Supplementary Appendix – Protocol and SAP

This appendix has been provided by the authors to give readers additional information about their work.

CLINICAL TRIAL PROTOCOL

TESTING Study

Therapeutic **E**valuation of **ST**eroids in **I**gA **N**ephropathy **G**lobal study

Protocol Number: GI-R-01-2011
Version Number: 1.0

Testing Study Final Protocol_Version 1.0_Dated 16 June 2011

"A collaboration between the Peking University Institute of Nephrology, the George Institute for Global Health and renal researchers around the world"

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Central Executive Committee Signature

I have read and approve this protocol. I assure that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Name (print):	
Signature:	
Date of Signature:	

Participating Centre Investigator Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make all reasonable efforts to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the study management committee to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study. I understand that the study may be terminated or enrolment suspended at any time by the study management committee, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Investigator's Name (print):	
Investigator's Signature:	
Date of Signature:	

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Abbreviations

ACE	Angiotensin-converting-enzyme
AIPRI study	Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency study
ARB	Angiotensin-II-receptor blocker
AZA	Azathioprine
BP	Blood Pressure
BMI	Body mass index
BUN	Blood Urea Nitrogen
CARI	Caring for Australians with Renal Impairment
CKD	Chronic kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CYCLO	Cylocphosphamide
CXR	Chest X-ray
DSMC	Data and Safety Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EQ-5D	EuroQol EQ-5D
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
HbA1C	Glycosylated Hemoglobin
HDL-C	High density lipoprotein cholesterol
HPF	High Power Field
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IgAN	IgA nephropathy
IRB	Institutional Review Board
ITT	Intent-to-treat
IVRS	Interactive Voice Response Systems
JNC 7	Seventh Joint National Committee guidelines for the management of hypertension
KDIGO	Kidney Disease: Improving Global Outcomes
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDL-C	Low density lipoprotein cholesterol
MDRD	Abbreviated Modification of Diet in Renal Disease study equation
MMF	Mycophenolate Mofetil
MOH	Ministry of Health
RAS	Renin-angiotensin-system
RBC	Red Blood Cell
REIN study	Ramipril Efficacy in Nephrology study
SAE	Serious Adverse Event
SCr	Serum Creatinine
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
SUA	Suspected unexpected serious adverse reaction
WBC	White Blood Cell

Overview of the study

1 Title of study:

TESTING study- **T**herapeutic **E**valuation of **ST**eroids in **I**gA **N**ephropathy **G**lobal study

2 Study purpose:

This study will evaluate the long-term efficacy and safety of oral methylprednisolone on a background of routine RAS inhibitor therapy, in preventing kidney events in patients with IgA nephropathy and features suggesting a high risk of progression

3 Study outcomes

3.1 Primary outcome

Progressive kidney failure, which is a composite of a 50% decrease in eGFR , the development of end stage kidney disease defined as a need for maintenance dialysis or kidney transplantation, and death due to kidney disease

3.2 Secondary outcomes

- The composite of ESKD, 50% decrease in eGFR and all cause death
- Each of ESKD, renal death and all cause death
- annual eGFR decline rate
- proteinuria remission

3.3 Safety outcomes

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

4 Population:

The target population will consist of patients with primary IgA nephropathy who are at high risk of progression to kidney failure.

4.1 Inclusion criteria

1) IgA nephropathy proven on renal biopsy within the previous 2 years yet can extend to 3 years
2) Proteinuria: >1.0g/day while receiving maximum tolerated dose of RAS blockade following the recommended treatment guidelines of each country where the trial is conducted.
3) eGFR: 20 to 70ml/min per 1.73m^2

4.2 Exclusion criteria:

1) Indication for immunosuppressive therapy with corticosteroids, such as:
   - Minimal change renal disease with IgA deposits
   - Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months.
2) Contraindication to immunosuppressive therapy with corticosteroids, including
   - Active infection, including HBV infection or clinical evidence of latent or active tuberculosis (nodules, cavities, tuberculoma etc)
   - Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (ie. 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 (See Appendix 5)
3) Systemic immunosuppressive therapy in the previous 1 year.
4) Malignant /uncontrolled hypertension（>160mm systolic or 110mmHg diastolic）.
5) Unstable kidney function for other reasons, e.g. macrohaematuria induced acute kidney injury
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

5 Investigational and reference therapy:

Individuals will be randomized 1:1 to one of two open-label treatment strategies:

a) A total 6-8 month course of oral methylprednisolone, 2 months with full-dose and followed by a gradually reducing dose, on top of routine guideline based care

b) Standard guideline based care, without steroid therapy

6. Study design:

This is a randomized, parallel-group, two-arm, long-term study utilizing a prospective, randomized open-label with blinded endpoint assessment (PROBE) design that comprises 3 study phases:

6.1 Pre-randomization Period (4 to 12 weeks):

During a 4 to 12 week screening period, the patient's eligibility for randomization into the trial will be evaluated. The patient should receive the maximum tolerated or labeled (whichever is reached first) dose of either an ACE inhibitors or an ARB along with optimal blood pressure control according to relevant guidelines. For patients that have already received ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks, while for patients that haven't receive such therapy, the run-in will be 12 weeks, so all participants have been on RAS blockade for at least 3 months prior to study entry. Other BP lowering agents should be adjusted or added during this stage to achieve guideline based targets.

6.2 study treatment Period:

At randomization, patients who fulfill all eligibility criteria and no exclusion criteria, will be randomized to either the steroid therapy or control group. Patients randomised to the steroid arm will be treated with methylprednisolone 0.8 mg/kg/d for 2 months (rounded to the nearest 4 mg and with a maximal dose of 48 mg/day) then tapered by 8 mg/day each month, with a total treatment period of 6-8 months. Throughout the trial investigators should to strive to manage BP and other background therapies according to relevant local guidelines.

6.3 Follow up phase

Participants will continued to be followed at regular intervals (see section '7.1 By Visit' below) for a total planned average of at least 5 years. Of note, the study is event driven and

will be continued until 335 primary endpoints have occurred, so the final follow up duration may be longer or shorter depending on the event rate.

7. Efficacy assessments:

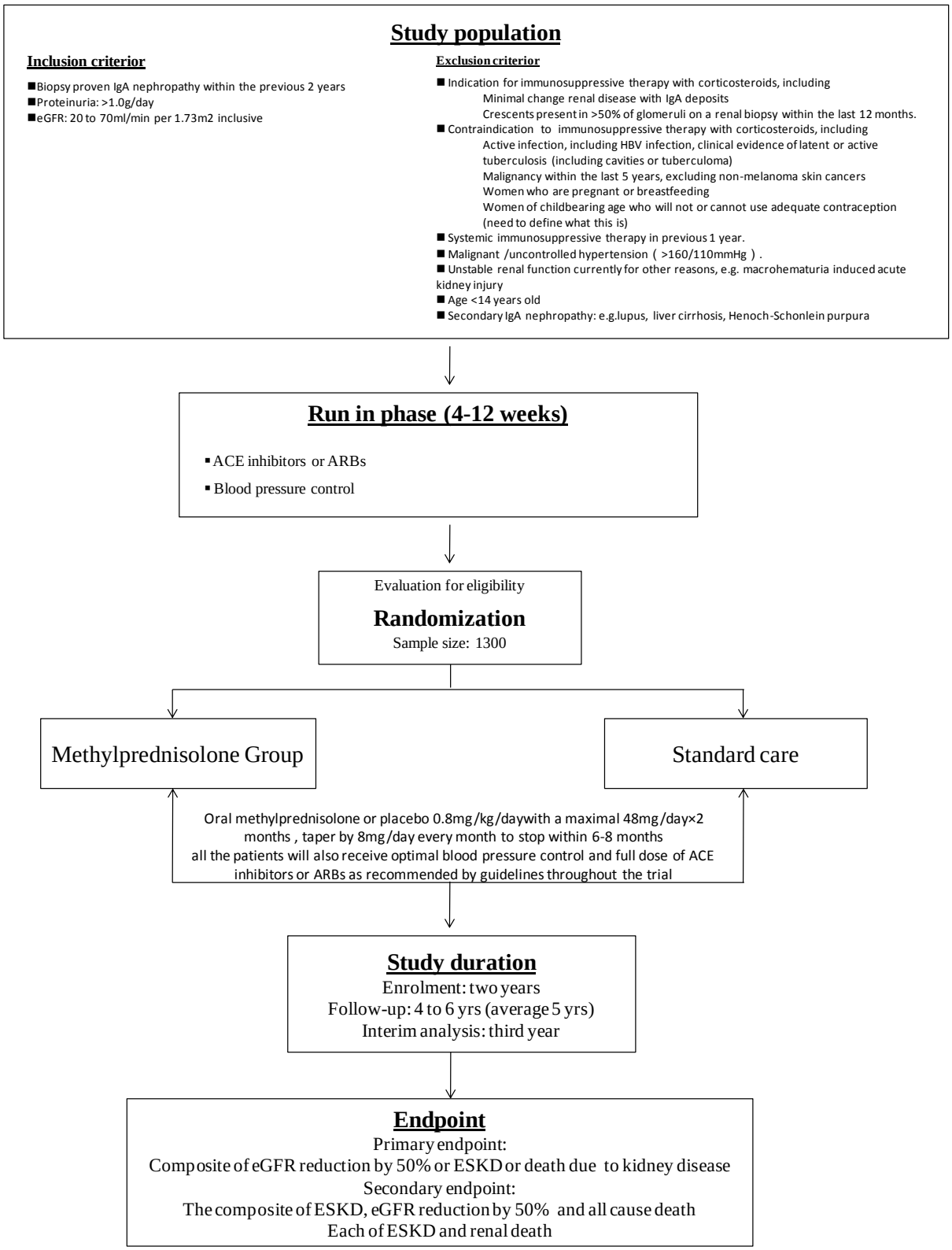
- Persistent reduction in eGFR by 50%, defined as an eGFR which is persistently reduced by more than 50% for a period of 6 months, or until the final available study visit
- End stage kidney disease requiring ongoing maintenance dialysis or renal transplantation
- Death due to kidney disease
- Annual rate of eGFR decline
- Average urinary protein excretion
- Laboratory evaluations (hematology, blood chemistry, urine measurements, glycosylated hemoglobin (HbA1C), lipid profile)
- EQ-5D questionnaire (Quality Of Life (QOL) questionnaire)

8. Safety assessments:

- Adverse events
- Physical examination
- Vital signs
- Height and weight

9. Sample Size:

The sample size calculations have been performed by using the log-rank test and assuming an annual combined event rate for the primary endpoint (50% GFR decrease, ESKD and death due to kidney disease) of 7%. A sample size of 1300 patients (with 650 in each group) will provide more than 90% power (α=0.05) to detect a 30% risk reduction with methylprednisolone, after an expected average follow-up of at least 5 years.



Overview of study design

Note : SCr : serum reatinine; ESKD: end stage of kidney disease;

2 Background & Rationale

2.1 Epidemiology

Immunoglobulin A (IgA) nephropathy is an immune-complex mediated glomerulonephritis defined immuohistologically by the presence of glomerular IgA accompanied by a variety of histopathologic lesions (Berger J 1968, Donadio JV 2002). It may occur at any age, but the clinical onset is most commonly in the second and third decades of life.

IgA nephropathy is recognized as one of, if not the most common primary glomerular disease worldwide, especially in young adults (D'Amico G 1987). IgA nephropathy is a histological diagnosis; few epidemiologic studies have examined the incidence in different populations around the world. Data from autopsy and renal allograft donors suggest that 1-2% of the population are affected by IgA nephropathy (Varis J 1993, Suzuki K 2003**)**. The reported incidence varies from 15-40 new cases per million population per year in Europe, to 42.9 in Australia, and 12 in USA (Table 1).

In most reports of cohort studies from referral based centres or renal biopsy registries, prevalence rates have been expressed as the proportion of cases of glomerulonephritis, or as a percentage of a total series of renal biopsies. IgAN is highly prevalent in Asia and Australia, accounting for 30-40% of cases of glomerulonephritis, compared with about 20% in Europe and the USA (Summarized in table 1). IgA nephropathy is also the most common cause of end stage of kidney disease (ESKD) in young adult Caucasians (Nair R 2006). The reason for this wide variance in incidence is partly attributable to indications for renal biopsy.

2.2 Pathogenesis

Although the pattern of glomerular IgA/IgG deposits has long suggested an immune complex-mediated mechanism, this remained a largely unproven assertion. Recent studies have established the crucial role of aberrantly glycosylated IgA1 and autoantibodies to the abnormal IgA1 in the pathogenesis of IgA nephroapthy (Novak J 2008, Glassock RJ 2009). These breakthrough studies have considerably clarified the likely pathogenesis of IgA nephropathy (Figure 2b). The IgA deposits in the mesangial zones of the patients with IgA nephropathy are mainly of the IgA1 subclass (Conley ME 1980). IgA1 is one of the very few serum proteins to possess O-linked glycans (containing N-acetylgalactosamine, galactose and sialic acid, Figure 2a) in the hinge region. It is now firmly established that serum IgA1

molecules are poorly O-galactosylated in patients with IgA nephropathy, and more importantly, mesangial IgA eluted directly from glomeruli predominantly comprises aberrant galactosylated IgA1(Hiki Y 1995, Allen AC 1995, Xu LX 2005, Moldoveanu Z 2007).

2.3 Risk factors and outcomes

IgA nephropathy is characterized by a highly variable clinical course ranging from a totally benign incidental condition to rapidly progressive renal failure, although most affected individuals develop chronic, slowly progressive renal injury and many patients will develop ESKD. (Nachman PH 2007). It is estimated that 1% to 2% of all patients with IgA nephropathy will develop ESKD each year from the time of diagnosis (Nachman PH 2007). In a study of 3620 patients derived from 18 separate series, the 10-year ESKD-free survival rate was estimated to be 80% and 85% overall in most of the European, Asian, and Australian studies, but it was lower than that from the United States (57% to 78%) (D'Amico G 2004).

The risk of developing ESKD has been shown to be higher in people with particular clinical and laboratory features. Studies using multivariate survival analysis have shown that impaired renal function, sustained hypertension, persistent proteinuria (especially proteinuria over 1 gram per day), and the nephrotic syndrome constitute poor prognostic markers (D'Amico G 2004, Manno C 2007, Lv J 2008) (summarized in table 2). A recent report from the Toronto Glomerulonephritis Registry revealed that proteinuria and blood pressure levels during follow-up were the most important predictor of the rate of GFR decline, which underscored the importance of proteinuria remission and blood pressure management (Reich HN 2008, Figure 1). The Oxford classification of IgA nephropathy has established specific pathological features as independent predictors of renal progression. Factors found to be important include mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, and tubular atrophy/interstitial fibrosis (Cattran DC 2009). Extensive crescentic disease also confers a worse short-term prognosis, often accompanied by a rapidly progressive loss of renal function. This new Oxford classification emphasizes the importance of proliferative lesions in the prognosis of IgA nephropathy.

Table 1. Epidemiological data regarding the frequency IgA nephropathy

Country	Author(year)	Study population (number of renal biopsy)	Proportion of primary GN (%)	Proportion of all GN (%)	Incidence (per 1 million person-years)
Asia					
China	Zhou FD (2009) Li LS (2004)	Single Centre-north China (5714) Single Centre-south China (13,519)	58.2 45.6		
Japan	1999	National Survey (1850)	47.3		
Korea	Chang JH(2009)	Single Centre (1818)	28.3		
Singapore	Woo KT (1999)	Review	45		
Oceania					
Australia	Briganti EM(2001)	Population-based (2030)	48.3	34.1	42.9
Europe					
Czech Republic	Rychlík I(2004)	National Registry of Renal Biopsies (4004)	34.5		
Italy	Schena FP (1997)	National Registry of Renal Biopsies (13835)	36.9		
	Stratta P 1996	Population based survey			14.7
Spain	Rivera F (2002)	National Registry of Renal Biopsies (7016)		17	7.9
UK	Hanko JB(2009)	Regional biopsy registry (1844)	38.8		3.4 (1976 to 1985) to 17.9 (1996-2005)
Netherland	Tiebosch AT (1987)	Population based survey			19
France	Simon P (2004)	Population based survey			28
Americas					
USA	Nair R (2006)	Nephropathology Associates from 24 states (4504)		22	
	Wyatt RJ (1998)	Population-based survey			5(1975-1979) to 12 (1990- 1994)
Brazil	M. G. Polito (2010)	National biopsy data	20.1		

Table 2: Clinical and Histological Prognostic Factors in IgA Nephropathy

Clinical[§]	Histological[¶]
Strong predictors*	
Elevated serum creatinine or reduced eGFR level Severe proteinuria Higher BP levels	mesangial hypercellularity segmental glomerulosclerosis endocapillary hypercellularity tubular atrophy/interstitial fibrosis
Weak predictors[#]	
Older age at presentation Male sex Absence of history of recurrent macroscopic hematuria	

[¶] Oxford classification of IgA nephropathy (Cattran D C 2009)
§ revised from D'Amico G 2004
[*] Significant by multivariate analysis in most studies
[#] Significant only by univariate analysis in many studies.

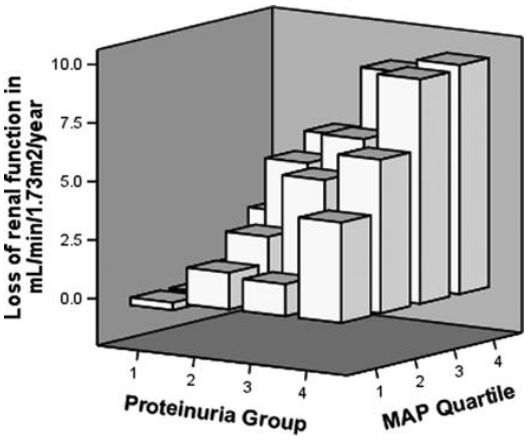


Figure 1: Relationship between proteinuria and MAP during follow-up, and loss of GFR. Group 1, time average proteinuria <1 g/d ; group 2, 1 to 2 g/d; group 3, 2 to 3 g/d; group 4, >3 g/d. (Reich HN 2008)

Another breakthrough in the past two years is a consequence of the cloning and immortalization of B cells from patients with IgA nephropathy. Novak and his colleagues have clearly demonstrated that a B cell abnormality involving premature enzymatic sialylation and/or reduced galactosylation of the O-linked serine residues at the hinge region of IgA1 is the basis for the production of aberrantly glycosylated IgA1(Suzuki H 2008); furthermore, IgG produced by the B cells binds to poorly galactosylated IgA1 and is capable of triggering the formation of IgA1-IgG immune complexes(Suzuki H 2009) . Thus, B cells in IgA nephropathy are programmed to manufacture both the autoantigen and the autoantibodies (*a situation unique in autoimmune disease*) for forming immune complexes (Glassock RJ 2009). These findings offer new sights into the disease pathogenesis, and suggest a possible rationale for immunosuppressive therapy in the management of IgA nephropathy.

2.4 Current therapy for IgA nephropathy- RAS inhibition and blood pressure management

Blood pressure lowering and RAS inhibition remain the cornerstone of management in people with IgA nephropathy. A series of randomized controlled trials, including the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study (AIPRI) study and the Ramipril Efficacy in Nephrology (REIN) study, have established the role of ACE inhibitors in the management of

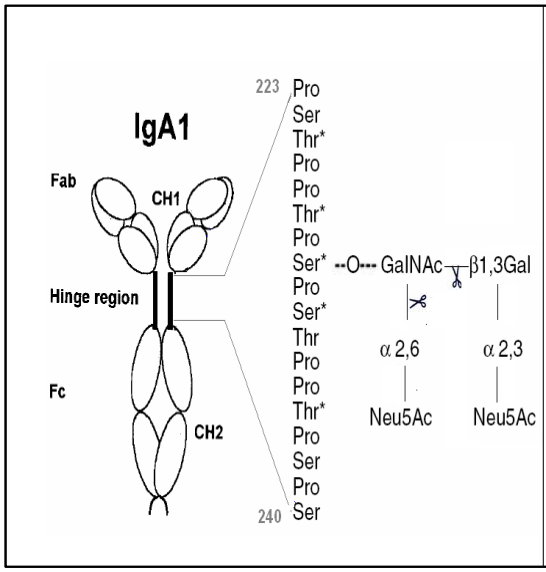


Figure 2a:Molecular structture of IgA1

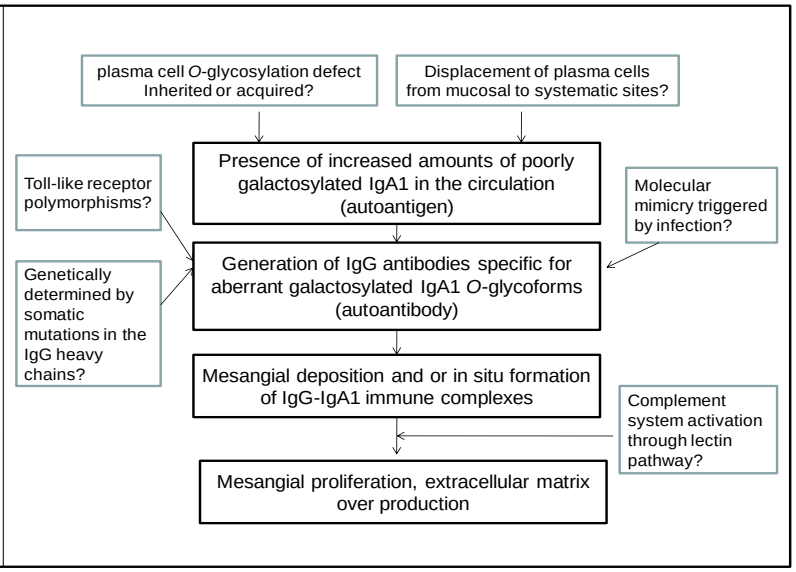


Figure 2b: Model of pathogenesis of IgA nephropathy (revised from Barrat J 2009)

glomerular disease (Maschio G 1996;Ruggenenti P 1998).In the AIPRI study which included 192 patients with glomerulonephritis, an ACE inhibitor (Benazepril) reduced the risk of ESKD or doubling SCr by 53% (95%CI, 27%-70%). The REIN study involved 160 participants with glomerular disease, including 75 with IgA nephropathy, showed that ramipril compared with conventional treatment decreased the rate of change in GFR by approximately 30%, and the risk for progression to ESRD by almost 50%. These effects have been suggested to be independent of their blood pressure lowering ability. Pooled results from 11 randomised controlled trials (including data from the AIPRI and REIN studies) indicated that risk of kidney failure or doubling SCr was reduced by about 33% (95% CI 0.16 to 0.47) with an ACE inhibitor compared with other classes of antihypertensive drugs in patients with chronic kidney disease and proteinuria greater than 0.5 g per day (Jafar TH 2003). Several studies have been conducted using ACE inhibitors (enapril, benazapril) or ARBs (valsartan) in IgA nephropathy aiming to slow the progression of renal failure. Most of the studies enrolled patients with proteinuria> 0.5-1.0g/day. In 2003, A Spanish group first

reported the effects of enalapril in 44 patients with IgA nephropathy. During long-term follow-up (74-78months), 13% (3/23) in the ACE inhibitor group and 57%(12/21) of the patients in the control group reached the end point of 50% increase in serum creatinine from baseline (OR, 0.18; 95% CI, 0.03 to 0.87; P =0.04) (Praga M 2003). More recently, the IgACE study, a European multicentre, randomized, double-blind trial, examined the effect of benazepril in 66 children or young people with IgA nephropathy. After a mean follow-up of 38 months, more placebo-treated patients experienced the end point of a 30% decrease of GFR (5 vs 1, 14.7% vs 3.1%) . Because of the small sample size and short follow-up peroid, the difference did not reach statistical significance (p=0.182) (Coppo R 2007). A randomized controlled trial in 109 Chinese adults with IgA nephropathy showed that valsartan reduced proteinuria and slowed the rate of renal function decline (Li PK 2006). A meta-analysis of the eleven RCTs including 585 IgA nephropathy patients concluded that the use of ACE inhibitors or ARBs produced a significant decrease in proteinuria and renal progression (Cheng J 2009). There is currently no strong evidence to suggest that the combination of ACE inhibitors and ARBs are superior to monotherapy with either class of agent alone for renal protection in proteinuric or non-proteinuric renal diseases including IgA nephropathy (Kunz R 2008). Based on these studies, the current recommended approach to IgA nephropathy with proteinuria and/or hypertension emphasizes rigorous BP control with maximal renin-angiotensin system blockade using either an ACEI or an ARB to minimize proteinuria (Barratt J 2006, MOH guidelines on glomerulonephritis 2007).

