A multi-centre, double blinded, randomised, controlled trial to evaluate the long-term efficacy and safety of oral methylprednisolone, on a background of routine renin angiotensin system (RAS) inhibitor therapy, in preventing kidney events in patients with IgA nephropathy and features suggestive of a high risk of progression.

Statistical Analysis Plan

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On behalf of the TESTING steering committee

Study identifiers:

Protocol Number: GI-R-01-2011

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1 Administrative information

1.1 Study identifiers

- Protocol Number: GI-R-01-2011, Version: 9.0, Date: 27 January 2021
- ClinicalTrials.gov register Identifier: [NCT01560052](#)

1.2 Revision history

Version	Date	Details
0.1 (draft)	22FEB2020	First draft adapted from the transitional analysis SAP
0.2 (draft)	02JUN2021	Further edits to SAP and mock tables
0.3 (final draft)	08JUL2021	Revised after receiving first round of comments from management committee members
1.0 (final version)	21JUL2021	Final version created after receiving further comments from the management committee

1.3 Contributors to the statistical analysis plan

1.3.1 Roles and responsibilities

Name and ORCID	Affiliation	Role on study	SAP contribution
Laurent Billot	The George Institute for Global Health, UNSW Sydney	Study statistician	Prepared first draft
Helen Monaghan	The George Institute for Global Health, UNSW Sydney	Project manager	Reviewed each draft
Muh Geot Wong	The George Institute for Global Health, UNSW Sydney	Study director	Reviewed each draft
Vlado Perkovic	UNSW Sydney	Chief investigator	Approved final version

1.3.2 Approvals

The undersigned have reviewed this plan and approve it as final. They find it to be consistent with the requirements of the protocol as it applies to their respective areas.

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22/7/21

2 Introduction

2.1 Study synopsis

The TESTING (Therapeutic Evaluation of STeroids in IgA Nephropathy Global) study is a multicenter, double-blinded, randomised, placebo-controlled trial designed to evaluate the long-term efficacy and safety of oral methylprednisolone, on a background of routine renin angiotensin system (RAS) inhibitor therapy, in preventing kidney events in patients with IgA nephropathy with features suggestive of a high risk of disease progression

The study will test the hypothesis that adding oral methylprednisolone to best available standard care for 6-8 months reduces the risk of the composite outcome of persistent 40% reduction in eGFR, end stage kidney disease and death due to kidney disease, compared to matching placebo, in patients with progressive IgA nephropathy

2.2 Study population

The target population consists of patients with primary IgA nephropathy who are at high risk of progression to kidney failure. The strongest clinical determinants of the risk of kidney failure are kidney function, proteinuria, and hypertension.

2.2.1 Inclusion Criteria

- 1) IgA nephropathy, proven on kidney biopsy.
- 2) Proteinuria (on most recent test): $\geq 1.0\text{g/day}$ while receiving the maximum tolerated dose of RAS blockade
 - $\geq 1.0\text{g/day}$ on most recent available lab tests on Visit 1
 - $\geq 1.0\text{g/day}$ while receiving the maximum tolerated dose of RAS blockade on Visit 3
- 3) eGFR (on most recent test): 20 to $120\text{mL/min per }1.73\text{m}^2$ (inclusive)
 - Serum creatinine and proteinuria evaluation for eligibility will be determined on at least two visits during run-in phase.
 - Estimated GFR will be calculated using the CKD-EPI equation (Appendix 1)
 - Patients with $\text{eGFR} > 120\text{ mL/min per }1.73\text{m}^2$ at screening stage, while reaching less than $120\text{ mL/min per }1.73\text{m}^2$ after tolerated RAS inhibition therapy at visit 3, are eligible for this study

2.2.2 Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be included in the trial

- 1) Indication for immunosuppressive therapy with corticosteroids, such as:
 - Minimal change kidney disease with IgA deposits

- Crescents present in >50% of glomeruli on a kidney biopsy within the last 12 months.
- 2) Contraindication to immunosuppressive therapy with corticosteroids, including
 - Active infection, including HBV infection (HBsAg-positive or HBeAg-positive, or serum detectable HBV-DNA) or clinical evidence of latent or active tuberculosis (nodules, cavities, tuberculoma, etc.)
 - Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (i.e. squamous or basal cell carcinoma)
 - Current or planned pregnancy or breastfeeding
 - Women of childbearing age who are not able or willing to use adequate contraception
- 3) Systemic immunosuppressive therapy in the previous 1 year.
- 4) Malignant/uncontrolled hypertension (>160mm systolic or >110mmHg diastolic) .
- 5) Current unstable kidney function for other reasons e.g. macrohaematuria induced acute kidney injury (past episodes are not a reason for exclusion)
- 6) Age <14 years old
- 7) Secondary IgA nephropathy: e.g. due to lupus, liver cirrhosis, Henoch-Schonlein purpura
- 8) Patients who are unlikely to comply with the study protocol in the view of the treating physician
- 9) Participation in another trial (current or within the last month)

2.3 Study interventions

2.3.1 Randomisation

Eligible patients are randomised to either the methylprednisolone group or matching placebo group in a 1:1 ratio using a web-based password-protected randomisation system. The random allocation uses a minimisation algorithm stratified by region, proteinuria, eGFR and kidney biopsy findings. Study participants, treating clinicians, study investigators and data collectors are blinded to study treatment allocation.

2.3.2 Study treatment

The original protocol, using the full dose regimen (up to Nov 30 2015), required participants to be treated with methylprednisolone 0.6-0.8 mg/kg/day for 2 months (exact dose decided by the site Investigator, rounded to the nearest 4 mg and with a maximal dose of 48mg/day) then tapered by 8 mg daily/month, with a total treatment period of 6-8 months.

The low dose regimen used after Nov 30 2015 required participants to be treated with methylprednisolone 0.4mg/kg/day (maximal dose of 32mg/day and minimum dose of 24mg/day) or

matching placebo, for 8 weeks (+/- 4 days) and then be tapered by 4 mg daily/month, for a total treatment period of 6- 9 months.

2.4 Outcomes

The overall outcomes described below combine TESTING and TESTING low-dose cohorts.

