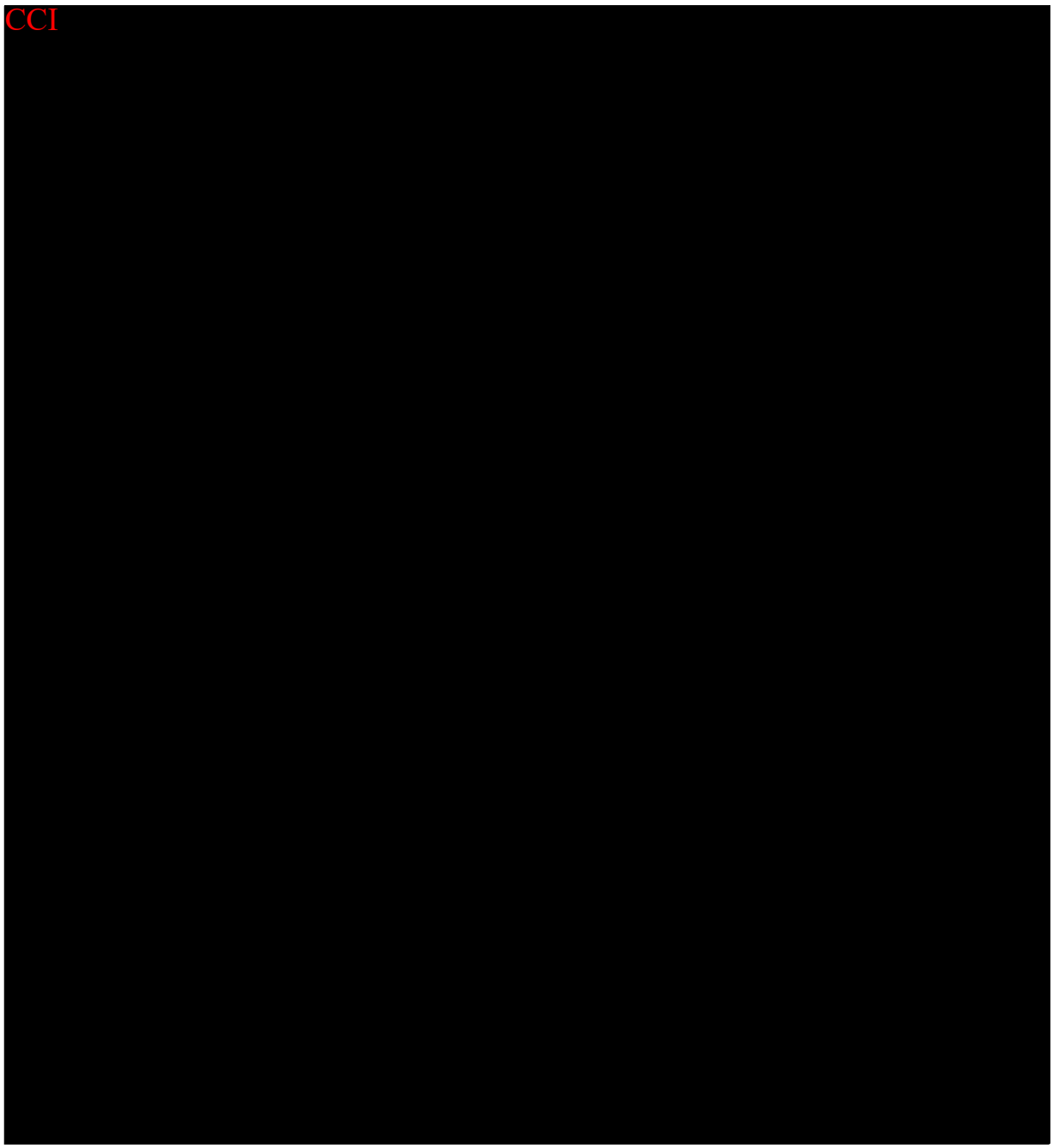
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