2.4 Corticosteroids in IgA nephropathy

The use of corticosteroids in IgA nephropathy remains controversial. Breakthroughs in the understanding of pathogenesis of IgA nephropathy, including identification of specific auto antigen/autoantibody (characteristic in autoimmune disease, *as discussed in the Pathogenesis section*), immune-complex mediated glomerulonephritis, and complement activation through lectin pathway, have provided a clear potential rationale for immunosuppressive therapy with corticosteroids in the management of progressive IgA nephropathy. Recently reported RCTs have tested interventions intended to slow immune and inflammatory events implicated in progressive IgA nephropathy with corticosteroids. There are two situations where the use of steroid therapy is often considered indicated, and they are (1) in patients with the nephrotic syndrome and minimal change lesions on renal biopsy and (2) in patients with crescenteric glomerulonephritis (MOH Singapore guidelines 2007)

The currently available data from randomised trials of steroids in IgA nephropathy are summarised in *table 3*.

Lai KN et al(1986) examined the effects of corticosteroid therapy in 34 Chinese people with documented IgA nephropathy and nephrotic syndrome. In the steroid arm, patients received 4-months of prednisone (40-60mg/day for 2 months, then ½ dose during the subsequent 2 months). During a mean study period of 38 months (range 12-106), corticosteroid treatment resulted in remission of nephrotic syndrome in 80% of patients with mild glomerular histopathological changes, but with no impact on kidney function.

In 1999, an Italian study first suggested that steroid therapy with methylprednisolone might protect kidney function in IgA nephopathy. In this randomized controlled trial, 86 proteinuric IgA nephropathy patients with preserved renal function (urine protein excretion 1-3g/day, serum creatinine<1.5mg/dl) were randomized to either a corticosteroid group (Methylprednsolone 1g × 3days at 1st ,3rd ,5th month ;then 0.5mg/kg on alternate day ×6months), or a control group (supportive therapy). After 5-years of follow-up, nine of the participants randomised to steroids (9/43, 21%) and 14 in the control group (14/43, 33%) reached the primary endpoint of 50% SCr increase (p=0.048) (Pozzi C 1999). In a post-trial 10-year extension of follow-up, steroid therapy significantly reduced proteinuria and prevented kidney failure with 13 patients reaching doubling of SCr in the control group compared to only 1 in the steroid group. Renal survival was significantly better in the steroid group (97% vs 53%, p=0.003) (Pozzi C 2004). Since this study was conducted between 1987 and1999, RAS blockade was used in only a minority of patients, (equally distributed between groups), and the achieved BP level was not in line with current recommendations. The ability of corticosteroids to achieve additional benefits on top of adequate BP control and full dosage RAS inhibitors was therefore questioned (Barratt J 2005).

In 2009, two randomized controlled trials reported the effects of corticosteroids on top of ACE inhibitors, suggesting this treatment could reduce proteinuria and preserve renal function better than ACE inhibitors alone in patients with IgA nephropathy (Lv J 2009, Mann 2009). The first was a pilot study from China, randomly allocating 63 Chinese patients (Proteinuria 1-5g/day and GFR>30ml/min per 1.73m^2) to prednisone on a background of

cilazepril (n=33) or to a control group (cilazepril alone, n=30). After 27-months of follow-up, the combination of steroids and ACE inhibitors significant reduced proteinuria and preserved renal function compared to ACE inhibitors alone; only one patient (1/33, 3%) progressed to the end point of a 50% increase in SCr in the corticosteroids group while 7(7/30, 23%) in the ACE inhibitors group reached this endpoint (p=0.001). Similar results were reported from a larger Italian multicentre RCT involving 97 patients and a median follow-up of 5 years. In this study corticosteroids significantly reduced the risk of doubling of SCr or ESKD (2/49, 4.2% *v.s.* 13/49,26.5% p=0.003) as compared to the control arm. These two trials strengthen the evidence that corticosteroid therapy in patients with proteinuric IgA nephropathy may be beneficial when used in combination with ACE inhibitors. However both trials did not achieve a full dosage of ACE inhibitors (in the Manno study, the average dose of ramipril was 6.5mg/day and Lv J study 3.75mg/day), leading to persisting uncertainty about the value of corticosteroids after supportive therapy has been optimized.

A search of Medline, EMBASE and CCRT database identified 7 small randomized controlled trials which evaluated the role of corticosteroids in IgA nephropathy. Nearly all studies observed a significant reduction in proteinuria with corticosteroids, however in four trials the effects on kidney function did not reach statistical significance likely due to the relatively small sample size, short follow-up (Lai 1986, Julian 1993, Shoji 2000,Ronald 2006) and possibly the modest dosage of steroids (Katafuchi 2003). A meta-analysis of these data (Figure 3) shows that corticosteroids significantly reduced the risk of doubling SCr or ESKD by 74% (RR 0.26, 95% confidence interval[CI] 0.1 to 0.71) and ESKD alone by 64% (RR 0.36, 95%CI, 0.15 to 0.91). Subgroup analysis suggested that high dose oral steroids are more effective than low dose (p=0.032, Figure 4)

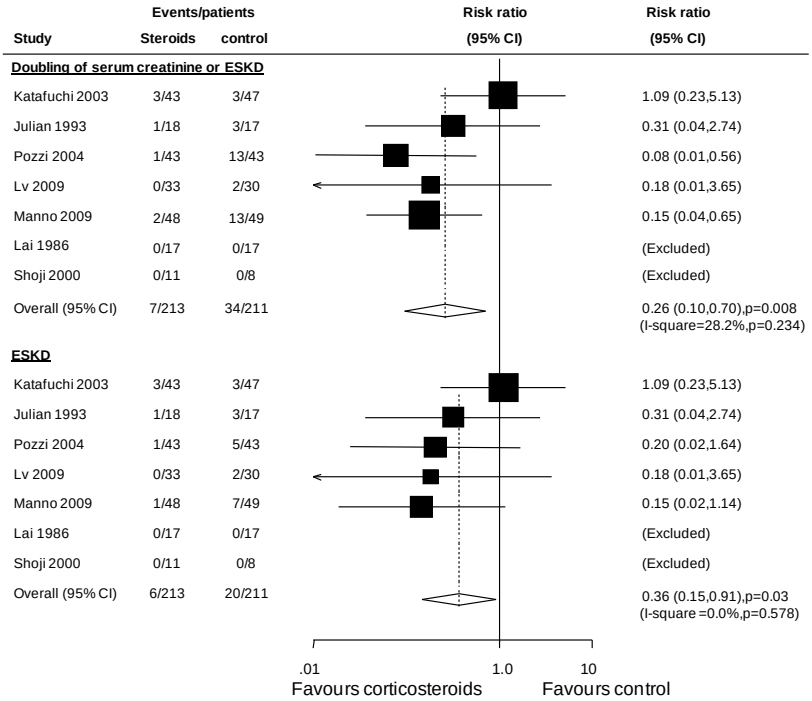
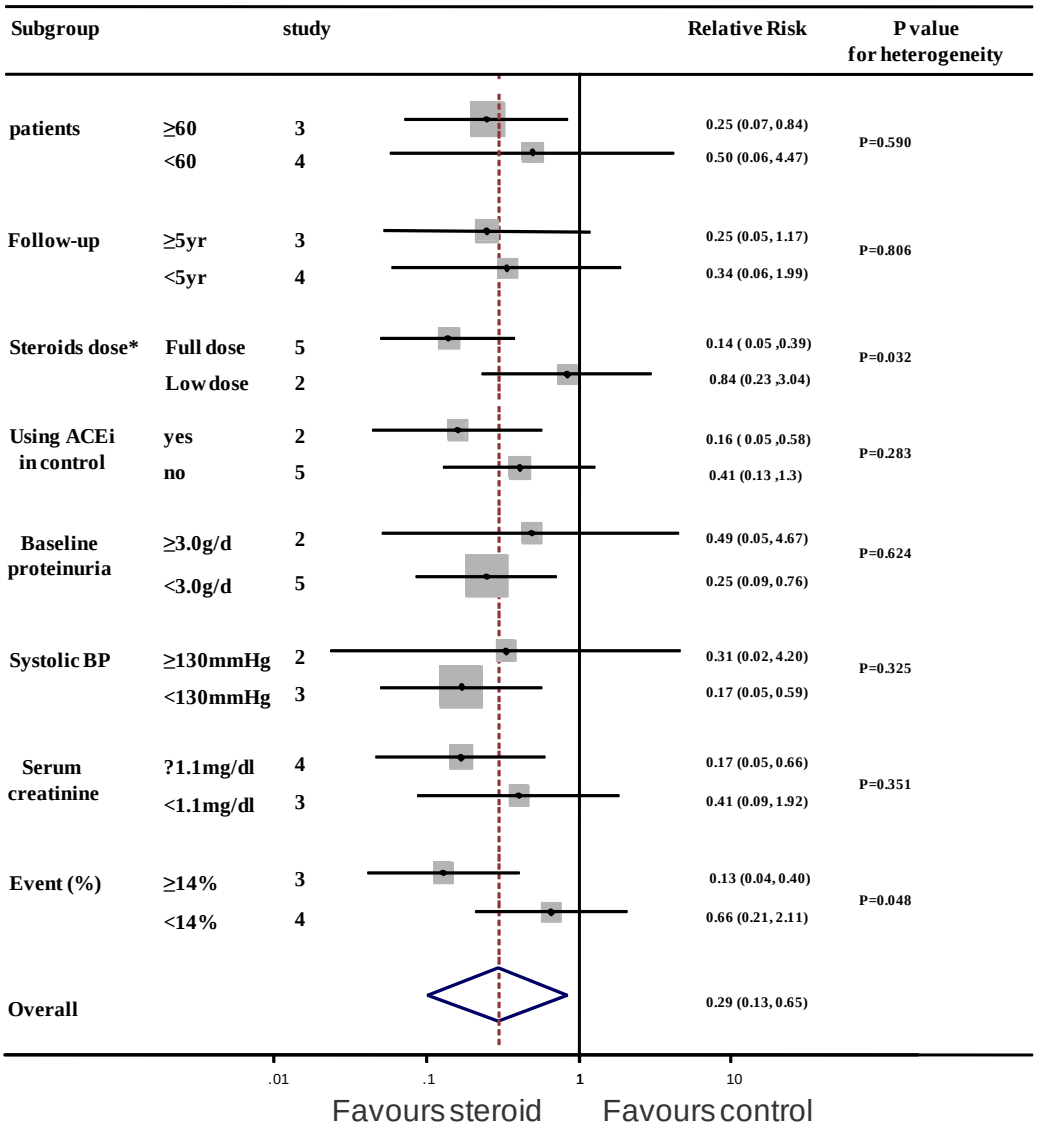


Figure 3: corticosteroids therapy on the outcomes of doubling of serum creatinine or ESKD



* Full dose: with oral prednisolone or prednisone >30mg/d, or receive pulse introvenous methylprednisolone therapy; low dose: with oral predniisolone or prednisone ≤30mg/d

Figure 4: subgroup analysis of steroids on the outcome of doubling serum creatinine or ESKD

2.5 Current guidelines and meta-analysis of corticosteroids in IgA nephropthy

There is no international guideline on the management of IgA nephropathy or other glomerular diseases at present, however KDIGO (Kidney Disease: Improving Global Outcomes) is currently conducting an evidence review process with the expectation of establishing clinical practice guidelines in 2011. Available national guidelines from CARI (Caring for Australians with renal impairment) and the Singaporean MOH have both addressed the potential benefits of steroids in patients with IgAN and persistent proteinuria, and suggest they may have a role.

A recent meta-analysis also revealed that steroids reduced proteinuria and renal progression (Cheng J 2009, Samuels JA 2003). However current recommendations from guidelines are based on small, single-centre trials and there is still much uncertainty on the use of steroids in patients with IgA nephropathy. For example, the guideline from CARI notes that *there is no evidence to suggest patients with IgA nephropathy and established renal impairment (< 60mL/min) benefit from steroid therapy* (CARI 2006); the Singaporean MOH guideline for glomerulonephritis pointed out although steroids are of likely benefit in selected IgA patients, *it is unknown if the immunosuppressive regimens would still be beneficial if optimal blood pressure control is achieved with the use of ACE inhibitors and/or ARBs* (MOH clinical guideline 2007)

2.6 Rationale for a large clinical trial of corticosteroids in patients with IgA nephropathy

IgA nephropathy is one of most common reasons for kidney failure in young adults. Decreased kidney function, hypertension and persistent proteinuria are the strongest risk factors for progressive loss of kidney function, and kidney failure. Current established therapies include full RAS inhibition and optimal blood pressure control for patients with proteinuria and/or hypertension, but a substantial risk of progression remains even when these therapies are employed.

The available evidence also suggest that corticosteroids may be effective in patients with IgA nephropathy at risk for progression. The completed studies have important shortcomings which have limited their implementation into guidelines and clinical practice. These include:

1. The completed studies were mostly conducted at a single centre, leading to uncertainty about the balance of benefits and risks when applied across multiple centres with varying expertise in this area
2. The studies generally used an intermediate primary endpoint, leading to uncertainty about the clinical importance of the findings
3. The available studies were generally of suboptimal quality
4. The completed studies were not adequately powered to detect moderate treatment benefits (each less than 100 participants),making them susceptible to type 1 errors and publication/reporting bias
5. Data regarding the potential harms of corticosteroid therapy were not collected in a systematic and consistent fashion
6. Supportive therapies were often suboptimally provided
7. The participants chosen were not necessarily who are at highest risk of progressive loss of kidney function and kidney failure

These limitations have led to reluctance to implement steroid therapy into guidelines and clinical practice in many parts of the world, and therefore a large well-designed and adequately powered multi-centre randomised trial is required to resolve these persistent uncertainties, and allow the role of steroid therapy in IgAN to be defined.

The supportive versus immunosuppressive therapy of progressive IgA nephropathy (STOP IgAN) trial is a multi-centre trial aiming to evaluate whether corticosteroids alone or combined with cyclophosphamide/azathioprine may improve proteinuria remission rates as compared with current supportive therapy, and is schedule to be finished in 2 or 3 years (Eitner F 2008). Although well designed, it is a small trial (n=148) with short follow-up (3 yrs) and is powered on a relatively soft endpoint: full clinical remission (proteinuria <0.2g/day and stable renal function) or GFR loss>15ml/min per 1.73m^2. Therefore it will not provide the strength of evidence required to reliably guide clinical practice.

Although IgA nephropathy is the most common glomerular disease worldwide, there are still no RCTs with adequate power and quality to reliably inform clinical practice (Leaf DE 2010,

Strippoli GF 2009). As a result, this large multicentre, randomized controlled trial has been designed to determine the efficacy of corticosteroids in progressive IgA nephropathy, involving more than one hundred clinical centres and 1300 patients.

Table 3: Characteristics of the participants, interventions, comparisons and outcomes in the included randomized controlled trials

Study	Patients	No. Patients	Steroids group	Control	Follow-up (Mon)	Event number (rate, per year)				Benefits
						Doubling SCr		ESKD		
						steroids	control	steroids	control	
Lai 1986	IgA nephropathy with nephrotic syndrome	34 (17/17)	Pred 40-60mg/d	No treatment	38	0(-)	0(-)	0(-)	0(-)	Reduced proteinuria No effect on the GFR
Julian 1993	CCr >25ml/min per 1.73m	31 (18/17)	Pred 60mg/qod	No treatment	6-24	1(-)	2(-)	1(-)	2(-)	No effect on change of Proteinuria; A trend to preserve renal function (defined by 1/SCr, p=0.06)
Shoji 2000	Proteinuria <1.5g/d Scr<1.5mg/dl	19 (11/8)	Pred 0.8mg/kg/d	Dypiridamole 300mg/d	12	0(-)	0(-)	0(-)	0(-)	Reduced Proteinuria, no effect on the GFR; Reducing renal lesion in histology
Katafuchi 2003	Scrn<1.5mg/dl	90(43/47)	Pred 20mg/d	Dypiredamole 150-300mg/d	65	3 (1.3%)	3 (1.2%)	3 (1.3%)	3 (1.2%)	Reduced proteinruia No effect on the renal survival (defined as ESKD)
Pozzi 2004	Scr <1.5mg/dl Proteinuria 1-3.5g/day	86 (43/43)	MP 1g × 3days;then 0.5mg/kg/day	Supportive	82	1 (0.3%)	13 (4.3%)	1 (0.3%)	5 (1.7%)	Reduced Proteinuria; Improve renal survival (defined as doubl of SCr)
Hogg* 2006	Proteinuria(UP/C) >1.0 or >0.5 with renal lesions at risk; GFR>50	64 (33/31)	Pred 60mg qod	placebo	24	-	-	-	-	No effect on the Proteinuria reduction or renal survival (defined as 60% decrease of GFR)
Lv JC 2009	Proteinuria 1-5g/day GFR>30ml/min.1.73m^2	63 (33/30)	Pred 0.8-1mg/kg/d	Cilazapril mean dosage 3.75mg/d	27.3	0 (-)	2 (3.0%)	0 (-)	2 (3.0%)	Reduced Proteinuria and improved renal survival (50% increase of SCr)
Manno 2009	Proteinuria>1g/day GFR>50ml/min.1.73m^2 Moderate renal lesions	97 (48/49)	Pred 1mg/kg/day	Ramipril mean dosage 7.5mg/d	60	2 (0.9%)	13 (5.7)	1 (0.4%)	7 (3.0%)	Reduced Proteinuria and improved renal survival (defined as doubling of SCr and or ESKD)

SCr: serum creatinine; **ESKD**: end stage kidney disease; **GFR**: glomerular filtration rate; **CCr**: creatinine clearance rate;
Pred: prednisone;**MP**: methylprednisone
* Ronald study including 3 trial arms: corticosteroids group (n=33),**O3FA** group (n=32) and placebo group (n=31)

2.7 Health significance of the proposed study

IgA nephropathy is the most common glomerular disease worldwide and also the most common reason for end stage of kidney disease in young adults(Nair R 2006). IgA nephropathy accounts for 44% of patients with ESKD due to glomerulonephritis in Australia (Briganti FM 2001) and it is estimated that IgA nephropathy accounts for up to 10% of all patients in need of renal replacement therapy in western countries. The percentage is even higher (up to 15% to 20%) in developing countries. In China, 50% of ESKD are due to glomerular disease (Wang HY 2005), and patients with IgA nephropathy pose a particularly important health care problem because the patients are usually relative young when they reach ESKD and have a relative good life expectancy. Therefore, renal replacement therapy carries a substantial social, emotional and financial burden. In Australia, the number of people with ESKD due to IgAN is estimated to be about 1700, generating an annual cost for renal replacement therapy of $426M to $452M. The trial we propose will provide reliable evidence regarding the benefits and harms of a preventive strategy for individuals with IgA nephropathy at high risk of reaching ESKD.

There is a dearth of high quality evidence for such clinical decisions, and an international consensus on this question is still lacking. This will be the largest trial in glomerular disease; through the successful completion of the present study, the research team will provide evidence that will form the basis of future treatment guidelines for IgA nephropathy.

3 Trial Hypotheses and Objectives

3.1 Trial hypotheses

A 6-8 month regimen of tapering corticosteroid therapy will reduce the risk of kidney failure in patients with high-risk IgA nephropathy

3.2 Trial Objectives

This study aims to evaluate the long-term efficacy and safety of oral methylprednisolone on a background of routine RAS inhibitor therapy in patients with IgA nephropathy and features suggesting a high risk of progression

Primary objective

To determine if adding oral methylprednisolone to best available standard care for 6-8 months reduces the risk of the composite outcome of persistent 50% reduction in eGFR, end stage kidney disease and death due to kidney disease, in patients with progressive IgA nephropathy

Secondary objectives

To determine if adding oral methylprednisolone to optimal background care:

1) Reduces the risk of the composite outcome comprising ESKD, persistent halving of eGFR and death due to any cause.
2) Reduces the risk of each of ESKD and renal death
3) Is safe, with particular reference to the risk of:
    a. serious infections requiring hospitalisation
    b. New onset diabetes mellitus
    c. Clinically apparent gastrointestinal haemorrhage requiring hospitalisation
    d. Clinically evident fracture or osteonecrosis
    e. Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease.

4 Trial Design

This is a randomized, parallel-group, two-arm, long-term study utilizing a prospective, randomized open-label with blinded endpoint assessment (PROBE) design that comprises 3 study phases.

The PROBE design is an efficient and highly cost-effective alternative to the double-blind design, particularly where the intervention (like the one being tested here) produces clinically evident effects that will lead to unblinding of a large proportion of participants. The continuous follow-up and treatment of patients will be conducted openly in a way that adheres to accepted clinical principles and medical practice. Strictly defined endpoints will be adjudicated by a blinded Endpoint Adjudication Committee (EAC), allowing unbiased comparison of therapies and evaluation of the study results.