2.4.1 Overall efficacy primary outcome

The primary outcome is progressive kidney failure, which is a composite of:

- **Persistent 40% decrease in eGFR:** reduction of eGFR by 40% from the baseline value (pre-randomisation) that is confirmed by a second value obtained at least 4 weeks after the initial decline or until the final available study visit.
- **Kidney failure:** situations that need kidney replacement therapy including kidney transplantation and maintenance dialysis therapy
- **Death due to kidney disease:** death due to kidney failure that needs dialysis and where the death could be avoided by timely dialysis

2.4.2 Overall efficacy secondary outcomes

- The composite of kidney failure, persistent 30% decrease in eGFR and all cause death
- The composite of kidney failure, persistent 40% decrease in eGFR and all cause death
- The composite of kidney failure, persistent 50% decrease in eGFR and all cause death
- Persistent 30% decrease in eGFR
- Persistent 40% decrease in eGFR
- Persistent 50% decrease in eGFR
- Kidney failure
- Death due to kidney disease
- All-cause death
- Annual eGFR decline rate
- Time averaged proteinuria post-randomisation

2.4.3 Primary efficacy outcome specifically for the low-dose cohort

- Change in proteinuria from baseline at 6 and 12 months
- Mean change in eGFR at 6 and 12 months

2.4.4 Exploratory efficacy outcomes

- Proportion of patients in complete proteinuria remission and stable kidney function
- Mean annual change of 1/creatinine concentration
- Disappearance of microhaematuria

- Proteinuria remission

2.4.5 Safety outcomes

Safety outcomes include adverse events and serious adverse events reported during the study. This includes the following study-specific reportable adverse events:

- Serious infections requiring hospitalisation
- New onset diabetes mellitus
- Clinically apparent gastrointestinal haemorrhage requiring hospitalisation
- Clinically evident fracture or osteonecrosis
- Major cardiovascular event, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease

2.5 Sample size

A sample size of 500 participants provides 90% power ($\alpha=0.05$) to detect a 40% risk reduction with a steroid based treatment approach after an average follow-up of 4 years across the combined TESTING and TESTING low-dose cohorts. It will also provide 80% power to detect a 35% RRR. The sample size calculations assume a log-rank test, an annual combined rate of 40% decline in eGFR or kidney failure/death of 12% in the placebo arm and 10% of participants lost to follow-up over 4 years. The study is event driven and will continue until at least 160 primary endpoints have been observed.

Each dose cohort will also have 90% power to detect a difference of 0.50 g/24-hour in change from baseline in urine protein at 6 months and 80% power to detect a difference of 5 mL/min in change from baseline in eGFR at 6 months. This assumes standard deviations for the change from baseline of 1.15 g/24-hour for urine protein and 13 mL/min for eGFR. These outcomes will be tested separately for each dose cohort to assess whether the effects of the two dose regimens are similar on these continuous outcomes.

2.6 Changes in the Conduct of the Study or Planned Analyses

2.6.1 Changes in the Conduct of the Study

After the randomisation of 262 participants to the TESTING trial in 2015, the independent Data Safety Monitoring Committee (DSMC) reviewed the unblinded data and noticed an imbalance in serious adverse events between the methylprednisolone and placebo arms of the trial. Although the data suggested possible benefits for steroids on kidney outcomes, an increased risk of severe adverse events was noted. This was mostly due to increased infections, including pneumocystis

Jirovecii pneumonia, but numerical imbalances in gastrointestinal bleeding, new diabetes and fracture were also observed.

Of note, the TESTING study suggested that steroids are likely to have kidney protective effects with substantial reductions in proteinuria, slower rates of eGFR loss and a reduction in the risk of the primary outcome (hazard ratio 0.37, $p=0.019$).

Based on the advice of the TESTING DSMC after they had reviewed the interim results, the Steering Committee decided to discontinue treatment with the dose of methylprednisolone being used at the time due to the safety concerns and to analyse and report the results given their clinical importance to people being treated with steroids around the world. As possible significant kidney benefits were also observed, a decision to recruit and randomise a second cohort of participants to a lower dose regimen was made with the expectation that the risks could be substantially reduced, with similar benefits.

2.6.2 Changes in Planned Analysis

Not applicable.

3 Statistical analysis

3.1 Software

Analyses will be conducted primarily using SAS Enterprise Guide (version 7.1 or above) and R (version 4.0.0 or above).

3.2 Interim analyses

The trial DSMC met regularly (approximately twice a year) to monitor safety data. No formal interim analysis for efficacy was performed; however, interim results for the high-dose cohort were unblinded and published in 2017 (See Section 2.6.1)

3.3 Multiplicity adjustment

All tests are to be two-sided with a nominal level of α set at 5%. Analyses of the primary outcome will be unadjusted for multiplicity; however, the outcomes are clearly categorised by degree of importance (primary, secondary and exploratory) and a limited number of subgroup analyses are pre-specified (see Section 3.10.1.4).

3.4 Data sets analysed

Analyses will be conducted on an intention-to-treat (ITT) basis. The ITT population is all patients randomised regardless of whether they receive study treatment and includes patients for whom there are no data available due to absence or revocation of consent. The ITT analyses consider all patients according to the group they were randomly allocated to and regardless of treatment adherence or protocol violations. The ITT analysis set will be used to assess both efficacy and safety.

3.5 Analyses by dose cohort

Unless otherwise specified, all analyses will be conducted on the overall trial population (both doses combined) as well as separately for each dose cohort. In addition, for the analysis of the primary endpoint as well as for analyses of eGFR decline and time-average proteinuria, we will assess interactions between the treatment effect and the dose (high vs lower). To do so, we will formally test the significance of the treatment-by-dose interaction; however, given the limited power, priority will be given to differences in effect size when assessing the potential clinical significance.

3.6 Subject disposition

The flow of patients through the trial will be displayed in a CONSORT¹ (CONsolidated Standards of Reporting Trials) diagram. The report will include the following: the number of screened patients who met study inclusion criteria and the number of patients who were included; and reasons for exclusion of non-included patients and number randomised by centre will be summarised.

3.7 Patient characteristics and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarised by frequencies and percentages. Percentages will be calculated according to the number of patients for whom data are available. Where values are missing, the denominator (which will be less than the number of patients assigned to the treatment group) will be stated in either the body or a footnote in the corresponding summary table. Continuous variables will be summarised by use of standard measures of central tendency and dispersion using mean and standard deviation and/or quartile where appropriate. Free text entries for fields collecting both categorical and free text information (e.g. ethnicity) will be assessed and assigned to a category in a blinded manner.

- Age
- Sex
- Ethnicity
- Body Mass Index
- Medical history and co-morbidities
 - Smoking status
 - Macrohaematuria
 - History of hypertension
 - History of tonsillectomy
 - Previous systemic exposure to corticosteroid.
 - Previous exposure to other immunosuppressant therapy
 - Family history of IgA nephropathy
 - Co-morbidity :
 - Diabetes Mellitus
 - Coronary heart disease
 - Stroke
 - Heart failure
 - Peptic ulcer
- IgA Nephropathy details at screening
 - eGFR
 - Mesangial hypercellularity
- Segmental glomerulosclerosis
- Endocapillary hypercellularity
- Tubular atrophy/ interstitial fibrosis
- Percentage of glomeruli with crescents in the kidney biopsy
- Medications
 - ACE/ARB
 - Proportion achieved maximum labelled dose of ACE/ ARB at randomisation

3.8 Concurrent medications

Concurrent medications will be summarised by treatment group. ACE/ARB medications will be looked at specifically and will be described over time from randomisation to end of study. The number of participants who took ACE or ARB at least once during the FUP period will also be presented. Other concurrent medications will be classified by class and subclass categories (see appendix 1 for the full list of classes and subclasses).

3.9 Compliance and protocol deviations

Compliance will be reported as the average daily dose and as the compliance ratio calculated as the number of tablets taken divided by the number of tablets given. This will be done overall as well as by 3-month period (randomisation to Month 3, Month 3 to Month 6 and Month 6 to Month 9).

Protocol deviations will be summarised as the number of deviations by type. All protocol deviations will be listed together with a description of the deviation.

3.10 Analysis of the Efficacy Outcomes

3.10.1 Overall primary outcome

3.10.1.1 Definition

Persistent 40% decrease in eGFR:

The baseline eGFR is defined as the mean of the two eGFRs from Visit 3 (pre-randomisation visit) and Visit 4 (randomisation visit), calculated by CKD-EPI formula (appendix A) from serum creatinine (mg/dl).

The follow-up eGFR values will be compared to the baseline eGFR to determine whether a 40% reduction relative to the baseline eGFR has occurred. A “persistent” $\geq 40\%$ eGFR reduction is established by the occurrence of 2 consecutive follow-up eGFR values which are at least 40% smaller than the baseline GFR, where the second value is obtained no less than 4 weeks after the initial decline or at the final available study visit

End stage kidney disease:

kidney failure is defined as the receipt of kidney transplantation, initiation of dialysis, the satisfaction of certain criteria where dialysis is unavailable or been refused by the patient as described further below, or kidney death where criteria for kidney failure has not previously been met. kidney failure will be diagnosed if dialysis is performed for 30 days or more that is known not to recover.

When dialysis is not readily available in some parts of the world or the patient refused dialysis, the diagnosis of kidney failure will be the presence of either symptomatic or advanced asymptomatic uremia defined using the following criteria:

- eGFR < 15 mL/min/1.73 m² on 2 blood tests at least 30 days apart and the presence of symptoms ascribed to uraemia
- eGFR < 8 mL/min/1.73 m² on two blood tests at least 30 days apart which may be with or without the presence of symptoms ascribed to uraemia

Death due to kidney disease:

Patients with eGFR < 15 mL/min/1.73 m² may die prior to initiating kidney replacement therapy. Such events will be classified as kidney death when they satisfy the following 3 criteria

1. The patient with eGFR < 15 mL/min/1.73 m² dies
AND
2. The patient has refused KRT or dialysis is not available
AND
3. The death cannot be attributed to a specific aetiology (e.g. cardiovascular death, stroke, progression of cancer, violence)

The diagnosis of kidney death is not intended for subjects in whom dialysis is not offered or withdrawn because of advanced cancer, severe sepsis, advanced heart failure, or terminal organ failure. In such instances, the primary diagnosis that led to withholding KRT will be designated the cause of death.

3.10.1.2 Main analysis

The primary outcome is time from randomisation to the first instance of a confirmed 40% decline in eGFR, kidney failure or death due to kidney disease. Survival curves and estimated median survival times will be generated according to the Kaplan-Meier method, and compared using the log-rank test. Cox proportional hazards analysis will be performed to generate a hazard ratio between the two groups. Analyses will be censored at the date when patients died (for causes other than kidney disease), were lost to follow up, withdrew from study, or at the end of study visit, whichever occurred first. The model will include the stratification variables (region, proteinuria, eGFR and kidney biopsy findings) as fixed covariates.

3.10.1.3 Adjusted analyses

No further adjustments are planned.

3.10.1.4 Subgroup analyses

The following protocol-specified subgroups will be applied for the primary endpoint:

- 1) Randomised steroid dose (full-dose versus lower-dose)
- 2) Baseline proteinuria (<3.0g/day, ≥3.0g/day),
- 3) Baseline kidney function (eGFR < 50 versus ≥50 mL/min per 1.73 m²),
- 4) Baseline histological lesion scoring (E1 vs E0)

- 5) Race (Chinese vs non-Chinese)
- 6) Age (<50 vs ≥50 years)
- 7) Time between biopsy and randomisation (<1 year vs ≥1 year)

Heterogeneity across subgroups will be tested by adding the subgroup variable of interest as well as its interaction with the intervention to the main Cox model. Given the limited power to detect interactions, for the dose subgroup (full-dose vs lower-dose), differences in effect sizes will take precedence over the interaction p-value in guiding the interpretation and potential clinical significance.

3.10.1.5 Treatment of missing data

All missing information will be treated as missing without imputation but will be appropriately censored at the time when the patient was last known to be free of event.

3.10.1.6 Other sensitivity analysis

As an exploratory analysis, we will rerun the main Cox model with the addition of a categorical variable (Interval) which corresponds to the following time intervals: 0-2 years; 2-4 years; 4-6 years; 6-8 years. The Interval-by-treatment interaction will be included in the model to estimate separate Hazard Ratios for each time intervals.

3.10.2 Overall Secondary outcomes

3.10.2.1 Survival secondary outcomes

Survival (time-to-event) secondary outcome events will be analysed similarly to the primary outcome analysis (see Section 3.10.1.2).

3.10.2.2 eGFR and proteinuria

The *rate of eGFR decline* (mL/min/1.73m² per year) for each individual patient will be calculated from the slope of a linear regression model (If the pattern of decline appears near linear) of all eGFR over time. The mean rate of eGFR decline will be compared between the two treatment groups using a t-test. Two sensitivity analyses will be performed using the same methodology but excluding eGFR values at the time of high-dose treatment exposure: one analysis excluding values from month 1 and month 3 and another excluding values from month 1, month 3 and month 6.

Individual *time-average proteinuria* will be calculated as a weighted-average of all-available proteinuria measurements for each patient i.e. using data collected at months 3, 6, 9, 12 and every year thereafter. It will be calculated as the mean of $(3 \times Y_0 + 3 \times Y_3 + 3 \times Y_6 + 3 \times Y_9) / 12$, Y_{12} , Y_{24} and each yearly measurement thereafter (where Y_i indicates the individual proteinuria value collected at Month i). The mean time average proteinuria for each treatment group will be compared using a t-test.

The *overall trajectory* of eGFR and proteinuria over time will be presented by graphing the mean value of for the two randomised groups at each time point using all data available. Differences between randomised groups will be estimated using linear mixed models. For the model, proteinuria values will be log-transformed using the natural logarithmic function to remove skewness. The model will include all post-randomisation measurements after reallocation of visits to the schedule based on assessment dates. Fixed effects will include the baseline measurement (i.e. baseline eGFR or baseline proteinuria), month (as a categorical variable), treatment group, the interaction between month and treatment group and the stratification variables. Random effects will include a random intercept by subject used to model within-subject correlations with a compound-symmetry structure.