Trial Flowchart

An overview of the study design is shown in Figure 5. In brief, after a 4 to 12 week run-in phase where treatment can be adjusted to ensure participants are receiving standard guideline based care (blood pressure control and the use of ACE inhibitors or ARBs at the maximum tolerated/labelled dose), eligible patients will be randomized to methylprednisolone on top of standard guideline based care, or standard guideline based care without steroid therapy. All participants will continue to receive standard care including opitmal blood pressure control and full dose of ACE inhbitors or ARBs in line with current guidelines throughout the trial. For patients that have already received ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks, while for patients that haven't received such therapy, the run-in will be 12 weeks, so all participants have been on RAS blockade for at least 3 months prior to study entry

This study will include 1300 patients with IgA nephropathy who are at high risk for renal progression. The recruitment period is two years; following randomization patients are schedule to undergo a 6-8 month intervention, and then be followed regularly until at

least 335 primary endpoints are observed, which is expected to require at least 4- to 6-years of follow-up (average 5 years or more).

5 Trial Medication

5.1 Investigational Medicinal Product

Study Medication will be administered in the following forms:

Table 4: study medication

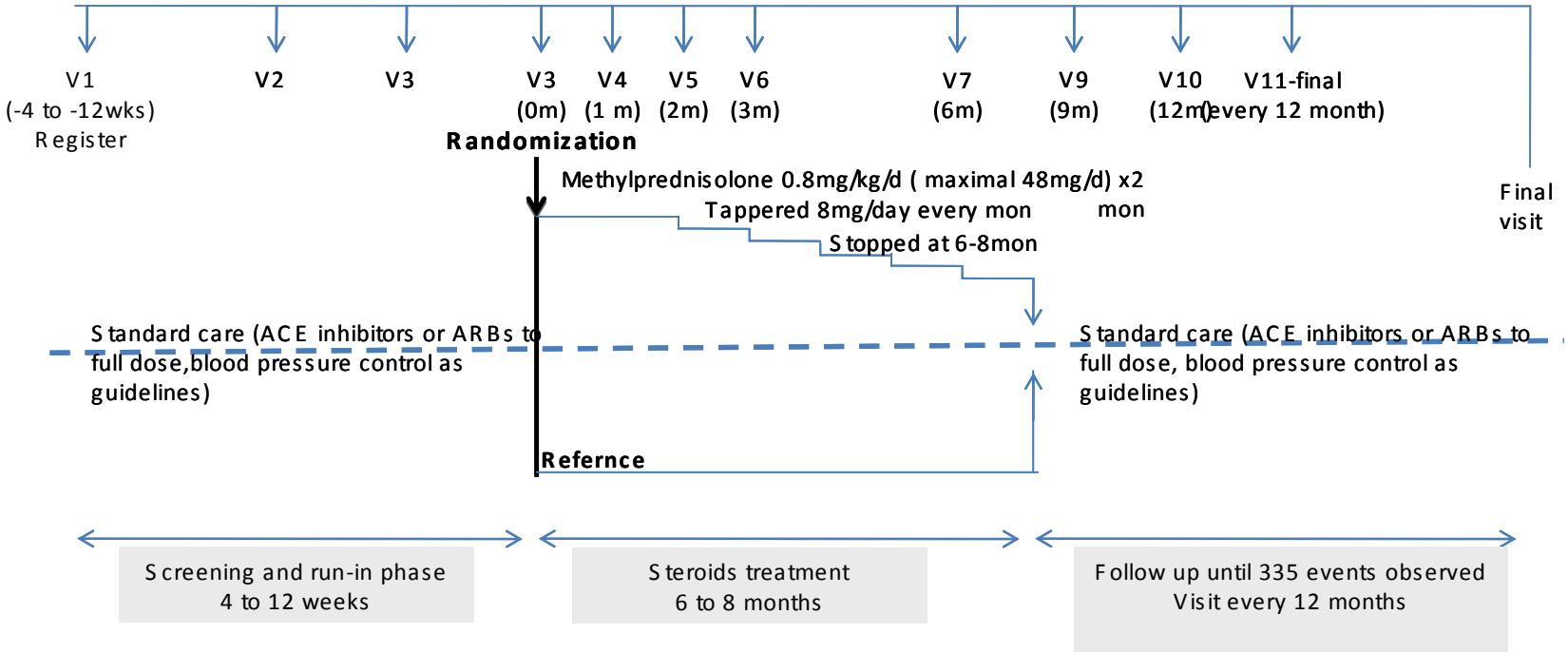
Drug/Ingredient	**Methylprednisolone**
Formulation	4mg/tablet 40 tablets/package
Manufacturer	Pfizer Pharmaceuticals

The study treatment will be packaged and supplied by the manufacturer, Pfizer Pharmaceuticals or designee. Blister cards will be used in this study. Each blister card will contain 20 tablets There will be extra tablets in each blister card to be used in case of loss during treatment. Each subject kit will contain 20 blister cards.

The study treatment will be contain information on the labels that will include: study treatment manufacturer's details, coordinating center's details, protocol number, packaging reference number, kit number, storage information, and the investigational caution statement. The labels will have space to write in the Subject Number. Additional statements will be printed on the label as required by local regulations.

All clinician's involved in the prescription of study treatment must read the Summary of Product Characteristics (SmPC)/Product Information which provides detailed information about the composition, indications, side effects, suggested dosage and contraindications of the study treatments. Study treatments must be kept at room temperature, between 20° and 25°C (68-77°F) away from heat and moisture.

Figure 5：Study period



a. For patients that are already receiving the maximum tolerated or labeled dose of ACE inhibitors or ARBs for more than 8 weeks, the run-in phase is at least 4 weeks and the pateint only receive a second visit (**V2**). The two visits are at a two-week interval. If all inclusions are fulfilled on the two visits, the pateints are randomized.
b. For patients that have received RAS inhibition less than 8 weeks, the patients will receive 2 additional visits (**V2 and V3**) during the 4-12 weeks . The third visit will be within 2 weeks before randomization. If all inclusions are fulfilled on the three visits, the pateints are randomized.

5.2 Dosing Regimen

After a 4-12 week run-in phase during which participants will not receive any study treatment but where background therapies will be optimised, people randomised to the intervention group will receive oral methylprednisolone 0.8mg/kg/d (up to a maximum of 48 mg/day) for 2 months. The dose is then tapered by 8mg every month until the course is completed. Investigators will have the option of reducing the treatment dose from 8mg to 4mg for one month prior to cessation. The total treatment duration will therefore be 6-8 months. Patients will be evaluated once every 1-3 months during methylprednisolone therapy as usual practice. Data collection will ocurr at 1^{st} ,3^{rd} ,6^{th} ,12^{th} month and then every 12 month as shown in table 7

Patients will be required to take study drug each morning with food to reduce the risk of gastrointestinal side effects. All subjects will receive conventional therapy for managing optimal blood pressure control that is in line with the current guidelines and maximal tolerated dose of ACE inhibitors or ARBs.

Diet: All participants will have standard dietary recommendations for CKD, eg. low-salt 3-6g/day (50-100mmol/day) and high calcium diet.

Patients will be advised to quit smoking and limit alcohol intake to safe levels during the study.

5.3 Drug Accountability

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the study treatments by faxing the signed investigator product receipt form contained in the shipment to the International Coordinating Centre. The study treatments must be kept in a locked area with restricted access. The study treatments must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments

dispensed, used, and returned by each subject using the investigator producr accountability form..

The study monitor will periodically check the supplies of study treatments held by the investigator or pharmacist to verify accountability of all study treatments used.

For reasons of safety, institutional regulations and storage capacity at sites, at the conclusion of the study all used and unused study treatments at the site will be destroyed by investigational site staff according to local guidelines following monitoring inspection unless prior arrangements have been approved by the coordinating centre in writing. Documentation of destruction with a complete and accurate account of study treatments destroyed must be available for verification by the study monitor and filed in the investigator site file.

5.4 Subject Compliance.

Study treatment will be distributed by the investigator or appropriately qualified designee. Subjects will be instructed to bring their unused study treatment to every visit. Compliance will be assessed by tablet counts with regard to the total number of tablets taken over the entire treatment period. Details will be recorded in the electronic case report form (eCRF).

Investigators and their study personnel will be instructed to be sure that all subjects take their prescribed number of tablets each month. If a subject forgets to take one of these tablets she/he should be instructed to take the skipped tablets on the next day after she remembers, and then continue to take the study drug daily, in sequence on the blister card, until the end of the monthly dosing period.

5.5 Concomitant Medication

Background care

Patients in this study, whether in the intervention or control arm, will all receive standard care for IgA nephropathy. The investigator should strive to control the blood pressure according to current guidelines. Throughout the trial all patients should receive ACE inhibitors or ARBs adjusted to the maximal labelled or tolerated dose (whichever is reached first) aiming at optimal blood pressure control. The recommended maximum dose of ACE inhibitors or ARBs from K/DOQI or JNC 7 is summarized in **table 5**. In general, the use of combination ACE inhibitor and ARB therapy will be discouraged.

Permitted Concomitant Medications

Any other antihypertensive medications, including diuretics, calcium channel blockers and beta-blockers can be used at any time point or can be added when monotherapy with ACE inhibitors or ARBs is not adequate to achieve blood pressure targets. Diuretics such as hydrochlorothiazide (Scr <1.5mg/day) or loop diuretics (Scr> 1.5mg/day) will be recommended as second line therapy on top of ACE inhibitors or ARBs given the benefits for the reduction of proteinuria and serum potassium. Other therapies such as statins or aspirin will be recommended for people fulfilling the required criteria according to local guidelines.

Chinese traditional medicine including Chinese herbs and acupuncture are a common treatment in China. These treatments are permitted but will be recorded on the eCRF.

Prohibited Concomitant Medications

Any other immunosuppressive therapies e.g. Mycophenolate Mofetil (MMF) cyclophosphamide (CYCLO) or azathioprine (AZA) are not permitted in this study, unless there are other definite indications for using these drugs.

Rifampin is also prohibited from this study as it interacts with methylprednisolone and makes the study drug less effective. The investigator should consult the product information of Medrol (Methylprednisolone) in appendix 7 for other prohibited concomitant medication.

Table 5. The recommended dose of ACE inhibitors or ARBs
(From JNC 7 and KDOQI)

Class	Drug (trade name)	Dose range (mg/day)	Usual daily frequence	Maximum doses used in major trials
ACE inhibitors				
	Benazepril (Lotensin)	20-40	1	30
	Captopril (Capoten)	25-100	2	100-150
	Enalapril (Vasotec)	5-40	1-2	20-40
	Fosinopril (Monopril)	10-40	1	
	Lisinopril (Prinivil, Zestril)	10-40	1	
	Moexipril (Univasc)	7.5-30	1	
	Perindopril (Aceon, Servier)	4-8 or 5-10	1	4
	Quinapril (Accupril)	10-80	1	
	Ramipril (Altace)	2.5-20	1	10
	Trandolapril (Mavik)	1-4	1	3
ARBs				
	Candesartan (Atacand)	8-32	1	16
	Eprosartan (Teveten)	400-800	1-2	
	Irbesartan (Avapro)	150-300	1	300
	Losartan (Cozaar)	25-100	1-2	100
	Olmesartan (Benicar)	20-40	1	
	Telmisartan (Micardis)	20-80	1	80
	Valsartan (Diovan)	80-320	1-2	160

6 Selection and Withdrawal of Subjects

6.1 Target population

The target population will consist 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 renal function, proteinuria, and hypertension. This trial will include patients with eGFR 20 to 70 ml/min per 1.73m^2 and proteinuria ≥1.0g/day, with or without hypertension. Patients with indications for the use of steroids (eg. crescentic glomerulonephritis (percentage of crescents >50%) or nephrotic syndrome and minimal change lesions on renal biopsy) are excluded from this study (MOH Singapore guidelines 2007). Data from the Peking University IgA Nephropathy Database (www.renal-online.org) suggest that approximately 28% of individuals with renal biopsy proven IgA nephropathy will qualify for participation in this study.

6.2 Inclusion Criteria

1) IgA nephropathy, proven on renal biopsy within the previous 2 years yet can extend to 3 years.

   This study encourages to recruit patients biopsied in the previous 2 years to evaluate the pathology score on the effect of steroids therapy. While for those sites that have difficulty of patient recruitment the period can extend to 3 years.

2) Proteinuria: ≥1.0g/day while receiving maximum tolerated dose of RAS blockade

3) eGFR: 20 to 70ml/min per 1.73m^2 (inclusive)

- *The diagnosis of IgA nephropathy will be based on the demonstration of IgA deposits on direct immunofluorescence examination or immunohistochemistry, with typical histological findings and no other likely explanation for the individuals kidney disease*
- *Serum creatinine and Proteinuria evaluation for eligibility will be determined on at least two visits during run-in phase (see section 6.5)*
- *Estimated GFR will be calculated using the equation of CKD-EPI (Levey AS 2009) (Summarized in table 6)*

6.3 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:
    a. Minimal change renal disease with IgA deposits
    b. Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months.
2) Contraindication to immunosuppressive therapy with corticosteroids, including
    a. Active infection, including HBV infection or clinical evidence of latent or active tuberculosis (nodules, cavities, tuberculoma, etc)
    b. Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (ie. squamous or basal cell carcinoma)
    c. Current or planned pregnancy or breastfeeding
    d. Women of childbearing age who are not able or willing to use adequate contraception (See Appendix 5)
3) Systemic immunosuppressive therapy in the previous 1 year.
4) Malignant /uncontrolled hypertension（>160mm systolic or 110mmHg diastolic）.
5) Unstable kidney function for other reasons, e.g. macrohaematuria induced acute kidney injury
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

Table 6. Equations for estimating GFR in this study

Race/Sex	Serum creatinine (mg/dl)	Equation
Asian (CKD-EPI formula)		
Female	≤0.7	$GFR=151\times (Scr/0.7)^{-0.328}\times(0.993)^{Age}$
	>0.7	$GFR=151\times (Scr/0.7)^{-1.210}\times(0.993)^{Age}$
Male	≤0.9	$GFR=149\times (Scr/0.9)^{-0.412}\times(0.993)^{Age}$
	>09	$GFR=149\times (Scr/0.9)^{-1.210}\times(0.993)^{Age}$
Black (CKD-EPI formula)		
Female	≤0.7	$GFR=166\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$
	>0.	$GFR=166\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
Male	≤0.9	$GFR=163\times (Scr/0.9)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=163\times (Scr/0.9)^{-1.209}\times(0.993)^{Age}$
White CKD-EPI formula)		
Female	≤0.7	$GFR=144\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$

Male	>0.7	$GFR=144\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
	≤0.9	$GFR=141\times (Scr/0.7)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=141\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$

6.4 Selection of Participants

This study will be international and conducted in more than 100 centres in a number of countries, including China, Australia, New Zealand, India, UK, Canada and other countries.

6.5 Screening and Run-in phase

All eligible patients who provide informed consent will be invited to enter the run-in phase. The aim of 4- to 12- week run-in phase is to evaluate eligibility for the trial, identify potential non–compliance and optimise background therapies. Participants will not receive any study treatment during the run-in period. All participants will be on RAS blockade for at least 3 months prior to randomization. E.g.

1) For patients who have received treatment with ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks;
2) For those not previously receive RAS blockade therapy, the run-in phase will be 12 weeks.
3) For those who have received RAS blockade therapy for less than 8 weeks, the run-in phase will be adjusted to ensure that all the participants will be on RAS inhibition for at least 12 weeks before randomization.

During the run-in phase, participants will receive standard background therapy for IgA nephropathy, including RAS inhibitors and blood pressure control according to current guidelines. All patients will receive ACE inhibitors (or ARBs if intolerant to ACE inhibitors) titrated to the maximum labelled or tolerated dose (whichever is reached first)

according to local or national guidelines. The recommended dose of ACE inhibitors or ARBs from K/DOQI or JNC-7 is summarized in **table 5**. Additional blood pressure lowering medications should be used to achieve treatment targets as per local guidelines.

Run-in phase study visits:

There will be 2-3 study visits during the run-in period:

Visit 1: The patient will be provided with information regarding the trial and offered an opportunity to consider and discuss this information. Those individuals who provide written informed consent will have eligibility for enrolment into the trial assessed. The screening procedures to be performed are described in table 7).

Visit 2-3: If all inclusion and no exclusion criteria are fulfilled, participants will attend the second or the third visits to confirm eligibility based on renal function(eGFR) and 24-hour Proteinuria.

c. For patients that are already receiving the maximum tolerated or labeled dose of ACE inhibitors or ARBs for more than 8 weeks, the run-in phase is at least 4 weeks and the patient only receive a second visit. The two visits are at a two-week interval. If all inclusions are fulfilled on the two visits, the pateints are randomized.
d. For patients that have received RAS inhibition less than 8 weeks, the patients will receive 2 additional visits (second and third visits) during the 4-12 weeks . The third visit will be within 2 weeks before randomization. If all inclusions are fulfilled on the three visits, the patients are randomized.

6.5.1 Screening Log

The screening log is designed to monitor patient recruitment at the study centre. A screening log of all patients evaluated for enrolment in the study will be compiled monthly by research co-ordinators at each study site. The log will record all screened patients, whether they are randomised into the study or considered ineligible for the study. Additionally, the reason patients were excluded or the reasons eligible patients were not enrolled will be recorded in the log. A copy of the log should be retained in the

investigator's study files. The co-ordinating centre will compile a cumulative screening log monthly, using information from each study site.

6.6 Randomisation Procedure / Code Break

All patients meeting inclusion and exclusion criteria and providing informed consent for whom all baseline data has been collected will be randomized to either the methylprednisolone group or the standard guideline based care group in a 1:1 ratio using a web based randomisation system developed and maintained by The George Institute for Global Health. Randomisation will be achieved using a minimisation algorithm via a password-protected encrypted website interface. The randomization schedule will be generated by the randomization code administrator at the coordinating centre. This password-protected and/or encrypted electronic Master Randomization List is kept by Data Management in their secure system and is only accessible to the authorised senior staff.

Patients should be randomized within 2 weeks after completion of the last evaluation.

Every patient who participates in any study related procedure will be assigned a unique patient number via the web-based randomization system. This system will be available 24 hours a day, 7 days a week.

Randomisation will be stratified using a minimisation method according to participating region, proteinuria (<3g/day or ≥ 3g/day), estimated GFR (<50ml/min.per 1.73m^2 or ≥50ml/min. 1.73m^2) and kidney biopsy findings.

6.7 Blinding

This is Prospective Randomized Open Blinded End-point (PROBE) Study. Both the patient and study personnel at each site will be aware of the treatment assignment. Primary outcomes will be assessed by individuals serving on the End Point Adjudication Committee who will be blinded to the treatment allocation of that individual.

In this study, blinding is neither possible nor essential for this trial for the following reasons: 1). The acute effects of steroids on appearance and body weight will allow patients and study staff to correctly identify the patients randomised to receive steroids within a few weeks of entry to the study, thus breaking any blind. 2) Attempting to blind the study would require the manufacture and distribution of a matching placebo that would substantially increase the cost of this international study, making it impractical. 3) The pharmaceutical company providing the study medication is not able to supply matching placebo. 4) The endpoints used in this study are objective and not likely to be influenced by knowledge of treatment group allocation, and will be adjudicated by a blinded central endpoint committee 5) the intervention is widely used, with a well recognised side effect profile so that the detection of previously unknown side effects is unlikely.

6.8 Withdrawal of Subjects

Patients have the right to refuse treatment (allowing follow-up for safety) or completely withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study treatment if they believe that is in the best interests of the patient due to intercurrent illness, SAE, treatment failure, protocol violations, non compliance, administrative reasons or other reasons.

Individuals withdrawing from study treatment will be asked to consent to phone contact according to the original protocol schedule. This will allow endpoint events or safety outcomes to be captured for the entire duration of the study. Participants will have the right to withdraw consent to any follow-up if they so wish.

If the reason for removal of a patient from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the eCRF.

Should a patient decide to withdraw consent or if they are withdrawn by the investigator for reasons mentioned above, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

An excessive rate of withdrawals may make study interpretation difficult; therefore, unnecessary withdrawal of patients should be avoided.

6.9 Expected Duration of Trial

This is an event driven trial, and will continue until at least 335 primary endpoint events are observed across the entire study population. The total duration of this study is expected to be at least 6 years with recruitment of 2 years and a subsequent follow up of at least 4 years, i.e. for the first patient, the follow-up is at least 6 years and for the last patient, the follow-up is 4 years or more. All randomised subjects will participate in the active treatment phase of up to 8 months duration and will be followed up for at least 4 to 6 years post-treatment until the earliest of any of the following:

- Completion of the follow-up period (final visit)
- Death or ESKD
- Withdrawal of consent, by the subject or legal surrogate, or withdrawal by the investigator due reasons mentioned above
- Premature study termination as defined in Section 12

The actual overall study duration or subject recruitment period may vary.

7 Trial Procedures

7.1 By Visit

Table 7 lists all of the assessments and indicates with an "X" the visits (data collection) when they are performed. During follow-up, participants will continue to receive routine clinical care, with visits at least 3-monthly as per current standard clinical practice.

In the first year all the scheduled visits are conducted face-to-face (Visit 1-7,9), whereas the subsequent visits over the remaining 3 to 5 years or more are scheduled as face to face visits at 12 month-intervals (visit 13, 17, 21, 25, 29) and telephone or face-to-face (at the choice of the investigator) visits at 3-month intervals (labeled ☎, visit 9, 10-12, 14-16, 18-20, 22-24,26-28).

Participants who discontinue study drug before completing the study, and those who prematurely withdraw from the study for any reason, should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit will be performed.

At a minimum, they will be contacted for safety evaluations during the 30 days following the last dose of study drug, including final contact at the 30-day point. Documentation of attempts to contact the patient will be recorded in the patient record.

All data obtained from the assessments listed in Table 7 must be supported in the patient's source documentation (e.g. medical charts, patient notes or electronic data). Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g. laboratory data) are listed by test name.

All data obtained from the assessments listed in Table 7 must be supported in the patient's source documentation. For the purpose of this trial certain information entered into the eCRF will act as source data as specified in Appendix 6

Whenever possible, study assessments will be made by the same person, at the same time of day, at each study visit. For face to face visits, each evaluation will be conducted in the morning wherever possible. Please note that if circumstances exist where the study patient is unable to attend morning site visits (i.e. evening shift worker, etc.), afternoon evaluations are permitted. If possible, patients should present for lab evaluations in a fasted state. Visit dates should be adhered to as closely as possible.

If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward. The next visit, if at all possible, should adhere to the original time schedule.

7.2 Physical examination

A complete physical examination will be performed at Visit 1 (**table 7**). It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart,

abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

A short physical exam will include the examination of general appearance and vital signs (BP, and pulserate). A short physical exam will be at all visits except where a complete physical exam is required. Additional physical examinations may be performed whenever clinically indicated.

Information about the all physical examinations must be present in the eCRF which will act as source data for the purpose of this study. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of an Suspected unexpected serious adverse reaction must be recorded on the Adverse Event screen of the patient's eCRF.