These analyses will be run on the overall cohort as well as separately on each dose cohort. In addition, to further quantify the potential heterogeneity in treatment effects, we will perform subgroup analyses of eGFR decline and time-average proteinuria via an analysis of covariance including the dose (high vs low) and its interaction with the treatment as additional covariates. The p-value associated with the dose-by-treatment interaction will be used to assess heterogeneity.

3.10.3 Exploratory outcomes

3.10.3.1 Definition

Exploratory outcomes include the following:

1. Proportion of patients in complete proteinuria remission (see #4 below) AND stable kidney function (eGFR loss of $< 5 \text{ mL/min/1.73m}^2$ from baseline eGFR)
2. Mean annual change of 1/creatinine concentration defined for each individual patient using the slope from least squares linear regression of all reciprocal of serum creatinine values over time.
3. Disappearance of microhaematuria defined as urine analysis of RBC $< 5\text{phf}$ at the end of the study/last available visit for those participants with micro or macrohaematuria at the randomisation visit.
4. Proteinuria remission defined as follows:
 - i) *Complete proteinuria remission* (CR) is defined as 24-hour urinary protein $< 200\text{mg/day}$.
 - ii) *Partial proteinuria remission* (PR) is defined as proteinuria less than 50% of baseline by 24-hour urinary protein, AND $< 1\text{gm/day}$.
 - iii) *Total proteinuria remission* (TR) which is a composite of either CR or PR.

3.10.3.2 Analysis

The *Proportion of patients in complete proteinuria remission AND stable kidney function* will be calculated at each visit (months 6, 12 and 24 and at each yearly visit thereafter) by treatment arm. Differences between arms will be evaluated using a random-effect logistic regression i.e. using a logistic regression with a random

subject intercept to account for correlations between visits. The effect of the treatment will be estimated as the overall (i.e. combining all visits) odds ratio and its 95% confidence interval.

Mean annual change of 1/creatinine concentration will be calculated for each individual subject by a linear regression line using the method described above for rate of eGFR decline. The mean rate of annual change will be compared between the two treatment groups using a t-test.

Disappearance of microhaematuria will be analysed using logistic regression using data collected at the last study visit. Visits with missing data will be handled as a treatment failure (i.e. no disappearance of microhaematuria).

Proteinuria remission will be analysed both as the *proportion achieving remission* and as *time to persistent remission*. The proportion of patients achieving CR, PR and TR at each visit will be calculated for each treatment arm. Differences between arms will be evaluated using a random-effect logistic regression i.e. using a logistic regression with a random subject intercept to account for correlations between visits. The effect of the treatment will be estimated as the overall (i.e. combining all visits) odds ratio and its 95% confidence interval. *Time to persistent proteinuria remission* will be analysed using CR and PR as separate outcomes, and a composite of total remission (CR or PR), censored at the end of follow-up (i.e. 3 different analyses). Cox proportional hazards models will be used to generate a HR to compare the two groups. Persistent remission will be defined as maintaining the CR, PR or TR definition on all subsequent measurements of proteinuria until the end of follow-up. Visits with missing data will be treated as failure (i.e. no remission).

3.11 Analysis of the Safety Outcomes

3.11.1 Safety outcomes

Serious adverse events and adverse events of special interest will be summarised as the number of events and the number (%) of patients experiencing at least one event. This will be done by treatment group and event category. Differences in the proportions of patients experiencing at least one event will be tested using Fisher's exact test. We will also analyse time to first serious adverse event using a Kaplan-Meier plot and Cox model, replicating the approach used for the analysis of the primary outcomes (see Section 3.10.1.2).

3.11.2 Laboratory parameters

3.11.2.1 Definition

Laboratory measures:

- Haemoglobin	- Lymphocytes
- Total white blood cell count	- Sodium
- Platelet count	- Potassium

- Chloride	- Total protein
- Fasting blood sugar	- Albumin
- Calcium	- Total bilirubin
- Phosphate	- Alanine aminotransferase
- Uric acid	- Alkaline phosphatase
- Bicarbonate	- C-reactive protein
- Urea	- Parathyroid Hormone
- Creatinine	- Total cholesterol
- eGFR (CKD-Epi)	

Urinary Measures

- 24-hour urine protein
- 24-hour urine creatinine
- 24-hour urine sodium

Twenty-four hour urinary collections are considered incomplete if collections have a measured volume of less than 500mL or greater than 6000mL, or an outlying 24-hour creatinine excretion (less than 4mmol/day or greater than 25mmol/day in women and less than 6mmol/day or greater than 30mmol/day in men). The values will be considered missing.

3.11.2.2 Analysis

All measures will be summarised by use of standard measures of central tendency and dispersion using mean and standard deviation as well as quartile points at 0.25, 0.5 and 0.75 where appropriate stratified by measurement time points and by treatment group. Longitudinal mean plots will be used to display means and 95% confidence bands over time by randomised group. To assess the treatment effect on laboratory variables, a linear mixed effects model with a random intercept by subject and with treatment, time (categorical) and a treatment by time interaction as fixed effects will be used. The effect of the treatment will be assessed as the adjusted mean difference and its 95% confidence interval.

3.11.3 Vital signs

3.11.3.1 Definition

- Height, weight, BMI (derived from height and ideal body weight)
- Blood pressure: systolic and diastolic blood pressure
- Heart rate

3.11.3.2 Analysis

Vital signs will be analysed using the same approach as laboratory values (see Section 3.11.2.2).

References

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Appendix 1: Concurrent Medications Class and Subclass Categories

Class/ Subclass	Class/ Subclass
Other Antihypertensive Agents *	Inhaler steroid
Calcium channel blocker - dihydropyridine	Insulin
Diuretic	Pain killer
Aldosterone antagonist	Anti-vertigo drug
Calcium channel blocker - non-dihydropyridine	Anticoagulant
Beta blocker	Anticonvulsant
Centrally acting	Antidepressant
Beta and alpha blocker	Beta blocker
Alpha blocker	Immunosuppressant
Others	Migraine drug
Lipid Lowering	Prostacyclin analogue
Statins	Sleeping tablets
Fibrates	SGLT2 inhibitors
Others	Others
Antacids - Subgroup PPI Or Non PPI	
Non PPI	
PPI	
Others (including but not limited to below subclass)	
Supplements	
Vitamins	
Uric acid lowering agent	
COVID-19 treatment	
Chinese traditional medication	
Antibiotics	
Sodium bicarbonate	
Oral hypoglycemic agent	
Steroid	
Alkalyting agent	
Antituberculosis	
Thyroxine	
Antiplatelet	
Iron	
Bronchodilator	

Appendix 2: CKD-EPI formula

$$\text{GFR} = 141 \times \min(S_{\text{cr}}/\kappa, 1)^{\alpha} \times \max(S_{\text{cr}}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 [\text{if female}] \times 1.159 [\text{if black}]$$

where:

S_{cr} is serum creatinine in mg/dL,
 κ is 0.7 for females and 0.9 for males,
 α is -0.329 for females and -0.411 for males,
min indicates the minimum of S_{cr}/κ or 1, and
max indicates the maximum of S_{cr}/κ or 1.