7.3 Height and weight

Height in centimeters (cm) or inches (inch) will be measured at Visit 3 (baseline).

Body weight (to the nearest 0.1 kilogram [kg] or 0.1 pounds [lbs] in indoor clothing, but without shoes) will be measured V3 and then at every 12month as listed in table 7.

Table 7. Schedule of Study Tests, Procedures and Clinic Visits

	Background therapy (ACE inhibitors or ARBs)																												
Phase	**Screening and run-in**			**Study Drug Treatment**						**Follow-up**																				
	Year 1									Year 2				Year 3				Year 4				Year 5				Year 6+			
	weeks			**month**																									
Time	-12 to -4			0	1	3	6	9 ☎	12	15 ☎	18 ☎	21 ☎	24	27 ☎	30 ☎	33 ☎	36	39 ☎	42 ☎	45 ☎	48	51 ☎	54 ☎	57 ☎	60	63 ☎	66 ☎	69 ☎	72
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	29	30
Informed consent form	x																												
In/exclusion criteria	x	x	x	x																									
Med History/ Demography	x																												
Height (H)				x																									
Weight(W)				x		x			x				x				x				x				x				x
Vital signs	x	x	x	x		x	x		x				x				x				x				x				x
Physical Exam	x																												x
Short physical exam	x			x		x	x		x				x				x				x				x				x
Screening log	x	x	x																										
Randomization				x																									
Chest X-ray(CXR)	x																												
Urinary analysis[a]	x			x		x	x		x				x				x				x				x				x
24-hour urine protein	x	x	x	x		x	x		x				x				x				x				x				x
24-hour urine sodium				x		x							x								x								x
HBV screening	x																												
Pregnancy urine tests	x																												
Hematology[b]	x			x		x	x		x				x				x				x				x				x
Blood chemistry panel-1[c]	x			x		x	x		x				x				x				x				x				x
Blood chemistry panel-2[d]		x	x																										
HbA1C (if diabetic)				x			x		x				x				x				x				x				x

Table 7. Schedule of Study Tests, Procedures and Clinic Visits

	Background therapy (ACE inhibitors or ARBs)																											
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	Year 1									Year 2				Year 3				Year 4				Year 5				Year 6+			
	weeks			**month**																									
Time	-12 to -4			0	1	3	6	9 ☎	12	15 ☎	18 ☎	21 ☎	24	27 ☎	30 ☎	33 ☎	36	39 ☎	42 ☎	45 ☎	48	51 ☎	54 ☎	57 ☎	60	63 ☎	66 ☎	69 ☎	72
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	29	30
Lipid profile[e]				x			x		x																				x
Pathology Scoring[f]				x																									
Study drug dispensation				x	x	x																							
Study drug accountability				x	x	x																							
Co-Med				x	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events					x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Endpoints					x	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EQ-5D				x		x	x		x																				x
No food or drink (except water for 8 hours)	x	x	x	x	x	x			x				x				x				x				x				x

a.
b. **Urinary analysis**: qualitative microscopic determination
c. **Hematology**: hemoglobin, hematocrit, reticulocytes, RBC, WBC, diff.count, platelet count
d. **Blood chemistry panel 1**: Blood urea, creatinine, total bilirubin, SGPT, alkaline phosphatase, sodium, potassium, calcium, phosphorous, total protein, albumin, glucose and uric acid
e. **Blood chemistry panel 2**: Blood urea, creatinine, sodium, potassium, uric acid
f. **Lipid profile:** total cholesterol, triglycerides, HDL-C, LDL-C
g. Pathology scoring according to Oxford classification (see appendix 1)

7.4 Chest x-ray (CXR)

A CXR screening in a *posteroanterior* view will be performed at screening (Visit 1) in countries with a high prevalence of tuberculosis or individuals considered to be at high risk, except for those individuals who have undergone chest radiography in the 1 month prior to screening. The main aim of CXR screening is to exclude asymptomatic infection e.g. tuberculosis. Interpretation of the tracing must be made by a qualified physician and documented on the CXR section of the eCRF. The CXR report should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the relevant medical history/Current medical conditions eCRF page.

7.5 Laboratory evaluations

Laboratory evaluation of all specimens will be performed in each nephrology unit.

- Renal endpoints that need determined by serum creatine including 50% decrease of eGFR, and ESRD have to be confirmed by two measurements at least 4-weeks apart and that persists for at least 6 months, or until the final available study visit. For this purpose, patients may need to attend an unscheduled visit one month after the study visit.
- Laboratory values that exceed the boundaries of a notable laboratory abnormality should be commented on by the investigator on the Comments screen of the patient's eCRF and additional evaluations should be performed if judged appropriate by the investigator. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the criteria for a Serious Adverse Event, then the procedure for notification of serious adverse events must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study, then the patient must be followed until the abnormality resolves or until it is judged to be permanent.

7.6 Hematology

Hemoglobin, hematocrit, , white blood cell count with differential, and platelet count will be measured at Visits 1, 4, 6,7, 9 and then at yearly intervals until the end of the study.

7.7 Blood chemistry

Blood chemistry: Blood urea, creatinine, total bilirubin, SGPT, alkaline phosphatase, sodium, potassium, calcium, phosphorous, total protein, albumin, glucose and uric acid will be measured at Visits 1, 4, 6, 7, 9, and then at yearly intervals until the end of the study.

Electrolyte measurement (sodium, potassium) as well as Blood Urea Nitrogen (BUN) and creatinine values, will be obtained from patients at every visit where a complete laboratory test is not done.

7.8 Creatinine Calibration

In China, a national central laboratory has been established at the Peking University First Hospital Central Laboratory, where serum creatinine levels will be measured using enzymatic method in a single laboratory. For other countries, the serum creatinine will be measured in the local laboratory of the study sites.

All the clinical laboratorieswill use a creatinine method that has calibration traceable to an IDMS (isotope dilution mass spectrometry) reference measurement procedure according to the recommendations of NKDEP's Laboratory Working Group in collaboration with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Communities Confederation of Clinical Chemistry (now called the European Federation of Clinical Chemistry and Laboratory Medicine). Methods based on either enzymatic or Jaffe method principles should have calibration traceable to IDMS.

7.9 Urinary analysis

A qualitative microscopic determination - white blood cells per high power field (WBCs/HPF) and red blood cells per high power field (RBCs/HPF) will be performed at each visit.

7.10 24-hour urine protein exretion

24 hour urine collection for protein excretion will be performed at Vistit 1,2,3,4,6,7,9 and then at a yearly intervals until the end of the study. Creatinine will also be measured as a marker of completeness of collection

7.11 24-hour urine sodium

24 hour sodium excretion will be measured on all 24 hour urine specimens at 6month (V6), 2year (V13), 4year (V21) and final visit

7.12 Glycosylated hemoglobin (HbA1C)

HbA1C will be measured in patients with diabetes at Visits 4,7,9 and then at yearly interval until the end of the study.

7.13 Lipid profile

Lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C) will be measured at Visits 4 ,7 and 9 then the final visit.

7.14 Scoring of histological lesions

The renal biopsy material or electronic images with PAS (periodic acid Schiff) stain will be collected from the study sites. The histological lesions will be reviewed centrally at Visit 4 and graded according to the Oxford Classification (*see apendix 1*)

7.15 Pregnancy

All female patients of childbearing potential will have a urine pregnancy test screening performed at Visit 1 to evaluate eligibility for the trial.

7.16 Health-related Quality of Life

Health outcomes will be measured at Baseline and months 1, 6, 12, 36, 60 and at the final visit using the EuroQol EQ-5D (EQ-5D) questionnaire which generates a composite index score representing the preference for a given health state (i.e., health utilities). The instrument includes a visual analog scale and 5 questions covering the following dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. There are 3 possible responses to each question (no problem; some problem; severe problem), thus enabling estimation for 243 possible health states.

The working hypothesis is that there will be no decrease in patient reported outcomes in the control arm relative to the active treatment arm of the study. The data from this study will be the first in terms of health utility for patients with IgA nephropathy taking methylprednisolone/steroids. The EQ-5D questionnaire should be completed by patient who should sign and date the questionnaire.

7.17 Early Withdrawal from the Trial

Patients who discontinue study drug or withdraw early from this study should return for the assessments regularly as indicated by **Table 7**. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to ask if any of the primary or secondary endpoints have occurred, at the foreseen visit dates, for the remaining duration of the study.

7.18 Biobanking

All participants will be invited to contribute baseline blood, urine and DNA speciments for biobanking to allow subsequent study of IgA nephropathy, and the response to therapy.

In participating centres, consenting individuals will contribute sequential urine and/or blood samples (24 hour urine or random urine or plasma) at 0, 1st, 3rd, 6th,12th and then every 12 month.

The samples to be collected are described in Appendix 8.

7.19 Data Handling & Management

The procedures for data review and query management are described in the Data Management Document and Monitoring Plan. Data will be reviewed throughout the study according to these documents.

Data for this study will be captured via a Web-based Electronic Data Capture system using the electronic Case Report Forms (eCRFs). The investigator should ensure the accuracy, completeness and timeliness of the data reported to the Coordinating Centre in the eCRF and in all required reports.

For each subject enrolled, an eCRF must be completed. It will be transcribed by the site from the paper source documents onto the eCRF. The participants will be identified only by initials and a participant ID number/identification code on the eCRF. The name and any other identifying detail will NOT be included in any study data electronic file.

Data will be validated for accuracy and reliability using two methods:

1. A comprehensive validation check program will centrally verify the data according to the Data Management Document and automatically generate discrepancies for resolution by the investigator. Manual discrepancies can also be raised if necessary.

2. Verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification) according to the Monitoring Plan, and the maintenance of a medication–dispensing log by the investigator.

An electronic audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person who made the change.

8 Assessment of Efficacy

8.1 Primary Efficacy Parameters

Progressive kidney failure, which is a composite of a persistent 50% decrease in eGFR , the development of end stage kidney disease, or death due to kidney disease. The outcomes will be defined as below:

- **Persistent 50% decrease in eGFR**: reduction of eGFR by 50% from the baseline value (pre-randomisation) that is confirmed by a second serum creatinine value obtained at least 4 wks after the initial doubling, and that persists for at least 6 months or until the final available study visit.

- **End stage kidney disease**: includes kidney transplantation, maintenance dialysis therapy, or situations where a patient dies due to kidney disease

- **Death due to kidney disease**: death due to kidney failure that need dialysis, and the death could be avoided by timely dialysis.

8.2 Secondary Efficacy Parameters

Secondary outcomes are each of eGFR reduction by 50%, end stage of kidney disease, as well as a composite outcome comprising both of these as well as death due to any cause.

In addition, the mean annual slope in eGFR during follow-up will be obtained by fitting a straight line through the calculated GFR using linear regression and the principal of least squares. Add proteinuria

8.3 Procedures for Assessing Efficacy Parameters

Serum Creatinine:

Serum creatinine to determine eligibility or endpoints will be conducted in the morning by the local laboratory centre of each nephrology unit included in this trial. If possible, patients should present for lab evaluations in a fasted state

Estimated Glomerular Filtration Rate (eGFR):

The eGFR to determine eligibility for enrolment into the trial will be calculated from the serum creatinine concentration at Visit 1.

The eGFR to determine the incidence of study endpoints will be confirmed by two measurements at least 4-weeks apart

The eGFR calculation will use the the equation of *CKD-EPI* (Levey AS 2009) (Summarized in table 6) .

Urine protein excretion (proteinuria):

24-hour urine protein excretion (g/day) to determine the will be determined during run-in phase (visit 1,2,3) baseline (visit 4) , 3 month (visit 6), 6 month (visit 7), and 12 month (visit 9) and then every 12 month to the final visit (summarized in table 7)

9 Assessment of Safety

9.1 Definitions

Adverse events (AEs)

According to the International Conference of Harmonization [ICH], an AE is any untoward medical occurrence in a patient or clinical investigation 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 or symptom, or disease temporally associated with the use of a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product. Pre-existing conditions which worsen during a study are AEs.

All reportable AEs encountered during the clinical study will be reported on the AE electronic form (eform) of the eCRF. Intensity of AEs will be graded on a three point scale [mild, moderate, severe] and reported in detail on the eCRF.

Mild	discomfort noticed but no disruption of normal daily activity.
Moderate	discomfort sufficient to reduce or affect daily activity.
Severe	inability to work or perform normal daily activity

Serious adverse events (SAEs)

Serious adverse events are defined as any untoward medical occurrence that meets one of more of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

The classification of 'serious adverse event' is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria.

If there is any doubt whether an event constitutes an SAE, this event should be considered a SAE.

Suspected unexpected serious adverse reaction (SUA)

SUA is defined as a serious adverse event for which the nature and severity of the event is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for products with a marketing authorisation.

9.2 Study specific reportable adverse events

For this trial, reporting of adverse events will be restricted to serious adverse events that are considered to be related to study treatment (possibly, probably or definitely). Therefore, death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be reportable events.

Serious adverse events will be grouped by body system as defined by the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), following

classification of investigator assessments into MedDRA preferred terms. Treatments will be compared with respect to the incidence of events by body system.

9.3 Safety alert terms for expedited reporting

In addition, if any of the following study treatment-related adverse events (serious or non-serious) occur in a subject in this study, they will be documented in the AE log of the eCRF and reported to the Coordinating Centre, using the procedure for serious adverse events, even if the criteria for seriousness are not fulfilled:

Adverse events leading to withdrawal from the study:

- New onset of diabetes mellitus (for criteria of diabetes mellitus see attachment 1)
- Severe Infection requiring hospitalization
- Clinically evident fracture or osteonecrosis
- Gastrointestinal bleeding requiring hospitalization
- Major cardiovascular event (non-fatal stroke, nonfatal myocardial infarction, heart failure requiring admission, and cardiovascular death]

These reportable adverse events are of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the investigators to the Coordinating Centre may be appropriate. Such events may require further investigation in order to characterize and understand them.

Pregnancy

Adequate human reproductive studies have not been conducted with corticosteroids (SmPC), therefore pregnancies occurring in female patients exposed to the study treatment must be reported within one working day to the coordinating centre.

A female patient must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. Study treatment will be permanently discontinued but the patient will remain in the study

until study completion. Monitoring of the patient should be continued at least until conclusion of the pregnancy.

The investigator should counsel and discuss with the patient the risks of continuing with the pregnancy and the possible effects of early exposure to study medication on the fetus. Pregnancies occurring up to 90 days after the completion of the study treatment must also be reported to the investigator.

Where a SAE occurs in the pregnant female patient (irrespective of whether the SAE is pregnancy-related or not), the SAE must be collected separately.

Significant Overdose

In addition, cases in which a "significant overdose" (accidental or intentional) of the study treatment was taken, whether or not an adverse event occurred, are to be reported to the Sponsor in an expedited manner in the AE log of the eCRF. For purposes of this study, a "significant overdose" is defined as a subject's taking on the same day 5 or more times the planned daily dose for that day.

In the cases of significant overdose in which no adverse event occurred, the diagnosis on the AE log should be recorded as "overdose without adverse event", and the "overdose" criteria on the AE log should be ticked. For cases in which an adverse event occurred with overdose, the event description should be recorded as the diagnosis, and the "overdose" criteria should be ticked.

9.4 Period of Observation

For the purposes of this study, the period of observation for collection of treatment-related serious adverse events will commence from the time of the first dose of study treatment until the end of the study. Serious Adverse events that occur intermittently should be recorded as one AE.

If the investigator detects a serious adverse event in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the coordinating centre to determine how the adverse event should be documented and reported.

9.5 Documentation and Reporting of Adverse Events

All reportable adverse events that occur during the observation period set in this protocol will be reported by the Investigator to the coordinating centre, The George Institute for Global Health, on the AE log of the eCRF. Instructions for reporting adverse events are provided in the investigator's study file.

Serious adverse events and adverse events that fulfill a reason for expedited reporting to the Coordinating Centre must be documented in the AE log of the eCRF within 24 hours of the site becoming aware of the event. When the site enters the AE on the eCRF and ticks "Yes" to the question "Is this a serious adverse event or an alert term?" an email notification is sent automatically to a specified list of Coordinating Centre representatives (including the medical monitor).

The investigator must also inform the study monitor in all cases. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study treatment. The Investigator will submit reportable adverse events to the relevant ethics committees in accordance with local ethics committee reporting requirements.

The coordinating centre will be responsible for reporting in an expedited manner, all SAEs that are both unexpected and at least reasonably related to study treatment (Suspected Unexpected Serious Adverse Reactions) to the Regulatory Authorities, IECs/IRBs as appropriate and to the Investigators within 7 days with an additional report within 8 days, and reporting of SUSARs to the study drug manufacturer within

3 working days of being notified of the adverse event. Any SAE not listed as an expected event in the SmPC will be considered as unexpected.

The George Institute will provide an Emergency 24 Hour Medical Coverage for study related medical emergencies outside regular business hours to allow for the provision of advice to investigators or research staff. Contact numbers will be distributed to all participating investigators in a separate document.

The study will adhere to the full requirements of the **ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2** and comply with local regulatory requirements.

10 Statistics

10.1 Statistical analyses:

Comparison will be made of the primary outcomes, comparing all those allocated methylprednisolone versus all those allocated control arm, on an intention to treat (ITT) basis. Cox proportional hazards analysis and Kaplan-Meier plots will be used to compare event rates among the two groups. Analysis will be stratified by proteinuria (~1g/day, 1-3.5g/day, >3.5g/day), renal function (eGFR <45 versus >45 ml/min per 1.73m^2), histological lesion scoring (M1 or Mo, E1 or E0) and race (Asian, Caucasian) .

10.2 Sample size calculation and reasoning

This trial has good power to detect clinically important effects. A sample size of 1300 patients will provide more than 90% power (α=0.05) to detect a 30% risk reduction with a steroid based treatment approach after an average follow-up of 5 years, equating to a 33% actual effect incorporating a 10% treatment drop out. We also have

80% power to detect a 26% RRR, equating to a 28% RRR due to the treatment after accounting for 10% treatment dropout

The sample size calculations have been performed using the log-rank test and assuming an annual combined rate of 50% decline in eGFR or ESKD of 7%. The study is event driven, and will therefore continue until at least 335 primary endpoints have been observed.

A study including up to 15 years of follow-up (including 293 cases) showed that the ESKD incidence was 6.7% per person-year (Lv J 2008) in patients with eGFR 20-70ml/min.1.73m^2. Based on a prospective Chinese Cohort with IgA nephropathy including 583 patients and 40-month follow-up, the composite endpoint of 50% eGFR decline and ESKD was 8.5% per person-year. We therefore conservatively estimate that the composite end point incidence of 50% decrease of eGFR (roughly 80% serum creatinine increase) and ESKD among the study population will be 7% per year. The prospective randomized controlled trial from Manno C. et al. (2009) showed the incidence was 6% in patients with ramipril therapy and preserved renal function, (eGFR>50ml/min/1.73m2). As this trial includes a higher-risk group (eGFR: 20-70ml/min/1.73m2), the incidence of ESKD is likely to be increased two-fold or more, supporting the conservative nature of the annual event rate estimate of 7%.

The meta-analysis described above suggests that methylprednisolone might reduce the risk of the primary endpoint by 64%, ie a relative risk (RR) of 0.36. This trial is conservatively powered to detect a risk reduction of 30%, which is equivalent to the upper limit of the 95% confidence interval obtained in the meta analysis of previous trials.

10.3 Interim analysis

The trial DSMB will monitor safety data on an ongoing basis, and will also perform two unblinded interim analyses for the primary outcome, based on a comparison of the primary endpoint in the two treatment groups with the use of a normal

approximation for a two-sided test, when one third and two thirds of the patients have completed one year of study follow-up. A group sequential approach (O'Brien Fleming method) will be utilised.

The analyses will be performed by an independent statistician from the George Institute For Global Health, who is not involved in managing the trial. The DSMB can recommend the Central Executive Committee of the TESTING-Trial should

- Adjust the duration of follow-up;
- Terminate the study early if there is clear and substantial evidence of benefit;
- Terminate the study early if the data suggests the risk of adverse events substantially outweighs the potential benefits

11. Participant Confidentiality & Record Keeping

11.1 Participant Confidentiality

The investigator and trial staff must ensure that subjects' anonymity will be maintained, that their identities are protected from unauthorized parties and take measures to prevent accidental or premature destruction of these documents. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

The investigator should keep a subject enrollment log showing codes, names and addresses. The investigator should maintain subjects' written consent forms documents in strict confidence.

When archiving or processing data pertaining to the investigator and/or to the patients, the co-ordinating centre shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.2. Investigator's Files / Source Documents/ Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (1) investigator's Study File, and (2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition, at the end of the study the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in readable format on CD which also has to be kept with the Investigator's Study File.

For this trial, electronic data entered into the eCRF will serve as source data, but some hard-copy source data must also be maintained as shown in appendix 6. Subject clinical source documents could include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrollment logs. The Investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, the Coordinating Centre must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Coordinating Centre to store these in a sealed container[s] outside

of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

11.3 Direct Access to Source Documents

The investigator shall supply the coordinating centre on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor of the Study, the Coordinating Centre, the study monitoring committee or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

12. Quality Assurance Procedures

The study will be conducted in accordance with the current approved protocol, ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 (ICH GCP), Declaration of Helsinki, relevant regulations and standard operating procedures.

12.1 Obtaining Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study;

the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they require to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

If the subject is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to subjects must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (e.g. the subject's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

12.2 Delegation of Investigator Duties

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should

maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 Ethics and Regulatory Approvals

Before the start of the study, the protocol, informed consent document, any proposed advertising material and any other appropriate documents will be submitted to the appropriate Human Research Ethics Committee (HREC) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all subsequent and substantial amendments to the original approved documents. If applicable, the documents will also be submitted to the Regulatory Authorities where the trial is taking place for Clinical Trial Authorization, in accordance with local legal requirements.

Study medication can only be supplied to the investigator after documentation on **all** ethical and regulatory requirements for starting the study has been received by the Coordinating Centre.

Safety reports, annual progress reports and a final report at conclusion of the trial will be submitted to the Regulatory Authorities, research ethics committees and if applicable, to the study treatment manufacturer within the timelines defined in the Regulations.

12.4 Management of Protocol Deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The investigator should not implement any deviation from or changes of the protocol without agreement by the study management committee and documented approval

from the Independent Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants the Investigator may implement any medical procedure deemed appropriate.

Deviations from the protocol must be documented and promptly reported to the study management committee and the Independent Ethics Committee (if applicable). The report should summarise the event and action taken.

12.5 GCP Training and Site Monitoring

Study monitors from the Coordinating Centre will conduct a site initiation visit prior to the start of the study to ensure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and ensure that acceptable facilities are available to conduct the study.