Appendix 3: Proposed Tables and figures

Figure 1: Consort flowchart

Programming note: do overall and by dose cohort

Table 1: Enrolment by centre and country

	Screened	Randomised
Centre	xxx	xxx
Royal North Shore Hospital (Australia)	xx (xx.x%)	xx (xx.x%)
Nepean Hospital (Australia)	xx (xx.x%)	xx (xx.x%)
Royal Adelaide Hospital (Australia)	xx (xx.x%)	xx (xx.x%)
Sunnybrooke Health Science Centre (Canada)	xx (xx.x%)	xx (xx.x%)
St Joseph's Hospital (Canada)	xx (xx.x%)	xx (xx.x%)
St Paul's Hospital (Canada)	xx (xx.x%)	xx (xx.x%)
University of Alberta (Canada)	xx (xx.x%)	xx (xx.x%)
Toronto General Hospital (Canada)	xx (xx.x%)	xx (xx.x%)
Maisonneuve Rosemont Hospital (Canada)	xx (xx.x%)	xx (xx.x%)
Central Hospital affiliated to Shenyang Medical Hospital (China)	xx (xx.x%)	xx (xx.x%)
Nanjing General Hospital of Nanjing Military Command (China)	xx (xx.x%)	xx (xx.x%)
Qilu Hospital, Shandong University (China)	xx (xx.x%)	xx (xx.x%)
The Chinese PLA General Hospital (301 Hospital) (China)	xx (xx.x%)	xx (xx.x%)
The 2nd Affiliated Hospital of Hebei Medical University (China)	xx (xx.x%)	xx (xx.x%)
Huashan Hospital, Medical Centre of Fudan University (China)	xx (xx.x%)	xx (xx.x%)
Ruijin Hospital, Affiliated Shanghai Second Medical University (China)	xx (xx.x%)	xx (xx.x%)
Renji Hospital, Affiliated Shanghai Second Medical University (China)	xx (xx.x%)	xx (xx.x%)
Peking University 1st Hospital (China)	xx (xx.x%)	xx (xx.x%)
Guangdong Provincial People's Hospital (China)	xx (xx.x%)	xx (xx.x%)
Post Graduate Institute of Medical Education and Research (India)	xx (xx.x%)	xx (xx.x%)
Nizam's Institute of Medical Sciences (India)	xx (xx.x%)	xx (xx.x%)
University of Malaya medical centre (UMMC) (Malaysia)	xx (xx.x%)	xx (xx.x%)
The First Affiliated Hospital of Zhengzhou University (China)	xx (xx.x%)	xx (xx.x%)
Shandong Provincial Hospital (China)	xx (xx.x%)	xx (xx.x%)
Affiliated Union Hospital, Tongji Medical College (China)	xx (xx.x%)	xx (xx.x%)
Osmania Medical College (India)	xx (xx.x%)	xx (xx.x%)
Peking University People's Hospital (China)	xx (xx.x%)	xx (xx.x%)
Hospital Sultanah Aminah Johor Baru (Malaysia)	xx (xx.x%)	xx (xx.x%)
First Affiliated Hospital of Inner Mongolia, Baotou Medical College (China)	xx (xx.x%)	xx (xx.x%)
The Second Affiliated Hospital of Shanxi Medical University (China)	xx (xx.x%)	xx (xx.x%)
Yantai Yuhuangding Hospital (China)	xx (xx.x%)	xx (xx.x%)
Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital (China)	xx (xx.x%)	xx (xx.x%)
Hospital Kuala Lumpur (Malaysia)	xx (xx.x%)	xx (xx.x%)
Hangzhou Chinese Medicine Hospital (China)	xx (xx.x%)	xx (xx.x%)
Zhejiang Provincial People's Hospital (China)	xx (xx.x%)	xx (xx.x%)
London Health Sciences Centre (Canada)	xx (xx.x%)	xx (xx.x%)
University of Calgary (Canada)	xx (xx.x%)	xx (xx.x%)
Hospital Umum Sarawak (KUCHING) (Malaysia)	xx (xx.x%)	xx (xx.x%)
Hospital Tuanku Ja'far Seremban (Malaysia)	xx (xx.x%)	xx (xx.x%)
Hospital Raja Permaisuri Bainun, Ipoh (Malaysia)	xx (xx.x%)	xx (xx.x%)
Sanjay Gandhi Post Graduate Institute of Medical Science (SGPGIMS) (India)	xx (xx.x%)	xx (xx.x%)
Madras Medical College (India)	xx (xx.x%)	xx (xx.x%)
Calicut Medical College (India)	xx (xx.x%)	xx (xx.x%)
Country	xxx	xxx
Australia	xx (xx.x%)	xx (xx.x%)
China	xx (xx.x%)	xx (xx.x%)

	Screened	Randomised
Canada	xx (xx.x%)	xx (xx.x%)
Malaysia	xx (xx.x%)	xx (xx.x%)
India	xx (xx.x%)	xx (xx.x%)

Figure 2: Cumulative recruitment

Cumulative recruitment

Programming note: Semestrial count over the extend of full dose and low dose recruitment (use different colors for each dose cohort within a stacked bar) + mark the time when low dose recruitment started

Table 2: Subject disposition by visit

	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Randomised	xxx	xxx	xxx
Month 1			
Assessed	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Not assessed	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Deceased	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Recently randomised *	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Withdrew	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Lost to FU	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 3			
Assessed	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Not assessed	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Deceased	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Recently randomised	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Withdrew	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Lost to FU	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Etc. (for each visit)			

Notes:

- For the proportion assessed/not assessed, the denominator is all patients randomised.
- For the reasons not assessed, the denominator is all patients not assessed
- Recently randomised = a patient who entered the study too recently to reach the corresponding assessment

Table 3: Demographic characteristics

Characteristics	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Age (yrs)			
N Mean (SD)	xxx xx.x (xx.x)	xxx xx.x (xx.x)	xxx xx.x (xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Gender			
Female	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Male	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Ancestry/Ethnic Origin			
Caucasian/European	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Chinese	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
South Asian	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
South-East Asian	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Japanese	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Other Eastern Asian	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Mixed	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Body Mass Index			
N Mean (SD)	xxx xx.x (xx.x)	xxx xx.x (xx.x)	xxx xx.x (xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x

Table 4: Medical history

Condition	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Smoking history			
Previous smoker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Current smoker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Macrohematuria	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Hypertension history	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Tonsillectomy history	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Past systematic corticosteroids therapy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Past other immunosuppressant therapy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Family history of IgA nephropathy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Diabetes Mellitus	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Coronary Heart Disease	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Stroke	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Heart Failure	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Peptic ulcer	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Table 5: IgA Nephropathy details at screening