In addition, periodic site monitoring will be performed according to ICH GCP, the Coordinating Centre's SOP and Monitoring Plan. For each site, a minimum of one site monitoring visit per year must be performed. The monitors will verify that the clinical trial procedures are being conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and the applicable regulatory requirements. Data recorded in the eCRF will be evaluated for compliance with the protocol and accuracy in relation to source documents.

On completion of all patient treatments and evaluations, the monitor will conduct a closure visit at the site.

12.6 Audits and Inspections

The Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities. The Investigator agrees to allow the

auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performance of the audits and inspections.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor (or Coordinating Centre) and authorize the Sponsor (or Coordinating Centre) to participate in this inspection. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor (or Coordinating Centre). The Investigator shall take appropriate measures required by the Sponsor (or Coordinating Centre) to take corrective actions for all problems found during the audit or inspections.

12.7 Trial Executive Committee

The study will be conducted under leadership of a central executive committee (CEC) that has overall responsibility for protocol design, study conduct and publication. The members of the executive committee have great experience in managing patients with IgA nephropathy or chronic kidney diseases, and have demonstrated experience and expertise in designing, conducting and analyzing clinical studies. The CEC will also oversee a national executive committee (NEC) in each participating country/region during the conduct of the study.

The NEC will facilitate the conduct of the trial in the countries that participate in this study, ensuring that the study is enrolled expeditiously and that data collection is performed according to Good Clinical Practice (GCP) guidelines.

Investigator proposed sub-studies will be evaluated by the CEC on scientific merit and must be approved by the CEC prior to being conducted.

12.8 Data and Safety Monitoring Committee (DSMC)

An independent DSMC will be established to review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate.

The DSMB will consist of physicians and a statistician experienced in clinical studies. The committee will be supported by an unblinded statistician at an independent research group. The independent DSMB will review safety data on an ongoing basis and may recommend the CSC/NSC to stop or amend the study based on safety findings.

12.9 Termination of the Study

The study must be closed at the site on completion of all participant treatment and evaluations. Furthermore, the study may be closed at any time at the request of the study steering committee, the Investigator, or a regulatory authority, with proper and timely notification of all parties concerned. As far as possible, early closure should occur after mutual consultation.

The Independent Ethics Committee will be informed and the Coordinating Centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements.

13 Publication Policy

The study will be conducted in the name of the TESTING study investigators.

- The principal publication from the study will be in the name of the TESTING study Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where an individuals' name is required for publication it will be that of the writing committee, with the chair of the

writing committee listed first and subsequent authors listed alphabetically. All the study investigators will be listed at the end of main reports.

- It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

14 Property Rights

All the results, data and documents, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Investigator shall not mention any information in any application for any intellectual property rights.

15 Finance and Insurance

Participating Centre agreements will be signed between the George Institute for Global Health, participating institutions and principal investigators and cover:

- Trial work and duration
- Obligations of the Principal Investigator
- Payment and withdrawal of funding
- Confidentiality
- Intellectual property
- Liability & Indemnity

The co-ordinating centre certifies that it has taken out a liability insurance policy. This insurance policy is in accordance with local laws and requirements. The insurance of the Coordinating Centre does not relieve the Investigator or manufacturers of the

study interventions of any obligation to maintain their own liability insurance policy as required by applicable law.Liability and insurance provisions for this study are given in separate agreements.

Appendix 1 the Oxford Classification of IgA nephropathy

(Kidney Int 2009;76:534)

Table A1.1 Definations of pathological variables used in the oxford classification of IgA nephropathy

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0 4–5 Mesangial cells/mesangial area=1 6–7 Mesangial cells/mesangial area=2 >8 Mesangial cells/mesangial area=3 The mesangial hypercellularity score is the mean score for all glomeruli	M0⩽0.5 M1>0.5[a]
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 – absent S1 – present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 – absent E1 – present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0–25% – T0 26–50% – T1 >50% – T2

[a]Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.

Table A1.2: Recommended elements in renal biopsy report for a case of IgA nephropathy

Detailed description of the features present on
Light microscopy
Immunohistochemistry
Electron microscopy
Summary of four key pathological features
Mesangial score⩽0.5 (M0) or >0.5 (M1)
Segmental glomerulosclerosis absent (S0) or present (S1)
Endocapillary hypercellularity absent (E0) or present (E1)
Tubular atrophy/interstitial fibrosis⩽25% (T0), 26–50% (T1), or >50% (T2)
Total number of glomeruli
Number of glomeruli with endocapillary hypercellularity, extracapillary proliferation, global glomerulosclerosis, and segmental glomerulosclerosis

Appendix 2 Equation for estimating GFR in this study

Race/Sex	Serum creatinine (mg/dl)	Equation
Asian (CKD-EPI formula)		
Female	≤0.7	$GFR=151\times (Scr/0.7)^{-0.328}\times(0.993)^{Age}$
	>0.7	$GFR=151\times (Scr/0.7)^{-1.210}\times(0.993)^{Age}$
Male	≤0.9	$GFR=149\times (Scr/0.9)^{-0.412}\times(0.993)^{Age}$
	>0.9	$GFR=149\times (Scr/0.9)^{-1.210}\times(0.993)^{Age}$
Black (CKD-EPI formula)		
Female	≤0.7	$GFR=166\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$
	>0.7	$GFR=166\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
Male	≤0.9	$GFR=163\times (Scr/0.9)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=163\times (Scr/0.9)^{-1.209}\times(0.993)^{Age}$
White (CKD-EPI formula)		
Female	≤0.7	$GFR=144\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$
	>0.7	$GFR=144\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
Male	≤0.9	$GFR=141\times (Scr/0.7)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=141\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$

Appendix 3 Criteria for the diagnosis of diabetes

1. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

   OR

2. Symptoms of hyperglycemia and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.

   OR

3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

* In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.

Reference: American Diabetes Association 2009

Appendix 4 Criteria for the diagnosis of obesity

Body mass index (BMI) is a simple index of weight-for-height that is commonly used in classifying overweight and obesity in adult populations and individuals. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m2).

As for the Asian population, overweight is defined as as a BMI equal to or more than 23, and obesity defined as BMI equal to or more than 25.

As for other population, it defines "overweight" as a BMI equal to or more than 25, and "obesity" as a BMI equal to or more than 30.

Table A4.1 WHO criteria for classification of adults according to BMI

Classification	BMI
Underweight	< 18.50
Normal range	18.50-24.99
Overweight	≥25.00
preobese	25.00-29.99
Obese class I	30.00-34.99
Obese class II	35.00-39.99
Obese class III	I 40

Table A4.2 Criteria for classification of Asian adults according to BMI

Classification	BMI
Underweight	< 18.50
Normal range	18.50-22.99
Overweight	≥23.00
preobese	23.00-24.99
Obese class I	25.00-29.99
Obese class II	I 30

Appendix 5 Contraception Protection

Women of childbearing potential must use an acceptable method of contraception to prevent pregnancy. Acceptable methods of contraception include the following:

- Barrier type devices (e.g. female condom, diaphragm and contraceptive sponge) used ONLY in combination with a spermicide.
- Intra-uterine devices.
- Oral contraceptive agents started at least 90 days before start of study.
- Depo-Provera (medroxyprogesterone acetate).
- Levonorgestrel implants.
- Naturally or surgically sterile (amenorrheic for at least 1 year and no record of child birth for naturally sterile persons).
- Male partner is sterile and is the only sexual partner

NB: True or periodic abstinence, the rhythm method or contraception by the partner only are NOT acceptable methods of contraception.

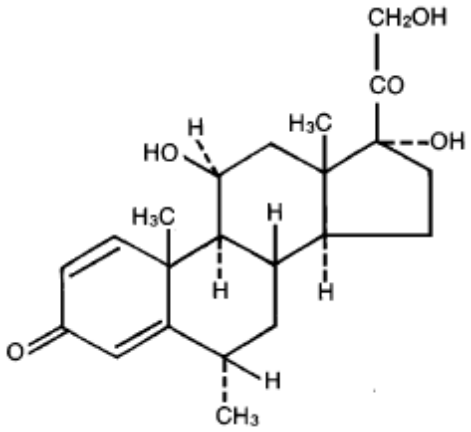
Appendix 6: Specification of Source data

Assessment	What will function as Source Data
Informed consent form	Individual consent form
In/exclusion criteria	eCRF
Med History/ Demography	eCRF, and copies of documents/letters where available to be filed in patient file
Renal biopsy report	Report filed in patient file
Height and Weight(W)	eCRF
Vital signs	eCRF
Physical Exam	eCRF
Short physical exam	eCRF
Screening log	Screening log maintained at each site
Randomization	eCRF
Chest X-ray(CXR)	X-ray report in the patient file
Urinary analysis[a]	eCRF
24-hour urine protein	Lab report – filed in the patient file signed and dated by the responsible clinician
24-hour urine sodium	eCRF
HBV screening	eCRF
Pregnancy urine tests	eCRF
Hematology[b]	eCRF
Blood chemistry panel-1[c]	Lab report – filed in the patient file signed and dated by the responsible clinician
Blood chemistry panel-2[d]	Lab report – filed in the patient file signed and dated by the responsible clinician
Fast blood glucose	eCRF
HbA1C (if diabetic)	eCRF
Lipid profile[e]	eCRF
Study drug dispensation	Drug accountability logs maintained at each site
Study drug accountability	Drug accountability logs maintained at each site
Co-Med	eCRF and referral letters or past med history information from medical records if available – to be filed in the patient file
Adverse events	Written information on diagnosis, hospital discharge summaries etc – filed in the patient file
Endpoints	Written information on diagnosis, hospital discharge summaries etc – filed in the patient file
EQ-5D	Completed questionnaire

Appendix 7: Medrol Product information:

DRUG CLASS AND MECHANISM: Methylprednisolone is a synthetic (man-made) corticosteroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located adjacent to the kidneys. Corticosteroids affect metabolism in various ways and modify the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The chemical name for methylprednisolone is pregna - 1,4 - diene - 3,20-dione, 11, 17, 21-trihydroxy-6-methyl-, (6α, 11β)-and the molecular weight is 374.48. The structural for-mula is represented below:



STORAGE: Tablets should be kept at room temperature, between 20° and 25°C (68-77°F).

PRESCRIBED FOR: Methylprednisolone is used to achieve prompt suppression of inflammation. Examples of inflammatory conditions for which methylprednisolone is used include rheumatoid arthritis, systemic lupus erythematosus, acute gouty arthritis, psoriatic arthritis, ulcerative colitis, and Crohn's disease. Severe allergic conditions that fail conventional treatment also may respond to methylprednisolone. Examples include bronchial asthma, allergic rhinitis, drug-induced dermatitis, and contact and atopic dermatitis. Chronic skin conditions treated with methylprednisolone include dermatitis herpetiformis, pemphigus, severe psoriasis and severe seborrheic dermatitis. Chronic allergic and inflammatory conditions of the uvea, iris, conjunctiva and optic nerves of the eyes also are treated with methylprednisolone.

DOSING: Dosage requirements of corticosteroids vary among individuals and the diseases being treated. In general, the lowest effective dose is used. The initial oral dose is 4-48 mg daily depending on the disease. The initial dose should be adjusted based on response. Corticosteroids given in multiple doses throughout the day are more effective but also more toxic than the same total daily dose given once daily, or every other day. Methylprednisolone should be taken with food.

DRUG INTERACTIONS: Troleandomycin (TAO), an infrequently used macrolide antibiotic, reduces the liver's ability to metabolize methylprednisolone (and possibly other corticosteroids). This interaction can result in higher blood levels of methylprednisolone and a higher probability of side effects. Erythromycin and clarithromycin (Biaxin) are likely to share this interaction, and ketoconazole (Nizoral) also inhibits the metabolism of methylprednisolone. Estrogens, including birth control pills, can increase the effect of corticosteroids by 50% by mechanisms that are not completely understood.

For all of the above interactions, the dose of methylprednisolone may need to be lowered. Cyclosporin reduces the metabolism of methylprednisolone while methylprednisolone reduces the metabolism of cyclosporin. When given together, the dose of both drugs may need to be reduced to avoid increased side effects. Methylprednisolone may increase or decrease the effect of blood thinners [for example, warfarin (Coumadin)]. Blood clotting should be monitored and therapy adjusted in order to achieve the desired level of blood thinning (anti-coagulation).

Phenobarbital, phenytoin (Dilantin), and rifampin (Rifadin, Rimactane) may increase the metabolism of methylprednisolone and other corticosteroids, resulting in lower blood levels and reduced effects. Therefore, the dose of methylprednisolone may need to be increased if treatment with phenobarbital is begun.

PREGNANCY: Methylprednisolone has not been adequately evaluated in pregnant women.

NURSING MOTHERS: Methylprednisolone has not been adequately evaluated in nursing mothers.

SIDE EFFECTS: Adverse effects of methylprednisolone depend on dose, duration and frequency of administration. Short courses of methylprednisolone are usually well-tolerated with few, mild side effects. Long term, high doses of methylprednisolone may produce predictable and potentially serious side effects. Whenever possible, the lowest effective doses of methylprednisolone should be used for the shortest length of time to minimize side effects. Alternate day dosing also can help reduce side effects.

Side effects of methylprednisolone and other corticosteroids range from mild annoyances to serious irreversible bodily damage. Side effects include fluid retention, weight gain, high blood pressure, potassium loss, headache, muscle weakness, puffiness of the face, hair growth on the face, thinning and easy bruising of the skin, glaucoma, cataracts, peptic ulceration, worsening of diabetes, irregular menses, growth retardation in children, convulsions, and psychic disturbances. Psychic disturbances may include depression, euphoria, insomnia, mood swings, personality changes, and even psychotic behavior.

Prolonged use of methylprednisolone can depress the ability of the body's adrenal glands to produce corticosteroids. Abruptly stopping methylprednisolone in these individuals can cause symptoms of corticosteroid insufficiency, with accompanying nausea, vomiting, and even shock. Therefore, withdrawal of methylprednisolone usually is accomplished by gradually lowering the dose. Gradually tapering methylprednisolone not only minimizes the symptoms of corticosteroid insufficiency, it also reduces the risk of an abrupt flare of the disease being treated.

Methylprednisolone and other corticosteroids can mask signs of infection and impair the body's natural immune response to infection. Patients on corticosteroids are more susceptible to infections and can develop more serious infections than individuals not on corticosteroids. For example, chickenpox and measles viruses can produce serious and even fatal illnesses in patients on high doses of methylprednisolone. Live virus vaccines, such as smallpox vaccine, should be avoided in patients taking high doses of methylprednisolone since even vaccine viruses may cause disease in these

patients. Some infectious organisms, such as tuberculosis (TB) and malaria, can remain dormant in patients for years. Methylprednisolone and other corticosteroids can allow these infections to reactivate and cause serious illness. Patients with dormant TB may require anti-TB medications while undergoing prolonged corticosteroid treatment.

By interfering with the patient's immune response, methylprednisolone can prevent vaccines from being effective. Methylprednisolone also can interfere with the TB skin test and cause falsely negative results in patients with dormant TB infections.

Methylprednisolone impairs calcium absorption and new bone formation. Patients on prolonged treatment with methylprednisolone and other corticosteroids can develop osteoporosis and an increased risk of bone fractures. Supplemental calcium and vitamin D are encouraged to slow this process of bone thinning. In rare individuals, destruction of large joints can occur while undergoing treatment with methylprednisolone or other corticosteroids (aseptic necrosis). These patients experience severe pain in the joints involved, and can require joint replacement. The reason behind such destruction is not clear. Methylprednisolone can be used in pregnancy, but is generally avoided.

Reference: FDA Prescribing Information

Appendix 8: Biobanking

All participants will be invited to contribute baseline blood, urine and DNA speciments for biobanking to allow subsequent study of IgA nephropathy, and the response to therapy. The samples to be collected stored in the each participating country for future study. Informed consent must be obtained before drawing blood or urine.

1. Urine

24 hour urine collection processing, shiping and storing

The preparation of a properly mixed aliquot from the 24-hour urine collection is key to the correct measurement of the analyte. Therefore the following procedure must be followed closely:

- 24 hour urine may be measured by thoroughly mixing and pouring the sample into a 2 Liter graduated cylinder. A clean graduated cylinder must be used for each specimen.
- Be sure to record the volume on the requisition and aliquot container.
- Affix pre-printed labels to the10mL cryovials.
- Transfer urine into aliquots of 9mL.
- Store the aliquots at -20 °C or -80 °C in a plastic rack or cardboard freezer box in an upright position wthin 4 fours.
- Label the racks or cardboard boxes with permanent marker or an adhesive label that says "TESTING 24 Hr Urine Refrigerated"

Random midstream urine collection processing, shipping and storing (for Proteomics)

- Encourage participants to stay hydrated even while fasting for the visit. However, do not collect samples after acute fluid load (>24 ounces) or after participant exertion. Collection will be random and, therefore, considered a "spot" urine collection.
- Place the sample on ice immediately after it is collected.
- Affix pre-printed labels to 2 airtight 10mL cryovials
- Transfer 9mL of urine into the 10mL cryovials.
- Store the aliquots at -20 °C or -80 °C in a plastic rack or cardboard freezer box in an upright position wthin 4 fours.
- Label the racks or cardboard boxes with permanent marker or an adhesive label that says "TESTING Random Urine Refrigerated"

2 Blood collection: participant should remain fasted

DNA collection

- Participant remains fasted
- 5mL EDTA (purple top) tubes
- Blood Mixing During Venipuncture
- DO NOT SHAKE TUBES
- Affix label for DNA extraction
- Refrigerate sample at 4ºC
- Genomic DNA is extracted within 72 hours
- Store the Genomic DNA at -20 °C or -80 °C
- Label with permanent marker or an adhesive label that says "TESTING DNA Refrigerated"

Serum collection

- Participant remains fasted
- 5mL (red top) tubes
- the drawn blood must be stored at room temperature for at least 30 minutes for complete clotting to occur.
- The serum must be separated from the clotted blood by centrifugation. Centrifuge at 2100 g for 15 minutes.
- Affix labels to aliquot cryovials
- Transfer all serum into one tube
- Label with permanent marker or an adhesive label that says "TESTING Serum Refrigerated"

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CLINICAL TRIAL PROTOCOL

TESTING Study

Therapeutic **E**valuation of **ST**eroids in **I**gA **N**ephropathy **G**lobal study

Protocol Number: GI-R-01-2011
Version Number: 5.0

Testing Study Amendment 4_Version 5.0_Dated 13May2015

"A collaboration between the Peking University Institute of Nephrology, the George Institute for Global Health and renal researchers around the world"

PRIVILEGED AND CONFIDENTIAL

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Jicheng Lv (Peking University and The George Institute for Global Health. China) Study Physician

Kathy You (The George Institute for Global Health, Australia) International Project Manager

Central Executive Committee Signature

I have read and approve this protocol. I assure that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Name (print):	
Signature:	
Date of Signature:	

Participating Centre Investigator Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make all reasonable efforts to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the study management committee to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study. I understand that the study may be terminated or enrolment suspended at any time by the study management committee, with or without cause, or by me if it becomes necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Investigator's Name (print):	
Investigator's Signature:	
Date of Signature:	

Table of Contents

Abbreviations

ACE	Angiotensin-converting-enzyme
AIPRI study	Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency study
ARB	Angiotensin-II-receptor blocker
AZA	Azathioprine
BP	Blood Pressure
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CARI	Caring for Australians with Renal Impairment
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CYCLO	Cyclophosphamide
CXR	Chest X-ray
DSMC	Data and Safety Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EQ-5D	EuroQol EQ-5D
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
HbA1C	Glycosylated Haemoglobin
HDL-C	High density lipoprotein cholesterol
HPF	High Power Field
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
IgAN	IgA Nephropathy
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response Systems
JNC 7	Seventh Joint National Committee guidelines for the management of hypertension
KDIGO	Kidney Disease: Improving Global Outcomes
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDL-C	Low density lipoprotein cholesterol
MDRD	Abbreviated Modification of Diet in Renal Disease study equation
MMF	Mycophenolate Mofetil
MOH	Ministry of Health
RAS	Renin-angiotensin-system
RBC	Red Blood Cell
REIN study	Ramipril Efficacy in Nephrology study
SAE	Serious Adverse Event
SCr	Serum Creatinine
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
SUA	Suspected unexpected serious adverse reaction
WBC	White Blood Cell

1. Overview of the study

1.1 Title of study:

TESTING study- **T**herapeutic **E**valuation of **ST**eroids in **I**gA **N**ephropathy **G**lobal study

1.2 Study purpose:

This study will evaluate the long-term efficacy and safety of oral methylprednisolone compared to matching placebo, on a background of routine RAS inhibitor therapy, in preventing kidney events in patients with IgA nephropathy and features suggesting a high risk of progression

1.3 Study outcomes

1.3.1 Primary outcome

Progressive kidney failure, which is a composite of a 40% decrease in eGFR, the development of end stage kidney disease defined as a need for maintenance dialysis or kidney transplantation, and death due to kidney disease

1.3.2 Secondary outcomes

- The composite of ESKD, 40% decrease in eGFR and all cause death
- The composite of ESKD, 50% decrease in eGFR and all cause death
- Each of ESKD, renal death and all cause death
- Annual eGFR decline rate
- Proteinuria remission

1.3.3 Safety outcomes

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

1.4 Population:

The target population will consist of patients with primary IgA nephropathy who are at high risk of progression to kidney failure.

1.4.1 Inclusion criteria

1) IgA nephropathy proven on renal biopsy

2) Proteinuria: ≥ 1.0g/day while receiving maximum tolerated dose of RAS blockade following the recommended treatment guidelines of each country where the trial is conducted.

3) eGFR: 20 to 120ml/min per 1.73m^2(inclusive) while receiving maximum tolerated RAS blockade

1.4.2 Exclusion criteria:

1) Indication for immunosuppressive therapy with corticosteroids, such as:
   - Minimal change renal disease with IgA deposits
   - Crescents present in >50% of glomeruli on a renal 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 (See Appendix 5)
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

1.5 Investigational and reference therapy:

Individuals will be randomised 1:1 to a total 6-8 month course of oral methylprednisolone or matching placebo: 2 months at full-dose followed by a gradually reducing dose

All participants will also receive standard guideline based care, without steroid therapy.

1.6 Study design:

This is a randomised, parallel-group, two-arm, double-blind, long-term study that comprises 3 study phases:

1.6.1 Pre-randomisation Period (4 to 12 weeks):

During a 4 to 12 week screening period, the patient's eligibility for randomisation into the trial will be evaluated. The patient should receive the maximum tolerated or labeled (whichever is

reached first) dose of either an ACE inhibitor or an ARB along with optimal blood pressure control according to relevant guidelines. For patients that have already received ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks, while for patients that haven't received such therapy, the run-in will be 12 weeks, so all participants have been on RAS blockade for at least 3 months prior to study entry. Other BP lowering agents should be adjusted or added during this stage to achieve guideline based targets.

1.6.2 Study treatment period:

At randomisation, patients who fulfill all eligibility criteria and no exclusion criteria, will be randomised to either the steroid therapy or matching placebo in a double-blind fashion. Patients will be treated with methylprednisolone 0.6-0.8 mg/kg/d 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/day each month or matching placebo at the same dosage, with a total treatment period of 6-8 months. Throughout the trial investigators should strive to manage BP and other background therapies according to relevant local guidelines.

1.6.3 Follow up phase

Participants will continue to be followed at regular intervals (see section '7.1 By Visit' below) for a total planned average of at least 5 years. Of note, the study is event driven and will be continued until 335 primary endpoints have occurred, so the final follow up duration may be longer or shorter depending on the event rate.

1.7 Efficacy assessments:

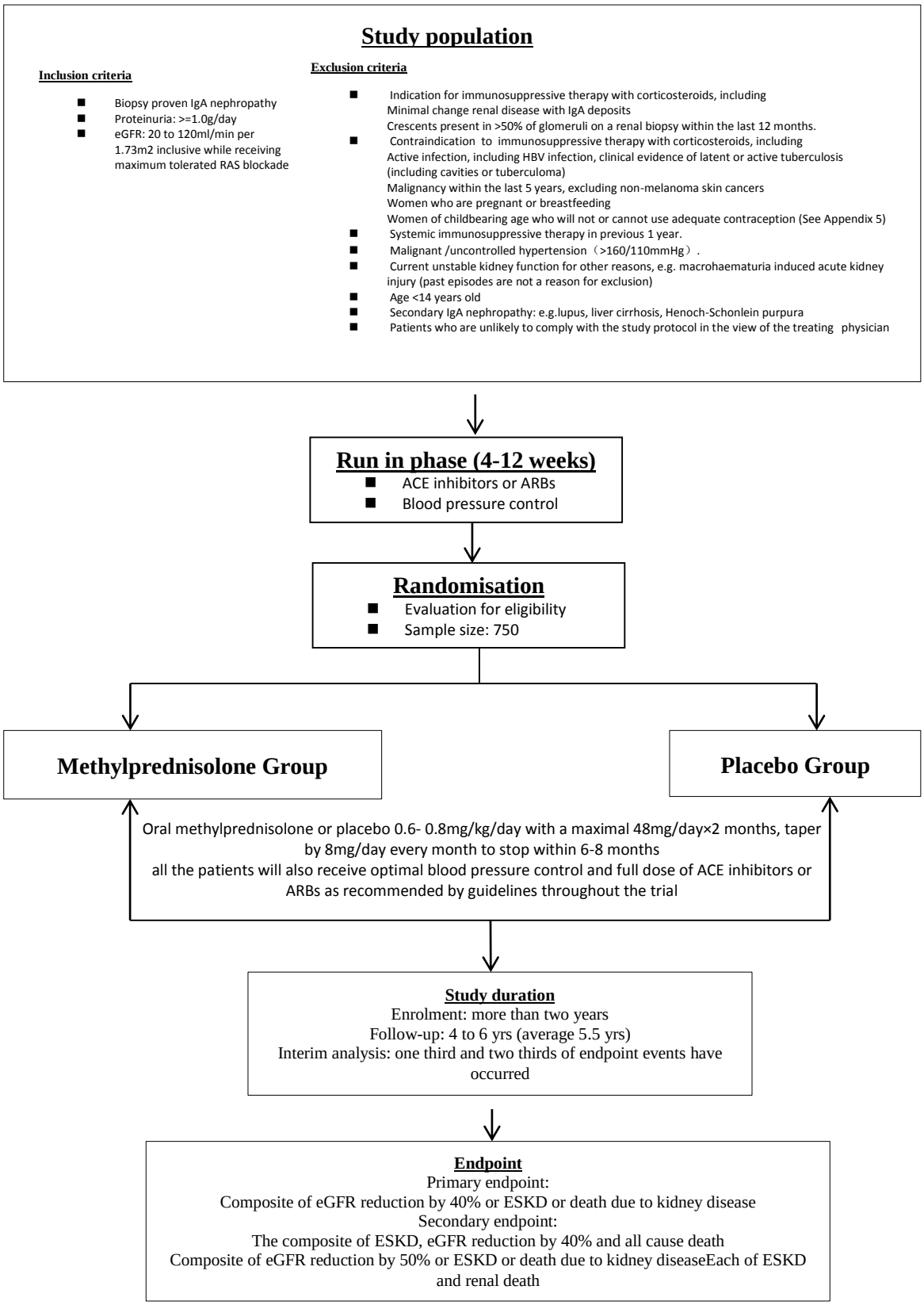
- Persistent reduction in eGFR by 40%, defined as an eGFR which is persistently reduced by more than 40% for a period of at least 4 weeks
- End stage kidney disease requiring ongoing maintenance dialysis or renal transplantation
- Death due to kidney disease
- Annual rate of eGFR decline
- Proteinuria reduction
- EQ-5D questionnaire (Quality Of Life (QOL) questionnaire)

1.8 Safety assessments:

- Adverse events
- Physical examination
- Vital signs
- Height and weight

1.9 Sample Size:

The sample size calculations have been performed by using the log-rank test and assuming an annual combined event rate for the primary endpoint (40% GFR decrease, ESKD and death due to kidney disease) of 12% in the placebo arm. A sample size of 750 patients (with 375 in each group) will provide more than 90% power (α=0.05) to detect a 30% risk reduction with methylprednisolone, after an expected average follow-up of 5.5 years.



Overview of study design

Note: SCr : serum creatinine; ESKD: end stage of kidney disease;

2. Background & Rationale

2.1Epidemiology

Immunoglobulin a (IgA) nephropathy is an immune-complex mediated glomerulonephritis defined immuohistologically by the presence of glomerular IgA accompanied by a variety of histopathologic lesions (Berger J 1968, Donadio JV 2002). It may occur at any age, but the clinical onset is most commonly in the second and third decades of life.

IgA nephropathy is recognized as one of, if not the most common primary glomerular disease worldwide, especially in young adults (D'Amico G 1987). IgA nephropathy is a histological diagnosis; few epidemiologic studies have examined the incidence in different populations around the world. Data from autopsy and renal allograft donors suggest that 1-2% of the population are affected by IgA nephropathy (Varis J 1993, SuzukiK 2003**)**. The reported incidence varies from 15-40 new cases per million population per year in Europe, to 42.9 in Australia, and 12 in USA (Table 1).

In most reports of cohort studies from referral based centres or renal biopsy registries, prevalence rates have been expressed as the proportion of cases of glomerulonephritis, or as a percentage of a total series of renal biopsies. IgAN is highly prevalent in Asia and Australia, accounting for 30-40% of cases of glomerulonephritis, compared with about 20% in Europe and the USA (Summarized in table 1). IgA nephropathy is also the most common cause of end stage of kidney disease (ESKD) in young adult Caucasians (Nair R 2006). The reason for this wide variance in incidence is partly attributable to indications for renal biopsy.

2.2 Pathogenesis

Although the pattern of glomerular IgA/IgG deposits has long suggested an immune complex-mediated mechanism, this remained a largely unproven assertion. Recent studies have established the crucial role of aberrantly glycosylated IgA1 and autoantibodies to the abnormal IgA1 in the pathogenesis of IgA nephropathy (Novak J 2008, Glassock RJ 2009). These breakthrough studies have considerably clarified the likely pathogenesis of IgA nephropathy (Figure 1). The IgA deposits in the mesangial zones of the patients with IgA nephropathy are mainly of the IgA1 subclass (Conley ME 1980). IgA1 is one of the very few serum proteins to possess O-linked glycans (containing N-acetylgalactosamine, galactose and sialic acid, Figure 1) in the hinge region. It is now firmly established thatserum IgA1 molecules are poorly O-galactosylated in patients with IgA nephropathy, and more

importantly, mesangial IgA eluted directly from glomeruli predominantly comprises aberrant galactosylated IgA1(Hiki Y 1995, Allen AC 1995, Xu LX 2005, Moldoveanu Z 2007).

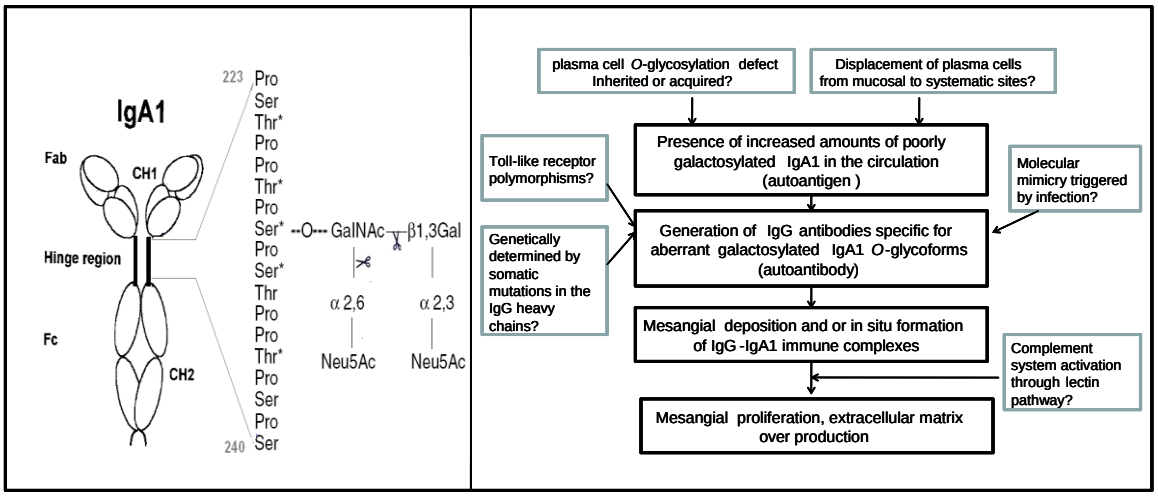


Figure 1a:Molecular structture of IgA1

Figure 1b: Model of pathogenesis of IgA nephropathy (revised from Barrat J 2009)

2.3 Risk factors and outcomes

IgA nephropathy is characterized by a highly variable clinical course ranging from a totally benign incidental condition to rapidly progressive renal failure, although most affected individuals develop chronic, slowly progressive renal injury and many patients will develop ESKD. (Nachman PH 2007). It is estimated that 1% to 2% of all patients with IgA nephropathy will develop ESKD each year from the time of diagnosis (Nachman PH 2007). In a study of 3620 patients derived from 18 separate series, the 10-year ESKD-free survival rate was estimated to be 80% and 85% overall in most of the European, Asian, and Australian studies, but it was lower in the United States (57% to 78%) (D'Amico G 2004).

The risk of developing ESKD has been shown to be higher in people with particular clinical and laboratory features. Studies using multivariate survival analysis have shown that impaired renal function, sustained hypertension, persistent proteinuria (especially proteinuria over 1 gram per day), and the nephrotic syndrome constitute poor prognostic markers (D'Amico G 2004, Manno C 2007, Lv J 2008) (summarized in Table 2). A recent report from the Toronto Glomerulonephritis Registry revealed that proteinuria and blood pressure levels during follow-up were the most important predictor of the rate of GFR decline, which underscored the importance of proteinuria remission and blood pressure management (Reich HN 2008, Figure 2). The Oxford classification of IgA nephropathy has established specific pathological features as independent predictors of renal progression. Factors found to be important include mesangialhypercellularity, segmental glomerulosclerosis, endocapillaryhypercellularity, and tubular atrophy/interstitial fibrosis (Cattran DC 2009). Extensive crescentic disease also confers a worse short-term prognosis, often accompanied

by a rapidly progressive loss of renal function. This new Oxford classification emphasizes the importance of proliferative lesions in the prognosis of IgA nephropathy.

Another breakthrough in the past two years is a consequence of the cloning and immortalization of B cells from patients with IgA nephropathy. Novak and his colleagues have clearly demonstrated that a B cell abnormality involving premature enzymatic sialylation and/or reduced galactosylation of the O-linked serine residues at the hinge region of IgA1 is the basis for the production of aberrantly glycosylated IgA1 (Suzuki H 2008); furthermore, IgG produced by the B cells binds to poorly galactosylated IgA1 and is capable of triggering the formation of IgA1-IgG immune complexes (Suzuki H 2009). Thus, B cells in IgA nephropathy are programmed to manufacture both the autoantigen and the autoantibodies (*a situation unique in autoimmune disease*) for forming immune complexes (Glassock RJ 2009). These findings offer new sights into the disease pathogenesis, and suggest a possible rationale for immunosuppressive therapy in the management of IgA nephropathy.

Table 1. Epidemiological data regarding the frequency IgA nephropathy

Country	Author(year)	Study population (number of renal biopsy)	Proportion of primary GN (%)	Proportion of all GN (%)	Incidence (per 1 million person-years)
Asia					
China	Zhou FD (2009) Li LS (2004)	Single Centre-north China (5714) Single Centre-south China (13,519)	58.2 45.6		
Japan	1999	National Survey (1850)	47.3		
Korea	Chang JH(2009)	Single Centre (1818)	28.3		
Singapore	Woo KT (1999)	Review	45		
Oceania					
Australia	Briganti EM(2001)	Population-based (2030)	48.3	34.1	42.9
Europe					
CzechRepublic	Rychlík I(2004)	National Registry of Renal Biopsies (4004)	34.5		
Italy	Schena FP (1997)	National Registry of Renal Biopsies (13835)	36.9		
	Stratta P 1996	Population based survey			14.7
Spain	Rivera F (2002)	National Registry of Renal Biopsies (7016)		17	7.9
UK	Hanko JB(2009)	Regional biopsy registry (1844)	38.8		3.4 (1976 to 1985) to 17.9 (1996-2005)
Netherland	Tiebosch AT (1987)	Population based survey			19
France	Simon P (2004)	Population based survey			28
Americas					
USA	Nair R (2006)	Nephropathology Associates from 24 states (4504)		22	
	Wyatt RJ (1998)	Population-based survey			5(1975-1979) to 12 (1990- 1994)
Brazil	M. G. Polito (2010)	National biopsy data	20.1		

Table 2: Clinical and Histological Prognostic Factors in IgA Nephropathy

Clinical[§]	Histological[¶]
Strong predictors*	
Elevated serum creatinine or reduced eGFR level Severe proteinuria Higher BP levels	mesangialhypercellularity segmental glomerulosclerosis endocapillaryhypercellularity tubular atrophy/interstitial fibrosis
Weak predictors[#]	
Older age at presentation Male sex Absence of history of recurrent macroscopic hematuria	

¶ Oxford classification of IgA nephropathy (Cattran D C 2009)
§ revised from D'Amico G 2004
* Significant by multivariate analysis in most studies

Significant only by univariate analysis in many studies.

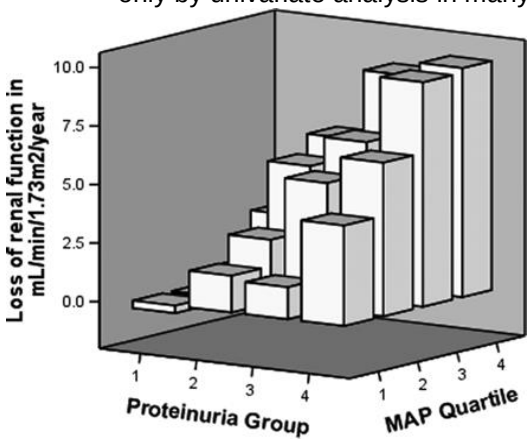


Figure 2: Relationship between proteinuria and MAP during follow-up, and loss of GFR. Group 1, time average proteinuria <1 g/d; group 2, 1 to 2 g/d; group 3, 2 to 3 g/d; group 4, >3 g/d. (Reich HN 2008)

2.4 Current therapy for IgA nephropathy- RAS inhibition and blood pressure management

Blood pressure lowering and RAS inhibition remain the cornerstone of management in people with IgA nephropathy. A series of randomised controlled trials, including the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study (AIPRI) study and the Ramipril Efficacy in Nephrology (REIN) study, have established the role of ACE inhibitors in the management of glomerular disease(Maschio G 1996;Ruggenenti P 1998).In the AIPRI study which included 192 patients with glomerulonephritis, an ACE inhibitor (Benazepril) reduced the risk of ESKD or doubling SCr by 53% (95%CI, 27%-70%). The REIN study involved 160 participants with glomerular disease, including 75 with IgA nephropathy, showed that ramipril compared with conventional treatment decreased the rate of change in GFR by approximately 30%, and the risk for progression to ESRD by almost 50%. These effects have been suggested to be independent of their blood pressure lowering ability. Pooled results from 11 randomised controlled trials (including data from the AIPRI and REIN studies) indicated that risk of kidney failure or doubling SCr was reduced by about 33% (95% CI 0.16 to 0.47) with an ACE inhibitor compared with other classes of antihypertensive drugs in patients with chronic kidney disease and proteinuria greater than 0.5 g per day (Jafar TH 2003). Several studies have been conducted using ACE inhibitors (enapril, benazapril) or ARBs (valsartan) in IgA nephropathy aiming to slow the progression of renal failure. Most of the studies enrolled patients with proteinuria> 0.5-1.0g/day. In 2003, A Spanish group first reported the effects of enalapril in 44 patients with IgA nephropathy. During long-term follow-up (74-78months), 13% (3/23) in the ACE inhibitor group and 57 %(12/21) of the patients in the control group reached the end point of 50% increase in serum creatinine from baseline (OR, 0.18; 95% CI, 0.03 to 0.87; P =0.04) (Praga M 2003). More recently, the IgACE study, a European multicentre, randomised, double-blind trial, examined the effect of benazepril in 66 children or young people with IgA nephropathy. After a mean follow-up of 38 months, more placebo-treated patients experienced the end point of a 30% decrease of GFR (5 vs 1, 14.7% vs. 3.1%) . Because of the small sample size and short follow-up period, the difference did not reach statistical significance (p=0.182) (Coppo R 2007). A randomised controlled trial in 109 Chinese adults with IgA nephropathy showed that valsartan reduced proteinuria and slowed the rate of renal function decline (Li PK 2006). A meta-analysis of the eleven RCTs including 585 IgA nephropathy patients concluded that the use of ACE inhibitors or ARBs produced a significant decrease in proteinuria and renal progression (Cheng J 2009). There is currently no strong evidence to suggest that the combination of ACE inhibitors and ARBs are superior to monotherapy with either class of agent alone for renal protection in proteinuric or non-proteinuric renal diseases including IgA nephropathy (Kunz R 2008). Based on these studies, the current recommended approach to

IgA nephropathy with proteinuria and/or hypertension emphasizes rigorous BP control with maximal renin-angiotensin system blockade using either an ACEI or an ARB to minimize proteinuria (Barratt J 2006, MOH guidelines on glomerulonephritis 2007).

2.5 Corticosteroids in IgA nephropathy

The use of corticosteroids in IgA nephropathy remains controversial. Breakthroughs in the understanding of pathogenesis of IgA nephropathy, including identification of specific auto antigen/autoantibody (characteristic in autoimmune disease, *as discussed in the Pathogenesis section*), immune-complex mediated glomerulonephritis and complement activation through lectin pathway, have provided a clear potential rationale for immunosuppressive therapy with corticosteroids in the management of progressive IgA nephropathy. Recently reported RCTs have tested interventions intended to slow immune and inflammatory events implicated in progressive IgA nephropathy with corticosteroids. There are two situations where the use of steroid therapy is often considered indicated, and they are (1) in patients with the nephrotic syndrome and minimal change lesions on renal biopsy and (2) in patients with crescenteric glomerulonephritis (MOH Singapore guidelines 2007)

The currently available data from randomised trials of steroids in IgA nephropathy are summarised in *table 3*.

Lai KN et al (1986) examined the effects of corticosteroid therapy in 34 Chinese people with documented IgA nephropathy and nephrotic syndrome. In the steroid arm, patients received 4-months of prednisone (40-60mg/day for 2 months, then ½ dose during the subsequent 2 months). During a mean study period of 38 months (range 12-106), corticosteroid treatment resulted in remission of nephrotic syndrome in 80% of patients with mild glomerular histopathological changes, but with no impact on kidney function.

In 1999, an Italian study first suggested that steroid therapy with methylprednisolone might protect kidney function in IgA nephropathy. In this randomised controlled trial, 86 proteinuric IgA nephropathy patients with preserved renal function (urine protein excretion 1-3g/day, serum creatinine<1.5mg/dl) were randomised to either a corticosteroid group (Methylprednsolone1g × 3days at 1st, 3rd, 5th month; then 0.5mg/kg on alternate day ×6months), or a control group (supportive therapy). After 5-years of follow-up, nine of the participants randomised to steroids (9/43, 21%) and 14 in the control group (14/43, 33%) reached the primary endpoint of 50% SCr increase (p=0.048) (Pozzi C 1999). In a post-trial 10-year extension of follow-up, steroid therapy significantly reduced proteinuria and

prevented kidney failure with 13 patients reaching doubling of SCr in the control group compared to only 1 in the steroid group. Renal survival was significantly better in the steroid group (97% vs. 53%, p=0.003) (Pozzi C 2004). Since this study was conducted between 1987 and1999, RAS blockade was used in only a minority of patients, (equally distributed between groups), and the achieved BP level was not in line with current recommendations. The ability of corticosteroids to achieve additional benefits on top of adequate BP control and full dosage RAS inhibitors was therefore questioned (Barratt J 2005).