Condition	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
eGFR level*			
N Mean (SD)	xxx xx.x (xx.x)	xxx xx.x (xx.x)	xxx xx.x (xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Mesangial hypercellularity			
M0 <= 0.5	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
M1 > 0.5	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Segmental glomerulosclerosis			
S0 - absent	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
S1 - present	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Endocapillary hypercellularity			
E0 - absent	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
E1 - present	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Tubular atrophy/interstitial fibrosis			
T0 - 0-25 %	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
T1 - 26 - 50%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
T2 - > 50%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Glomeruli with crescents			
C0 - none	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
C1 - <1/4 th	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
C2 - >1/4 th	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

* eGFR calculated using the CKD-EPI equation

Table 6: Comparison of baseline characteristics between the two dose cohorts

Parameter	Full dose protocol		Low dose protocol		Testing for differences
	Methylpredni- solone (N = xxx)	Placebo (N = xxx)	Methylpredni- solone (N = xxx)	Placebo (N = xxx)	
Age					0.xxx
N	xxx	xxx	xxx	xxx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (IQR)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	
Sex					0.xxx
Female	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Male	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Race					0.xxx
Caucasian/European	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Chinese	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
South Asian	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
South-East Asian	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Japanese	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Other Eastern Asian	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Mixed	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
BMI					0.xxx
N	xxx	xxx	xxx	xxx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (IQR)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	
Smoking history					0.xxx
Non-smoker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Previous smoker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Current smoker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Macrohematuria					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Hypertension history					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Tonsillectomy history					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Past systematic corticosteroids therapy					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	

Parameter	Full dose protocol		Low dose protocol		Testing for differences
	Methylpredni- solone (N = xxx)	Placebo (N = xxx)	Methylpredni- solone (N = xxx)	Placebo (N = xxx)	
Past other immunosuppressant therapy					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Family history of IgA nephropathy					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Diabetes Mellitus					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Coronary Heart Disease					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Stroke					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Peptic ulcer					0.xxx
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Y	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Heart Failure					
N	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
eGFR level					0.xxx
N	xxx	xxx	xxx	xxx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (IQR)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	
Urine protein (g/24-hour)					0.xxx
N	xxx	xxx	xxx	xxx	
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	
Median (IQR)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	xx.x (xx.x; xx.x)	
Mesangial hypercellularity					0.xxx
M0	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
M1	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Segmental glomerulosclerosis					0.xxx
S0	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
S1	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	

Parameter	Full dose protocol		Low dose protocol		Testing for differences
	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Methylprednisolone (N = xxx)	Placebo (N = xxx)	
Endocapillary hypercellularity					0.xxx
E0	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
E1	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
Tubular atrophy/interstitial fibrosis					0.xxx
T0	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
T1	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	
T2	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	

Note: continuous parameters are compared between study parts and treatment using an ANCOVA, categorical parameters are compared between study parts and treatment using a Chi-Squared test.

Table 7: Percentage of maximum tolerated dose of ACE/ARB at randomisation

Condition	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
ACE - Percentage achieved of maximum tolerated dose			
No ACE	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
< 50%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
50 - 80%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
> 80%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
ARB - Percentage achieved of maximum tolerated dose			
No ARB	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
< 50%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
50 - 80%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
> 80%	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Note: the number of randomised patients is used to compute percentages.

Table 8: Compliance to study medication

	High-dose cohort		Low-dose cohort	
	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Methylprednisolone (N = xxx)	Placebo (N = xxx)
Randomisation to Month 3				
<i>Average daily dose (mg)</i>	n=xxx	n=xxx	n=xxx	n=xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1 - Q3)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
<i>Compliance (%)</i>	n=xxx	n=xxx	n=xxx	n=xxx
0% - < 20%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
20% - < 40%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
40% - < 60%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
60% - < 80%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
80% - 100%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 3 to month 6				
<i>Average daily dose (mg)</i>	n=xxx	n=xxx	n=xxx	n=xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1 - Q3)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
<i>Compliance (%)</i>	n=xxx	n=xxx	n=xxx	n=xxx
0% - < 20%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
20% - < 40%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
40% - < 60%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
60% - < 80%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
80% - 100%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Month 6 to Month 9				
<i>Average daily dose (mg)</i>	n=xxx	n=xxx	n=xxx	n=xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1 - Q3)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
<i>Compliance (%)</i>	n=xxx	n=xxx	n=xxx	n=xxx
0% - < 20%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
20% - < 40%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
40% - < 60%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
60% - < 80%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
80% - 100%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Overall compliance				
<i>Average daily dose (mg)</i>	n=xxx	n=xxx	n=xxx	n=xxx
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (Q1 - Q3)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)	xx (xx - xx)
Min, Max	xx, xx	xx, xx	xx, xx	xx, xx
<i>Compliance (%)</i>	n=xxx	n=xxx	n=xxx	n=xxx
0% - < 20%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
20% - < 40%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
40% - < 60%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
60% - < 80%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
80% - 100%	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

Figure 3: Cumulative dose of study drug

Cumulative dose of study drug

Programming note: one plot per dose cohort

Table 9: Concurrent Medications: ACE and ARB

	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
ACE			
Taken at least once during FU	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Randomisation	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 1 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 3 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 6 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 8 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 12 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 24 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Etc.	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
ARB			
Taken at least once during FU	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Randomisation	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 1 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 3 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 6 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 8 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 12 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Month 24 visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Etc.	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Note: the following patients were prescribed both ARB and ACE at randomisation: list participants here .

Table 10: Concomitant Medications by Treatment Groups

Class/ Subclass	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Other Antihypertensive Agents *	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Calcium channel blocker - dihydropyridine	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Diuretic	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Aldosterone antagonist	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Calcium channel blocker - non- dihydropyridine	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Beta blocker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Centrally acting	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Beta and alpha blocker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Alpha blocker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Others	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Lipid Lowering	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Statins	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Fibrates	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Others	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Antacids - Subgroup PPI Or Non PPI	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Non PPI	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
PPI	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Others	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Supplements	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Vitamins	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Uric acid lowering agent	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Others	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Chinese traditional medication	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Antibiotics	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Sodium bicarbonate	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Oral hypoglycemic agent	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Steroid	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Alkalyting agent	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Antituberculosis	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Thyroxine	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Antiplatelet	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Iron	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Bronchodilator	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Inhaler steroid	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Insulin	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Pain killer	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Anti-vertigo drug	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Anticoagulant	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Anticonvulsant	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Antidepressant	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Class/ Subclass	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Beta blocker	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Immunosuppressant	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Migraine drug	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Prostacyclin analogue	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Sleeping tablets	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Note: proportions correspond to patients who took a medication from the corresponding class at least once during follow-up (this excludes medications taken only before randomisation)

Note: Steroids which were prescribed as concomitant medications were prescribed after the 6 month treatment period.

Note: Other Antihypertensive Agents exclude ACEi and ARBs as all participant should have received the maximum tolerated or labelled (whichever is reached first) dose of either an ACE inhibitor or an ARB along with optimal blood pressure control according to relevant local guidelines unless medically contraindicated.