In 2009, two randomised controlled trials reported the effects of corticosteroids on top of ACE inhibitors, suggesting this treatment could reduce proteinuria and preserve renal function better than ACE inhibitors alone in patients with IgA nephropathy (Lv J 2009, Mann 2009). The first was a pilot study from China, randomly allocating 63 Chinese patients (Proteinuria 1-5g/day and GFR>30ml/min per 1.73m^2) to prednisone on a background of cilazepril (n=33) or to a control group (cilazepril alone, n=30). After 27-months of follow-up, the combination of steroids and ACE inhibitors significant reduced proteinuria and preserved renal function compared to ACE inhibitors alone; only one patient (1/33, 3%) progressed to the end point of a 50% increase in SCr in the corticosteroids group while 7(7/30, 23%) in the ACE inhibitors group reached this endpoint (p=0.001). Similar results were reported from a larger Italian multicentre RCT involving 97 patients and a median follow-up of 5 years. In this study corticosteroids significantly reduced the risk of doubling of SCr or ESKD (2/49, 4.2% *vs.* 13/49, 26.5% p=0.003) as compared to the control arm. These two trials strengthen the evidence that corticosteroid therapy in patients with proteinuric IgA nephropathy may be beneficial when used in combination with ACE inhibitors. However both trials did not achieve a full dosage of ACE inhibitors (in the Manno study, the average dose of ramipril was 6.5mg/day and Lv J study 3.75mg/day), leading to persisting uncertainty about the value of corticosteroids after supportive therapy has been optimized. Another limitation of available trials is that subjects with impaired kidney function (eGFR<50ml/min per 1.73m^2) were excluded from most studies, so currently there are no data of efficacy and safety of steroids in this population

A search of Medline, EMBASE and CCRT database identified 7 small randomised controlled trials which evaluated the role of corticosteroids in IgA nephropathy (Lv J 2012). Nearly all studies observed a significant reduction in proteinuria with corticosteroids, however in four trials the effects on kidney function did not reach statistical significance likely due to the relatively small sample size, short follow-up (Lai 1986, Julian 1993, Shoji 2000,Ronald 2006) and possibly the modest dosage of steroids (Katafuchi 2003). A meta-analysis of these data (Figure 3) shows that corticosteroids significantly reduced the risk of doubling

SCr or ESKD by 74% (RR 0.26, 95% confidence interval[CI] 0.1 to 0.71) and ESKD alone by 64% (RR 0.36, 95%CI, 0.15 to 0.91). Subgroup analysis suggested that high dose oral steroids are more effective than low dose (p=0.032, Figure 4)

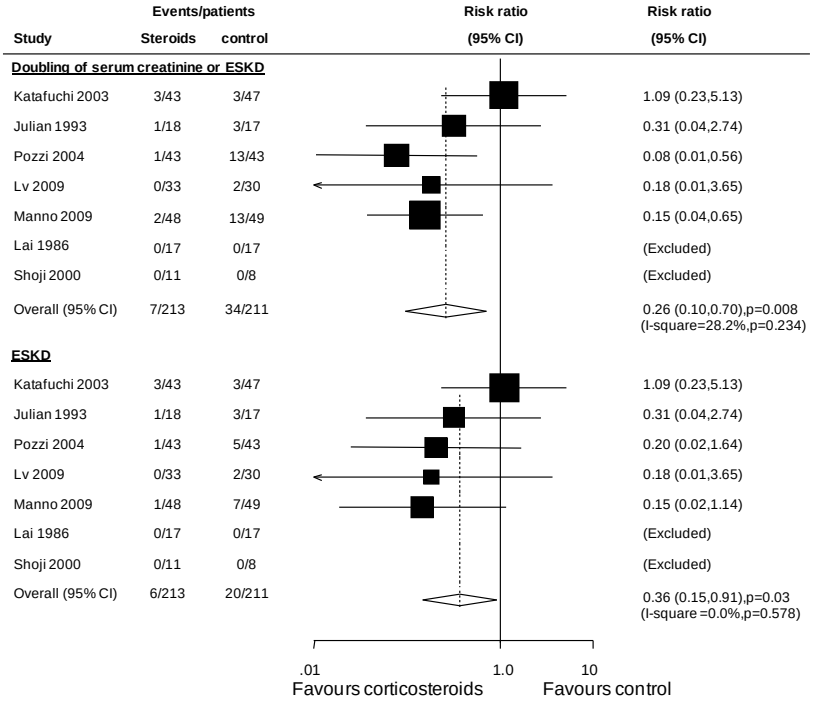


Figure 3: corticosteroids therapy on the outcomes of doubling of serum creatinine or ESKD

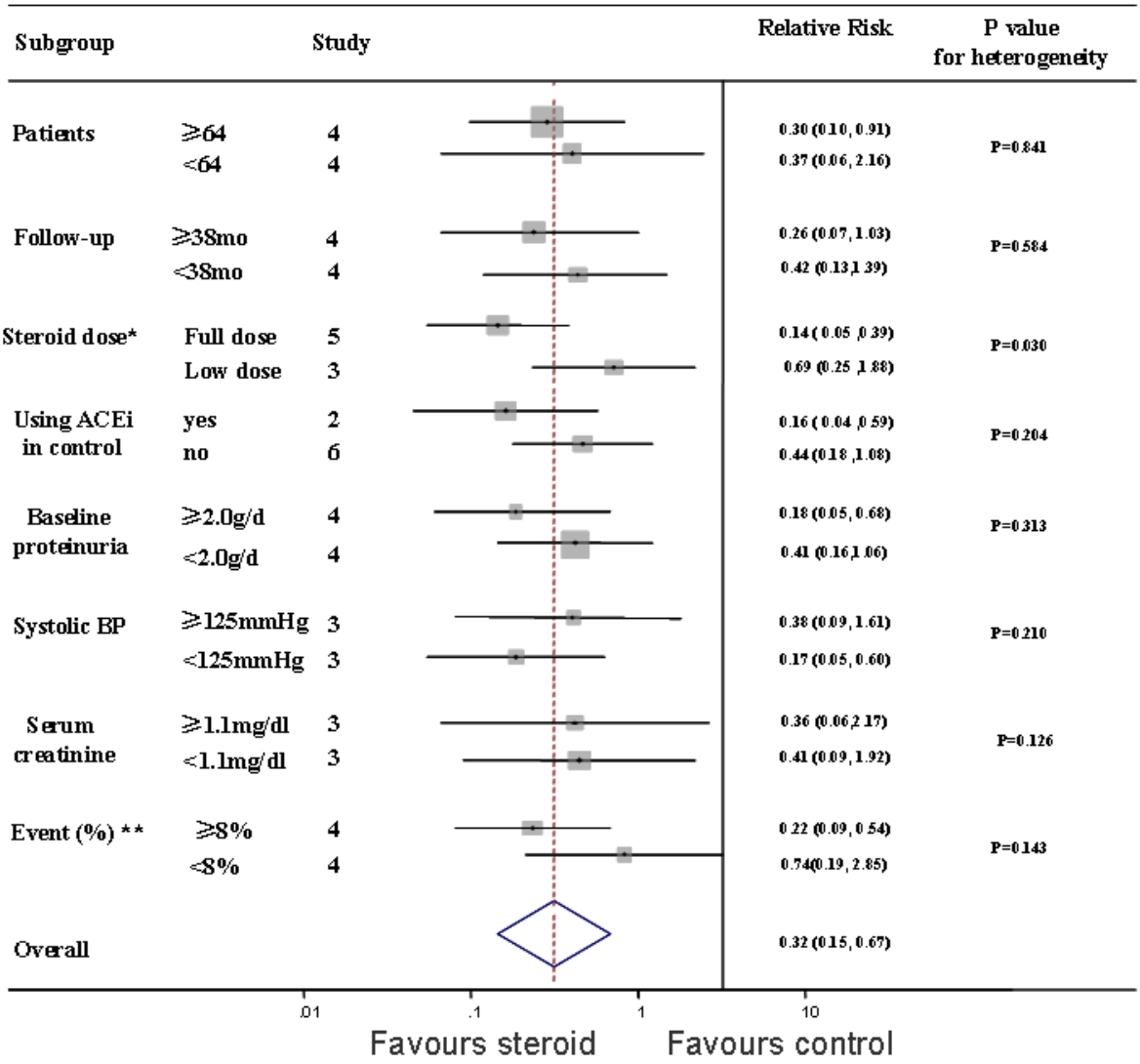


Figure 4: subgroup analysis of steroids on the outcome of doubling serum creatinine or ESKD

*Full dose: prednisone>30mg/d or methylprednisolone pulse therapy;
Low dose: prednisone<30mg/d

**Percentage of patients progressed to composite renal endpoints in each trial

CI, confidence intervals; RR, relative risk.

2.6 Current guidelines and meta-analysis of corticosteroids in IgA nephropathy

There is no international guideline on the management of IgA nephropathy or other glomerular diseases at present, however KDIGO (Kidney Disease: Improving Global Outcomes) is currently conducting an evidence review process with the expectation of establishing clinical practice guidelines in 2011. Available national guidelines from CARI (Caring for Australians with renal impairment) and the Singaporean MOH have both addressed the potential benefits of steroids in patients with IgAN and persistent proteinuria, and suggest they may have a role.

A recent meta-analysis also revealed that steroids reduced proteinuria and renal progression (Cheng J 2009, Samuels JA 2003). However current recommendations from guidelines are based on small, single-centre trials and there is still much uncertainty on the use of steroids in patients with IgA nephropathy. For example, the guideline from CARI notes that *there is no evidence to suggest patients with IgA nephropathy and established renal impairment (< 60mL/min) benefit from steroid therapy* (CARI 2006); the Singaporean MOH guideline for glomerulonephritis pointed out although steroids are of likely benefit in selected IgA patients, *it is unknown if the immunosuppressive regimens would still be beneficial if optimal blood pressure control is achieved with the use of ACE inhibitors and/or ARBs* (MOH clinical guideline 2007); The recent KDIGO guideline for glomerulonephritis states that '*there is low low-quality evidence that corticosteroids provide additional benefit to optimized supportive care', however 'there is no evidence to suggest the use of corticosteroids in patients with GFR<50ml/min*

2.7 Rationale for a large clinical trial of corticosteroids in patients with IgA nephropathy

IgA nephropathy is one of most common reasons for kidney failure in young adults. Decreased kidney function, hypertension and persistent proteinuria are the strongest risk factors for progressive loss of kidney function, and kidney failure. Current established therapies include full RAS inhibition and optimal blood pressure control for patients with proteinuria and/or hypertension, but a substantial risk of progression remains even when these therapies are employed.

The available evidence also suggests that corticosteroids may be effective in patients with IgA nephropathy at risk for progression. The completed studies have important shortcomings which have limited their implementation into guidelines and clinical practice. These include:

1. The completed studies were mostly conducted at a single centre, leading to uncertainty about the balance of benefits and risks when applied across multiple centres with varying expertise in this area
2. The studies generally used an intermediate primary endpoint, leading to uncertainty about the clinical importance of the findings
3. The available studies were generally of suboptimal quality
4. The completed studies were not adequately powered to detect moderate treatment benefits (each less than 100 participants),making them susceptible to type 1 errors and publication/reporting bias
5. Data regarding the potential harms of corticosteroid therapy were not collected in a systematic and consistent fashion
6. Supportive therapies were often sub-optimally provided
7. The participants chosen were not necessarily who are at highest risk of progressive loss of kidney function and kidney failure

These limitations have led to reluctance to implement steroid therapy into guidelines and clinical practice in many parts of the world, and therefore a large well-designed and adequately powered multi-centre randomised trial is required to resolve these persistent uncertainties, and allow the role of steroid therapy in IgAN to be defined.

The supportive versus immunosuppressive therapy of progressive IgA nephropathy (STOP IgAN) trial is a multi-centre trial aiming to evaluate whether corticosteroids alone or combined with cyclophosphamide/azathioprine may improve proteinuria remission rates as compared with current supportive therapy, and is scheduled to be finished in 2 or 3 years (Eitner F 2008). Although well designed, it is a small trial (n=148) with short follow-up (3 yrs.) and is powered on a relatively soft endpoint: full clinical remission (proteinuria <0.2g/day and stable renal function) or GFR loss>15ml/min per 1.73m^2. Therefore it will not provide the strength of evidence required to reliably guide clinical practice.

Although IgA nephropathy is the most common glomerular disease worldwide, there are still no RCTs with adequate power and quality to reliably inform clinical practice (Leaf DE 2010, Strippoli GF 2009). As a result, this large multicentre, randomised controlled trial has been designed to determine the efficacy of corticosteroids in progressive IgA nephropathy, involving more than one hundred clinical centres and 750 patients.

Table 3: Characteristics of the participants, interventions, comparisons and outcomes in the included randomised controlled trials

Study	Patients	No. Patients	Steroids group	Control	Follow-up (Mon)	Event number (rate, per year)				Benefits
						Doubling SCr		ESKD		
						steroids	control	steroids	control	
Lai 1986	IgA nephropathy with nephrotic syndrome	34 (17/17)	Pred 40-60mg/d	No treatment	38	0(-)	0(-)	0(-)	0(-)	Reduced proteinuria No effect on the GFR
Julian 1993	CCr >25ml/min per 1.73m	31 (18/17)	Pred 60mg/qod	No treatment	6-24	1(-)	2(-)	1(-)	2(-)	No effect on change of Proteinuria; A trend to preserve renal function (defined by 1/SCr, p=0.06)
Shoji 2000	Proteinuria <1.5g/d Scr<1.5mg/dl	19 (11/8)	Pred 0.8mg/kg/d	Dypiridamole 300mg/d	12	0(-)	0(-)	0(-)	0(-)	Reduced Proteinuria, no effect on the GFR; Reducing renal lesion in histology
Katafuchi 2003	Scrn<1.5mg/dl	90(43/47)	Pred 20mg/d	Dypiredamole 150-300mg/d	65	3 (1.3%)	3 (1.2%)	3 (1.3%)	3 (1.2%)	Reduced proteinuria No effect on the renal survival (defined as ESKD)
Pozzi 2004	Scr<1.5mg/dl Proteinuria 1-3.5g/day	86 (43/43)	MP 1g × 3days;then 0.5mg/kg/day	Supportive	82	1 (0.3%)	13 (4.3%)	1 (0.3%)	5 (1.7%)	Reduced Proteinuria; Improve renal survival (defined as doubl of SCr)
Hogg* 2006	Proteinuria(UP/C) >1.0 or >0.5 with renal lesions at risk; GFR>50	64 (33/31)	Pred 60mg qod	placebo	24	-	-	-	-	No effect on the Proteinuria reduction or renal survival (defined as 60% decrease of GFR)
Lv JC 2009	Proteinuria 1-5g/day GFR>30ml/min.1.73m^2	63 (33/30)	Pred 0.8-1mg/kg/d	Cilazapril mean dosage 3.75mg/d	27.3	0 (-)	2 (3.0%)	0 (-)	2 (3.0%)	Reduced Proteinuria and improved renal survival (50% increase of SCr)
Manno 2009	Proteinuria>1g/day GFR>50ml/min.1.73m^2 Moderate renal lesions	97 (48/49)	Pred 1mg/kg/day	Ramipril mean dosage 7.5mg/d	60	2 (0.9%)	13 (5.7)	1 (0.4%)	7 (3.0%)	Reduced Proteinuria and improved renal survival (defined as doubling of SCr and or ESKD)

SCr: serum creatinine; **ESKD**: end stage kidney disease; **GFR**: glomerular filtration rate; **CCr**: creatinine clearance rate;
Pred: prednisone; **MP**: methylprednisone
* Ronald study including 3 trial arms: corticosteroids group (n=33),**O3FA** group (n=32) and placebo group (n=31)

2.8 Health significance of the proposed study

IgA nephropathy is the most common glomerular disease worldwide and also the most common reason for end stage of kidney disease in young adults (Nair R 2006). IgA nephropathy accounts for 44% of patients with ESKD due to glomerulonephritis in Australia (Briganti FM 2001) and it is estimated that IgA nephropathy accounts for up to 10% of all patients in need of renal replacement therapy in western countries. The percentage is even higher (up to 15% to 20%) in developing countries. In China, 50% of ESKD are due to glomerular disease (Wang HY 2005), and patients with IgA nephropathy pose a particularly important health care problem because the patients are usually relative young when they reach ESKD and have a relative good life expectancy. Therefore, renal replacement therapy carries a substantial social, emotional and financial burden. In Australia, the number of people with ESKD due to IgAN is estimated to be about 1700, generating an annual cost for renal replacement therapy of $426M to $452M. The trial we propose will provide reliable evidence regarding the benefits and harms of a preventive strategy for individuals with IgA nephropathy at high risk of reaching ESKD.

There is a dearth of high quality evidence for such clinical decisions, and an international consensus on this question is still lacking. This will be the largest trial in glomerular disease; through the successful completion of the present study, the research team will provide evidence that will form the basis of future treatment guidelines for IgA nephropathy.

3 Trial Hypotheses and Objectives

3.1 Trial hypotheses

A 6-8 month regimen of tapering corticosteroid therapy compared to matching placebo will reduce the risk of kidney failure in patients with high-risk IgA nephropathy

3.2 Trial Objectives

This study aims to evaluate the long-term efficacy and safety of oral methylprednisolone compared to matching placebo, on a background of routine RAS inhibitor therapy, in patients with IgA nephropathy and features suggesting a high risk of progression.

Primary objective

To determine if 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.

Secondary objectives

To determine if adding oral methylprednisolone to optimal background care, compared to placebo:

1) Reduces the risk of the composite outcome comprising ESKD, persistent 40% reduction in eGFR and death due to any cause.
2) Reduces the risk of the composite outcome comprising ESKD, persistent 50% reduction in eGFR and renal death.
3) Reduces the risk of each of ESKD and renal death
4) Is safe, with particular reference to the risk of:
    - Serious infections requiring hospitalisation
    - New onset diabetes mellitus
    - Clinically apparent gastrointestinal haemorrhage requiring hospitalisation
    - Clinically evident fracture or osteonecrosis
    - Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease.

4. Trial Design

This is a double blind, randomised, parallel-group, two-arm, long-term study that comprises 3 study phases.

Trial Flowchart

An overview of the study design is shown in Figure 5. In brief, after a 4 to 12 week run-in phase where treatment can be adjusted to ensure participants are receiving standard guideline based care (blood pressure control and the use of ACE inhibitors or ARBs at the maximum tolerated/labelled dose), eligible patients will be randomised to methylprednisolone or matching placebo. All participants will continue to receive standard care including optimal blood pressure control and full dose of ACE inhibitors or ARBs in line with current guidelines throughout the trial. For patients that have already received ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks, and the patients only receive a second visit (V3) while for patients that haven't received such therapy, the run-in will be 12 weeks, and patients will receive 2 additional visits (V2 and V3), so all participants have been on RAS blockade for at least 3 months prior to study entry.

This study will include 750 patients with IgA nephropathy who are at high risk for renal progression. The recruitment period is more than two years; following randomisation patients are schedule to undergo a 6-8 month intervention, and then be followed regularly until at least 335 primary endpoints are observed, which is expected to require at least 4- to 6-years of follow-up (average 5.5 years or more).

5. Trial Medication

5.1 Investigational Medicinal Product

Study Medication will be administered in the following forms:

Table 4: study medication

Drug/Ingredient	Methylprednisolone/Medrol	Matching Placebo
Formulation	methylprednisolone/Medrol tablets 4mg/tablet	Tablets containing excipient, identical in appearance to methylprednisolone/Medrol but without the active ingredient
Manufacturer	Pfizer Pharmaceuticals	Pharmaceuticals

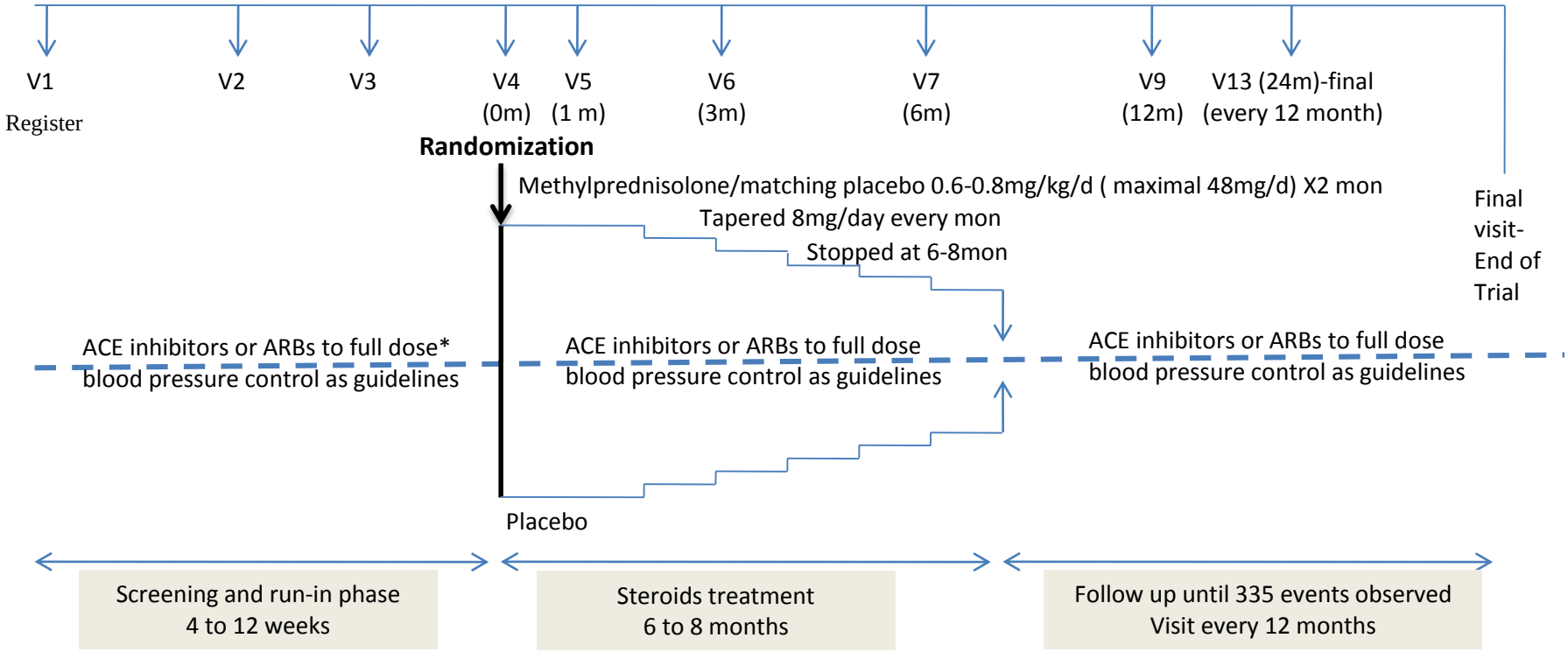
Medrol will be used where provided by Pfizer including in China, but other agents of equivalent dosage may be used where Medrol is not provided.

The study treatment will be packaged and supplied by a manufacturer. Blister cards or bottles will be used in this study. There will be extra tablets to be used in case of loss during treatment.

The study treatment will contain information on the labels that will include: protocol number, packaging reference number, kit number, storage information, and the investigational caution statement. The labels will have space to write in the Subject Number. Additional statements will be printed on the label as required by local regulations.

All clinician's involved in the prescription of study treatment must read the Summary of Product Characteristics (SmPC)/Product Information which provides detailed information about the composition, indications, side effects, suggested dosage and contraindications of the study treatments.

Figure 5：Study period



Note:

1. The intervals between v1 and v4 should be more than 4 weeks.
2. For patients that are already receiving the maximum tolerated or labeled dose of ACE inhibitors or ARBs for more than 8 weeks, the run-in phase is at least 4 weeks and the patient only receive a second visit (V3). If all inclusions are fulfilled on the two visits, the patients are randomised.
3. For patients that have received RAS inhibition less than 8 weeks, the patients will receive 2 additional visits (V2 and V3) during the 4-12 weeks. If all inclusions are fulfilled on both V1 and V3, the patients are randomised.
4. For ACE inhibitors (or ARB if intolerant to ACE inhibitors) titrate to full dose as guidelines recommend.