Table 11: Concomitant Medications post Month 3 period by Treatment Groups

Repeat table 15a excluding concomitant medication received at month 1 and month 3

NOTE: this table excludes treatment periods Month 1 and Month 3)

Note: proportions correspond to patients who take a medication from the corresponding class at least once during follow-up (this excludes medications taken only before randomisation)

Note: treatments occurring post Month 3 period have been summarised in this table

Table 12: List of medications classified into Other class and Other subclass

Class	Subclass	Medication
Lipid Lowering	Others	Ezetimibe
Other Antihypertensive Agents *	Others	Almarl
Others	Others	6% Sulphur In Calamine Lotion Acetaminophen Alfacalcidol Alfacalcidol Soft Capsules Benralizumab Biomega Fish Oil Cetrimide 2% Shampoo Champix Clotrimazole Cocois Ointment Codeine Colchicine Cooling Foot Gel Coq 10 Curcumin Diphenhydramine Docusate Sodique Doxazosin Mesylate Enoxaparin Fastum Gel Glucosamine Hcl Hcq Heparin Hydroxychloroquine Sulphate Hypromellose Eye Drops Influenza Vaccin Inj.Emeset Inj.Tramdol Iv Fluids Iv Maxalon Lactulose Melatonin Mirena Mometasone Furoate 0.1 % Ossified Three Alcohol Paracetamol Pregabalin Pulmicort Rivaroxaban

Class	Subclass	Medication
		Sodium Polystyrene
		Sulodexidesoftcapsules
		T. Enam
		T. Nephro Omega
		T.Hicet
		Xylometazoline Nasal
		Zopiclone
		Zovirax Cream

Table 13: Primary and secondary outcomes – descriptive analysis

Outcome	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Primary composite outcome			
With 40% eGFR reduction *	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Secondary composite outcome			
With 30% eGFR reduction **	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
With 40% eGFR reduction **	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
With 50% eGFR reduction**	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Component outcomes			
kidney failure	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Death due to kidney failure	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Death due to any cause	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
40% eGFR reduction	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
30% eGFR reduction	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
50% eGFR reduction	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

* Death due to kidney disease, kidney failure or eGFR reduction

** Death due to any cause, kidney failure or eGFR reduction

Table 14: Primary and secondary outcomes – Cox proportional hazards

Outcome	Methylprednisolone (xxxxx patient-years) Annual event rate (95% CI)	Placebo (xxxxx patient-years) Annual event rate (95% CI)	Hazard Ratio (95% CI)	p-value
Primary composite outcome				
With 40% eGFR reduction *	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
Secondary composite outcome				
With 30% eGFR reduction **	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
With 40% eGFR reduction **	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
With 50% eGFR reduction **	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
Component outcomes				
kidney failure	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
Death due to kidney failure	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
Death due to any cause	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
40% eGFR reduction	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
30% eGFR reduction	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx
50% eGFR reduction	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xx (x.xx;x.xx)	x.xxx

* Death due to kidney disease, kidney failure or eGFR reduction

** Death due to any cause, kidney failure or eGFR reduction

Figure 4: Kaplan Meier analysis of time to kidney death, kidney failure or 40% eGFR reduction

Repeat the Kaplan Meier analysis/graph for all secondary outcomes:

Figure 5: Kaplan Meier analysis of time to all cause death, kidney failure or 30% eGFR reduction

Figure 6: Kaplan Meier analysis of time to all cause death, kidney failure or 40% eGFR reduction

Figure 7: Kaplan Meier analysis of time to all cause death, kidney failure or 50% eGFR reduction

Figure 8: Kaplan Meier analysis of time to kidney failure

Figure 9: Kaplan Meier analysis of time to death due to kidney failure

Figure 10: Kaplan Meier analysis of time to death due to any cause

Figure 11: Kaplan Meier analysis of time to 30% eGFR reduction

Figure 12: Kaplan Meier analysis of time to 40% eGFR reduction

Figure 13: Kaplan Meier analysis of time to 50% eGFR reduction

Figure 14: Forest Plot -Time to kidney death, kidney failure or 40% eGFR reduction by subgroups

Programming note: refer to above forest plot as an example. Also present Cox proportional Hazard Ratios with 95% CI and corresponding heterogeneity p-values on the right of the graph. Subgroups are defined in section 3.1.9.4

Figure 15: Average eGFR by visit

Methylprednisolone						Placebo				
Month	N	Mean	SD	95% CI		N	Mean	SD	95% CI	
0	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
3	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
6	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
12	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
24	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
Etc.	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx

Table 15: Yearly decline in eGFR and time-averaged proteinuria

	N	Mean	95% CI	Mean	p-value
e-GFR					
With all visits					
Methylprednisolone	xxx	x.xx	x.xx	x.xx	
Placebo	xxx	x.xx	x.xx	x.xx	
Diff (1-2)		x.xx	x.xx	x.xx	0.xxxx
Without Months 1 and 3					
Methylprednisolone	xxx	x.xx	x.xx	x.xx	
Placebo	xxx	x.xx	x.xx	x.xx	
Diff (1-2)		x.xx	x.xx	x.xx	0.xxxx
Without Months 1, 3 and 6					
Methylprednisolone	xxx	x.xx	x.xx	x.xx	
Placebo	xxx	x.xx	x.xx	x.xx	
Diff (1-2)		x.xx	x.xx	x.xx	0.xxxx
Time-averaged proteinuria					
With all visits					
Methylprednisolone	xxx	x.xx	x.xx	x.xx	
Placebo	xxx	x.xx	x.xx	x.xx	
Diff (1-2)		x.xx	x.xx	x.xx	0.xxxx

Note: p-value from Student's t-test

Note: We will perform subgroup analyses of eGFR decline and time-average proteinuria via an analysis of covariance including the dose (high vs low) and its interaction with the treatment as additional covariates. The p-value associated with the dose-by-treatment interaction will be used to assess heterogeneity

Figure 16: Average proteinuria by visit

Month	Methylprednisolone					Placebo				
	N	Mean	SD	95% CI		N	Mean	SD	95% CI	
0	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
3	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
6	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
12	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
24	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
Etc.	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx

Table 16: eGFR and proteinuria trajectory using mixed models

	Methylprednisolone		Placebo		Difference		
	Mean	SE	Mean	SE	Mean	95% CI	p-value
eGFR							
Month 3	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 6	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 12	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 24	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 36	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Overall	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	0.xxx
Proteinuria							
Month 3	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 6	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 12	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 24	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Month 36	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	
Overall	xx.xx	(x.xx)	xx.xx	(x.xx)	x.xx	(xx.xx ; xx.xx)	0.xxx

The model includes all post-randomisation measurements after reallocation visits to the schedule based on assessment dates. Fixed effects include baseline measurement, month (as a categorical variable with X categories), treatment group and the interaction between month and treatment group. Random effects include a random intercept by subject used to model within-subject correlations with a compound-symmetry structure.

These analyses will be run on the overall cohort as well as separately on each dose cohort. In addition, to further quantify the potential heterogeneity in treatment effects, we will perform subgroup analyses of eGFR decline and time-average proteinuria via an analysis of covariance including the dose (high vs low) and its interaction with the treatment as additional covariates. The p-value associated with the dose-by-treatment interaction will be used to assess heterogeneity

Programming note: for proteinuria, apply natural log transformation then back-transform estimates and 95% CIs.

Table 17: Yearly decline in 1/Creatinine

	Mean	95% CI Mean		p-value
With all visits				
Methylprednisolone	X.XXXXX	X.XXXXX	X.XXXXX	
Placebo	X.XXXXX	X.XXXXX	X.XXXXX	
Diff (1-2)	X.XXXXX	X.XXXXX	X.XXXXX	0.xxxx
Without Month 3				
Methylprednisolone	X.XXXXX	X.XXXXX	X.XXXXX	
Placebo	X.XXXXX	X.XXXXX	X.XXXXX	
Diff (1-2)	X.XXXXX	X.XXXXX	X.XXXXX	0.xxxx
Without Months 1, 3 and 6				
Methylprednisolone	X.XXXXX	X.XXXXX	X.XXXXX	
Placebo	X.XXXXX	X.XXXXX	X.XXXXX	
Diff (1-2)	X.XXXXX	X.XXXXX	X.XXXXX	0.xxxx

Table 18: Proteinuria remission

Outcome	Month	Methylpred-nisolone (N = 136)	Placebo (N = 126)	Risk/Hazard ratio (95% CI)	P-value(6)
Complete proteinuria remission	Month 6	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 12	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 24	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 36	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Partial proteinuria remission	Month 6	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 12	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 24	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 36	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Total proteinuria remission	Month 6	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 12	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 24	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 36	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Complete proteinuria remission and stable kidney function	Month 6	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 12	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 24	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
	Month 36	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Time to persistent proteinuria remission					
Complete remission				x.xx (x.xx; x.xx)	0.xxxx
Partial remission				x.xx (x.xx; x.xx)	0.xxxx
Total remission				x.xx (x.xx; x.xx)	0.xxxx

1. Complete proteinuria remission: 24 hour urinary protein <0.2g/day.

2. Partial proteinuria remission: proteinuria less than 50% of baseline by 24 hour urinary protein and <1g/day.

3. Total proteinuria remission: complete or partial remission (combined).

4. Stable kidney function: eGFR loss of < 5 mL/min/1.73m² from baseline eGFR.

5. Persistent remission defined as maintaining the remission on all subsequent measurements of proteinuria until the end of follow-up.

6. Risk ratio and Fisher's exact test to compare proportions. Hazard ratio and cox model p-value for survival analyses.

Table 19: Disappearance microhaematuria

	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)	Relative risk (95% CI)	Fisher p-value
Month 3	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Month 6	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Month 12	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Month 24	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Month 36	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx
Last visit	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	x.xx (x.xx; x.xx)	0.xxxx

Disappearance microhaematuria defined as urine analysis of RBC < 5 phf for those participants with micro or macrohaematuria at randomisation visit. Macrohaematuria has been defined as urine analysis of RBC ≥ 5 phf.

Only patients with a micro or macrohaematuria at randomisation visit have been selected and counted for this table.

Non-missing urine RBC values have been included in this analysis.

Table 20: Adverse Events during Treatment Period

	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Number of AEs reported	x	x	x
Number of patients reporting at least one AE	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Number of pregnancies	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Pregnancies among female participants	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Number of patients reporting the following study treatment-related AEs:			
new onset of diabetes mellitus	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
clinically evident fracture/osteonecrosis	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Table 21: Serious Adverse Events - All events

	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)	Fisher exact p-value
Number of SAEs	xxx	xxx	xxx	
Number of patients with at least one SAE	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
Resulted in death	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
Life-threatening	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
Hospitalisation/Prolongation of hospitalisation	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
Persistent/Significant disability/Incapacity	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
Congenital anomaly/Birth defect	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
Important medical event	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
Number of patients reporting the following SAEs of special interest per protocol:				
severe infection requiring hospitalisation	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
gastrointestinal bleeding requiring hospitalisation	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx
cardiovascular events	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	0.xxx

Figure 17: Kaplan-Meier plot of time to first SAE

Hazard ratio : x.xx (95% CI x.xx; x.xxx), p=0.xxx

Note to programmer: add logrank pvalue, patients at risk; number of events; number censored;

Figure 18: Vital signs and laboratory data – Mean plot over time

Programming note: create mean plot for all laboratory and vital signs parameters

Table 22: Treatment effect on vital signs and laboratory results using a mixed model

	Methylprednisolone Mean (SE)	Placebo Mean (SE)	Mean difference and 95% CI	p-value
Haemoglobin	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x; xx.x)	0.xxx
Etc. (do for all parameters)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x; xx.x)	0.xxx

Estimated using a linear mixed effects model with a random intercept by patient, with treatment and time (categorical) as fixed effects. The model includes data from months 3, 6, 12, 24 etc. Correlations are modelled using an exchangeable covariance matrix.

Table 23: Vital Signs

Parameter reallocated visit	Methylprednisolone (N = xxx)	Placebo (N = xxx)	Total (N = xxx)
Heart rate (bpm)			
<i>Screening</i>			
N Mean (SD)	xxx xx.x(xx.x)	xxx xx.x(xx.x)	xxx xx.x(xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
<i>Baseline</i>			
N Mean (SD)	xxx xx.x(xx.x)	xxx xx.x(xx.x)	xxx xx.x(xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
<i>Month 3</i>			
N Mean (SD)	xxx xx.x(xx.x)	xxx xx.x(xx.x)	xxx xx.x(xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
<i>Month 6</i>			
N Mean (SD)	xxx xx.x(xx.x)	xxx xx.x(xx.x)	xxx xx.x(xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
<i>Month 12</i>			
N Mean (SD)	xxx xx.x(xx.x)	xxx xx.x(xx.x)	xxx xx.x(xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x
<i>Month 24</i>			
N Mean (SD)	xxx xx.x(xx.x)	xxx xx.x(xx.x)	xxx xx.x(xx.x)
Q1 Q2 Q3	xx.x xx.x xx.x	xx.x xx.x xx.x	xx.x xx.x xx.x
Min Max	xx.x xx.x	xx.x xx.x	xx.x xx.x

Table 24: Hematology values**Table 25: Blood chemistry****Table 26: 24 hour urine protein excretion****Listing 1: Serious Adverse Events**

Treatment group	Patient ID	SAE term	SAE type	SAE of special interest	Other SAE, specify	Date of onset	Status	Cause of death	Seriousness criteria	Relationship to study drug