5.2 Dosing Regimen

After a 4-12 week run-in phase during which participants will not receive any study treatment but where background therapies will be optimised, people randomised to the intervention group will receive oral methylprednisolone 0.6-0.8mg/kg/d (up to a maximum of 48 mg/day) for 2 months. The dose is then tapered by 8mg every month until the course is completed. Investigators will have the option of reducing the treatment dose from 8mg to 4mg for one month prior to cessation. Individuals randomised to the placebo group will follow an identical protocol using matching placebo tablets. The total treatment duration will therefore be 6-8 months for all participants. Patients will be evaluated once every 1-3 months during methylprednisolone therapy as usual practice. Data collection will occur at visits as shown in table 7

Patients will be required to take study drug each morning with food to reduce the risk of gastrointestinal side effects. All subjects will receive conventional therapy for managing optimal blood pressure control that is in line with the current guidelines and maximal tolerated dose of ACE inhibitors or ARBs.

Diet: All participants will have standard dietary recommendations for CKD, eg. low-salt 3-6g/day (50-100mmol/day) and high calcium diet.

Patients will be advised to quit smoking and limit alcohol intake to safe levels during the study.

5.3 Drug Accountability

The investigator or pharmacist will inventory and acknowledge receipt of all shipments of the study treatments by faxing or emailing the signed investigator product receipt form contained in the shipment to the International Coordinating Centre. The study treatments must be kept in a locked area with restricted access. The study treatments must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate

records of the quantities of the study treatments dispensed, used, and returned by each subject using the an accountability form.

The study monitor will periodically check the supplies of study treatments held by the investigator or pharmacist to verify accountability of all study treatments used.

For reasons of safety, institutional regulations and storage capacity at sites, at the conclusion of the study all used and unused study treatments at the site will be destroyed by investigational site staff according to local guidelines following monitoring inspection unless prior arrangements have been approved by the coordinating centre in writing. Documentation of destruction with a complete and accurate account of study treatments destroyed must be available for verification by the study monitor and filed in the investigator site file.

5.4 Subject Compliance.

Study treatment will be distributed by the investigator or appropriately qualified designee. Subjects will be instructed to bring their unused study treatment to every visit. Compliance will be assessed by tablet counts with regard to the total number of tablets taken over the entire treatment period. Details will be recorded in the electronic case report form (eCRF).

Investigators and their study personnel will be instructed to be sure that all subjects take their prescribed number of tablets each month. If a subject forgets to take one of these tablets she/he should be instructed to take the skipped tablets on the next day after she remembers, and then continue to take the study drug daily, in sequence on the blister card/bottles allocated to each treatment month, until the end of the monthly dosing period.

5.5 Concomitant Medication

Background care

Patients in this study, whether in the intervention or control arm, will all receive standard care for IgA nephropathy. The investigator should strive to control the blood pressure

according to current guidelines. Throughout the trial all patients should receive ACE inhibitors or ARBs adjusted to the maximal labelled or tolerated dose (whichever is reached first) aiming at achieving proteinuria <1g/d . The recommended maximum dose of ACE inhibitors or ARBs from K/DOQI or JNC 7 is summarized in **table 5**. In general, the use of combination ACE inhibitor and ARB therapy will be discouraged.

Permitted Concomitant Medications

The goal of blood pressure treatment in IgAN should be <130/80mmHg in patients with proteinuria. Any other antihypertensive medications, including diuretics, calcium channel blockers and beta-blockers can be used at any time point or can be added when monotherapy with ACE inhibitors or ARBs is not adequate to achieve blood pressure targets. Diuretics such as hydrochlorothiazide (Scr<1.5mg/day) or loop diuretics (Scr> 1.5mg/day) will be recommended as second line therapy on top of ACE inhibitors or ARBs given the benefits for the reduction of proteinuria and serum potassium. Other therapies such as statins or aspirin will be recommended for people fulfilling the required criteria according to local guidelines.

Chinese traditional medicine including Chinese herbs and acupuncture are a common treatment in China. These treatments are permitted and will be recorded on the eCRF.

Prohibited Concomitant Medications

Any other immunosuppressive therapies e.g. MycophenolateMofetil (MMF) cyclophosphamide (CYCLO) or azathioprine (AZA) are not permitted in this study, unless there are other definite indications for using these drugs.
Rifampin is also prohibited from this study as it interacts with methylprednisolone and makes the study drug less effective. The investigator should consult the product information of Medrol (Methylprednisolone) in appendix 7 for other prohibited concomitant medication.

Table 5. The recommended dose of ACE inhibitors or ARBs
(From JNC 7 and KDOQI)

Class	Drug (trade name)	Dose range (mg/day)	Usual daily frequency	Maximum doses used in major trials
ACE inhibitors				
	Benazepril (Lotensin)	20-40	1	30
	Captopril (Capoten)	25-100	2	100-150
	Enalapril (Vasotec)	5-40	1-2	20-40
	Fosinopril (Monopril)	10-40	1	
	Lisinopril (Prinivil, Zestril)	10-40	1	
	Moexipril (Univasc)	7.5-30	1	
	Perindopril (Aceon, Servier)	4-8 or 5-10	1	4
	Quinapril (Accupril)	10-80	1	
	Ramipril (Altace)	2.5-20	1	10
	Trandolapril (Mavik)	1-4	1	3
ARBs				
	Candesartan (Atacand)	8-32	1	16
	Eprosartan (Teveten)	400-800	1-2	
	Irbesartan (Avapro)	150-300	1	300
	Losartan (Cozaar)	25-100	1-2	100
	Olmesartan (Benicar)	20-40	1	
	Telmisartan (Micardis)	20-80	1	80
	Valsartan (Diovan)	80-320	1-2	160

6 Selection and Withdrawal of Subjects

6.1 Target population

The target population will consist 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 renal function, proteinuria, and hypertension. This trial will include patients with eGFR 20 to 120 ml/min per 1.73m^2 and proteinuria ≥1.0g/day, with or without hypertension. Patients with indications for the use of steroids (e.g. crescentic glomerulonephritis (percentage of crescents >50%) or nephrotic syndrome and minimal change lesions on renal biopsy) are excluded from this study (MOH Singapore guidelines 2007). Data from the Peking University IgA Nephropathy Database (www.renal-online.org) suggest that approximately 62% of individuals with renal biopsy proven IgA nephropathy will qualify for participation in this study.

6.2 Inclusion Criteria

1) IgA nephropathy, proven on renal biopsy.

   This study encourages to recruit patients biopsied in the previous 2 years where possible to facilitate evaluation of the relationship between the pathological score and the effect of steroid therapy.

2）Proteinuria (on most recent test): ≥1.0g/day while receiving maximum tolerated dose of RAS blockade

- *≥1.0g/day on most recent available lab tests on Visit 1*
- *≥1.0g/day while receiving maximum tolerated dose of RAS blockade on Visit 3*

3）eGFR (on most recent test): 20 to 120ml/min per 1.73m^2 (inclusive)

- *The diagnosis of IgA nephropathy will be based on the demonstration of IgA deposits on direct immunofluorescence examination or immunohistochemistry, with typical histological findings and no other likely explanation for the individuals kidney disease*

- *Serum creatinine and Proteinuria evaluation for eligibility will be determined on at least two visits during run-in phase (see section 6.5)*
- *Estimated GFR will be calculated using the equation of CKD-EPI (Levey AS 2009) (Summarized in table 6)*
- *Patients with eGFR >120 ml/min per 1.73m^2 at screening stage while reaching less than 120 ml/min per 1.73m^2 after tolerated RAS inhibition therapy at visit 3 are eligible for this study*

6.3 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:

- **a.** Minimal change renal disease with IgA deposits
- **b.** Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months.

2) Contraindication to immunosuppressive therapy with corticosteroids, including

- **a.** 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.)
- **b.** Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (i.e. squamous or basal cell carcinoma)
- **c.** Current or planned pregnancy or breastfeeding
- **d.** Women of childbearing age who are not able or willing to use adequate contraception (See Appendix 5)

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-Schonleinpurpura

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)

Table 6. Equations for estimating GFR in this study

Race/Sex	Serum creatinine (mg/dl)	Equation
Black (CKD-EPI formula)		
Female	≤0.7	$GFR=166\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$
	>0.7	$GFR=166\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
Male	≤0.9	$GFR=163\times (Scr/0.9)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=163\times (Scr/0.9)^{-1.209}\times(0.993)^{Age}$
White or others CKD-EPI formula)		
Female	≤0.7	$GFR=144\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$
	>0.7	$GFR=144\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
Male	≤0.9	$GFR=141\times (Scr/0.9)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=141\times (Scr/0.9)^{-1.209}\times(0.993)^{Age}$

6.4 Selection of Participants

This study will be international and conducted in more than 100 centres in a number of countries, including China, Australia, New Zealand, Hong Kong, India, UK, Canada and other countries.

6.5 Screening and Run-in phase

All eligible patients who provide informed consent will be invited to enter the run-in phase. The aim of 4- to 12- week run-in phase is to evaluate eligibility for the trial, identify potential non–compliance and optimise background therapies. Participants will not receive any study treatment during the run-in period.

All participants will be on RAS blockade for at least 3 months prior to randomisation. E.g.

1) For patients who have received treatment with ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks;
2) For those not previously receiving RAS blockade therapy, the run-in phase will be 12 weeks.

3) For those who have received RAS blockade therapy for less than 8 weeks, the run-in phase will be adjusted to ensure that all the participants will be on RAS inhibition for at least 12 weeks before randomisation.

During the whole study period including run-in phase, participants will receive standard background therapy for IgA nephropathy, including RAS inhibitors and blood pressure control according to current guidelines. All patients will receive ACE inhibitors (or ARBs if intolerant to ACE inhibitors) titrated to the maximum labelled or tolerated dose (whichever is reached first) according to local or national guidelines. The recommended dose of ACE inhibitors or ARBs from K/DOQI or JNC-7 is summarized in **table 5**. Additional blood pressure lowering medications should be used to achieve treatment targets as per local guidelines.

Run-in phase study visits:

There will be 2-3 study visits during the run-in period:

Visit 1: The patient will be provided with information regarding the trial and offered an opportunity to consider and discuss this information. Those individuals who provide written informed consent will have eligibility for enrolment into the trial assessed. The screening procedures to be performed are described in table 7).

Visit 2-3: If all inclusion and no exclusion criteria are fulfilled, participants will attend the second or the third visits to confirm eligibility based on renal function (eGFR) and 24-hour Proteinuria.

a. For patients that are already receiving the maximum tolerated or labeled dose of ACE inhibitors or ARBs for more than 8 weeks, the run-in phase is at least 4 weeks and the patient only attends a second visit (V3). If all inclusions are fulfilled on the two visits, the patients are randomised.
b. For patients that have received RAS inhibition less than 8 weeks, the patients will receive 2 additional visits (second and third visits-V2 and V3) during the 4-12 weeks. Any two visits are at least two-week intervals. The third visit will be within

2 weeks before randomisation. If all inclusions are fulfilled on the both V1 and V3, the patients are randomised.

6.5.1 Screening Log

The screening log is designed to monitor patient recruitment at the study centre. A screening log of all patients evaluated for enrolment in the study will be compiled monthly by research co-ordinators at each study site. The log will record all screened patients, whether they are randomised into the study or considered ineligible for the study. Additionally, the reason patients were excluded or the reasons eligible patients were not enrolled will be recorded in the log. A copy of the log should be retained in the investigator's study files. The coordinating centre will compile a cumulative screening log monthly, using information from each study site.

6.6 Randomisation Procedure / Code Break

All patients meeting inclusion and exclusion criteria and providing informed consent for whom all baseline data has been collected will be randomised to either the methylprednisolone group or matching placebo group in a 1:1 ratio using a web based randomisation system developed and maintained by Data Management at The George Institute for Global Health.Randomisation will be achieved using a minimisation algorithm via a password-protected encrypted website interface. The randomisation schedule will be generated by the randomisation code administrator at The George Institute for Global Health. This password-protected and/or encrypted electronic Master Randomisation List is kept by Data Management in their secure system and is only accessible to the authorised senior staff.

Patients should be randomised within 2 weeks after completion of the last evaluation.

Every patient who participates in any study related procedure will be assigned a unique patient number via the web-based randomisation system. This system will be available 24 hours a day, 7 days a week.

Randomisation will be stratified using a minimisation method according to participating region, proteinuria (<3g/day or ≥3g/day), estimated GFR (<50ml/min.per1.73m^2 or ≥50ml/min. 1.73m^2) and kidney biopsy findings (endocapillary proliferation according Oxford classification, E1 or E0).

Randomization data are kept confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the members of the DSMC and the independent biostatistician who will perform the interim analysis. Unblinding of participants should only be performed when knowledge of the treatment allocation will influence the participant's management in a significant fashion. The precise reason for unblinding must always be provided, together with details of the name of the clinician making the decision, the date and time the decision was made and any supporting documentation that supports the decision (such as laboratory reports). In any case of unblinding, the follow-up schedule of data collection should be maintained to enable full analysis of all patient data on an intention-to-treat basis.

The investigator will contact the coordinating centre if they consider there is a need for unblinding and this will be adjudicated by the Study Management Committee.

As per regulatory reporting requirement, the coordinating centre will unblind the identity of the study medication for all unexpected serious adverse events that are considered by the investigator to be related to study drug.

Unblinding for ongoing safety monitoring by the DSMC will be performed according to adequate procedures in place to ensure integrity of the data as outlined in a separate DSMC charter.

6.7 Blinding

This is double blind prospective randomized controlled trial. Both the patient and study personnel at each site will be blinded to treatment assignment, as will individuals serving on the End Point Adjudication Committee.

6.8 Withdrawal of Subjects

Patients have the right to refuse treatment (allowing follow-up for safety) or completely withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study treatment if they believe that is in the best interests of the patient due to intercurrent illness, SAE, treatment failure, protocol violations, non- compliance, administrative reasons or other reasons.

Individuals withdrawing from study treatment will be asked to consent to phone contact according to the original protocol schedule. This will allow endpoint events or safety outcomes to be captured for the entire duration of the study. Participants will have the right to withdraw consent to any follow-up if they so wish.

If the reason for removal of a patient from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the eCRF.

Should a patient decide to withdraw consent or if they are withdrawn by the investigator for reasons mentioned above, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. A complete final evaluation at the time of the patient's withdrawal should be made with an explanation of why the patient is withdrawing from the study.

An excessive rate of withdrawals may make study interpretation difficult; therefore, unnecessary withdrawal of patients should be avoided.

6.9 Expected Duration of Trial

This is an event driven trial, and will continue until at least 335 primary endpoint events are observed across the entire study population. The total duration of this study is expected to be at least 6 years with recruitment of at least 2 years and a subsequent follow up of at least 4 years, i.e. for the first patient, the follow-up is at least 6 years and for the last patient, the follow-up is 4 years or more. All randomised subjects will participate in the active treatment phase of up to 8 months

duration and will be followed up for at least 4 years post-treatment until the earliest of any of the following:

- Completion of the follow-up period (final visit)
- Death or ESKD
- Withdrawal of consent, by the subject or legal surrogate, or withdrawal by the investigator due reasons mentioned above
- Premature study termination as defined in Section 12

The actual overall study duration or subject recruitment period may vary.

7 Trial Procedures

7.1 By Visit

Table 7 lists all of the assessments and indicates with an "X" the visits (data collection) when they are performed. During follow-up, participants will continue to receive routine clinical care, with visits at least 3-monthly as per current standard clinical practice.

In the first year all the scheduled visits are conducted face-to-face (Visit 1-7,9) except that V8 can be telephone visit at the choice of the investigator, whereas the subsequent visits over the remaining 3 to 5 years or more are scheduled as face to face visits at 12 month-intervals (visit 13, 17, 21, 25, 29) and telephone or face-to-face (at the choice of the investigator) visits at 3-month intervals (labeled ☏, visit 8, 10-12, 14-16, 18-20, 22-24,26-28).

Participants', who discontinue study drug before completing the study, should be encouraged to attend scheduled study visits for the duration of the follow-up.

At a minimum, they will be contacted for safety evaluations during the 30 days following the last dose of study drug, including final contact at the 30-day point. Documentation of attempts to contact the patient will be recorded in the patient record.

All data obtained from the assessments listed in Table 7 must be supported in the patient's source documentation (e.g. medical charts, patient notes or electronic data). Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g. laboratory data) are listed by test name.

All data obtained from the assessments listed in Table 7 must be supported in the patient's source documentation. For the purpose of this trial certain information entered into the eCRF will act as source data as specified in Appendix 6

Whenever possible, study assessments will be made by the same person, at the same time of day, at each study visit. For face to face visits, each evaluation will be conducted in the morning wherever possible. Please note that if circumstances exist where the study patient is unable to attend morning site visits (i.e. evening shift worker,

etc.), afternoon evaluations are permitted. If possible, patients should present for lab evaluations in a fasted state. Visit dates should be adhered to as closely as possible.

If one visit is postponed or brought forward, it should not result in the next visit being postponed or brought forward. The next visit, if at all possible, should adhere to the original time schedule.

7.2 Physical examination

A complete physical examination will be performed at Visit 1 (**table 7**) and the last End of Trial Visit. It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. A short physical exam will include the examination of general appearance and vital signs (BP, and pulse rate). A short physical exam will be at all visits except where a complete physical exam is required. Additional physical examinations may be performed whenever clinically indicated.

Information about the all physical examinations must be present in the eCRF which will act as source data for the purpose of this study. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after the start of study drug which meet the definition of a suspected unexpected serious adverse reaction must be recorded on the Serious Adverse Event screen of the patient's eCRF.

7.3 Height and weight

Height in centimetres (cm) will be measured at Visit 4 (randomisation).

Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Visit 4 (randomisation), at 6 months, 12 months and then every 12 months as listed in table 7.

Table 7. Schedule of Study Tests, Procedures and Clinic Visits

	Background therapy (ACE inhibitors or ARBs)																												
Phase	**Screening and run-in**			**Study Drug Treatment**						**Follow-up**																				
	Year 1									Year 2				Year 3				Year 4				Year 5				Year 6+			
	weeks			**month**																									
Time	-12 to -4[g]			0	1	3	6	9 ☎	12	15 ☎	18 ☎	21 ☎	24	27 ☎	30 ☎	33 ☎	36	39 ☎	42 ☎	45 ☎	48	51 ☎	54 ☎	57 ☎	60	63 ☎	66 ☎	69 ☎	72
Visit	1	2	3	4	5	6	7	8[i]	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 EOT[h]
Informed consent form	x																												
In/exclusion criteria	x	x	x	x																									
Med History/ Demography	x																												
Height (H)				x																									
Weight(W)				x			X		x				x				x				x				x				x
Vital signs	x	x	x	x		x	x		x				x				x				x				x				x
Physical Exam	x																												x
Short physical exam	x			x		x	x		x				x				x				x				x				x
Screening log	x	x	x																										
Randomisation				x																									
Chest X-ray(CXR)	x																												
Urinary analysis[a]	x			x		x	x		x				x				x				x				x				x
24-hour urine protein[j]	x	x	x	x		x	x		x				x				x				x				x				x
24-hour urine sodium				x		x							x								x								x
HBV screening	x																												
Pregnancy urine tests	x																												
Hematology[b]	x			x		x	x		x				x				x				x				x				x
Blood chemistry panel-1[c]	x			x		x	x		x				x				x				x				x				x

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	Background therapy (ACE inhibitors or ARBs)																											
Phase	**Screening and run-in**			**Study Drug Treatment**						**Follow-up**																			
	Year 1									Year 2				Year 3				Year 4				Year 5				Year 6+			
	weeks			**month**																									
Time	-12 to -4[g]			0	1	3	6	9 ☎	12	15 ☎	18 ☎	21 ☎	24	27 ☎	30 ☎	33 ☎	36	39 ☎	42 ☎	45 ☎	48	51 ☎	54 ☎	57 ☎	60	63 ☎	66 ☎	69 ☎	72
Visit	1	2	3	4	5	6	7	8[i]	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 EOT[h]
Blood chemistry panel-2[d]		**x**	**x**																									
HbA1C (if diabetic)				**x**			**x**		**x**				**x**				**x**				**x**				**x**				**x**
Lipid profile[e]				**x**			**x**		**x**																				**x**
Pathology Scoring[f]				x																									
Study drug dispensation				**x**	**x**	**x**																							
Study drug accountability				**x**	**x**	**x**	**x**	**x**																					
Co-Med				**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Adverse events					**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Endpoints					**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
EQ-5D				**x**		**x**			**x**				**x**				**x**				**x**				**x**				**x**
No food or drink (except water for 8 hours)	**x**			**x**		**x**	**x**		**x**				**x**				**x**				**x**				**x**				**x**

a) **Urinary analysis**: qualitative microscopic determination
b) **Hematology**: hemoglobin, , WBC, Lymphocyte, platelet count
c) **Blood chemistry panel 1**: Blood urea, creatinine, total bilirubin, SGPT, alkaline phosphatase, sodium, potassium, calcium, phosphorous, total protein, albumin, glucose and uric acid, total cholesterol
d) **Blood chemistry panel 2**: Blood urea, creatinine, sodium, potassium, uric acid
e) **Lipid profile:** total cholesterol, triglycerides, HDL-C, LDL-C
f) Pathology scoring according to Oxford classification (see appendix 1)
g) If the participant has been on an ACE inhibitor or ARB for at least 8 weeks on visit 1, will go into visit 3 directly in two weeks. If the participant has not been on an ACE inhibitor or an ARB for at least 8 weeks on visit 1, will go to visit 2 and then Visit 3 with the 2 weeks interval of V2-V3, and on visit 2, participants should have received an ACE inhibitor or ARB for at least 8 weeks. The Interval between V3 and V4 is two weeks. Rescreening is allowable after discussion with medical monitor.

Table 7. Schedule of Study Tests, Procedures and Clinic Visits

	Background therapy (ACE inhibitors or ARBs)																														
Phase	**Screening and run-in**			**Study Drug Treatment**						**Follow-up**																						
	Year 1									Year 2				Year 3				Year 4				Year 5				Year 6+					
	weeks			**month**																											
Time	-12 to -4[g]			0	1	3	6	9 ☎	12	15 ☎	18 ☎	21 ☎	24	27 ☎	30 ☎	33 ☎	36	39 ☎	42 ☎	45 ☎	48	51 ☎	54 ☎	57 ☎	60	63 ☎	66 ☎	69 ☎	72		
Visit	1	2	3	4	5	6	7	8[i]	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29 EOT[h]		

h) Visit 29 is end of trial visit. It's required for all randomised patients and not necessary to be in year 6+.

i) If participants continue on study drugs after V7, V8 can on-site visit for participants to return the remaining study drugs.

j) Creatinine will also be measured as a marker of completeness of collection

k) Visit window after V4 will be as: for V5-V8 ±2 weeks; for V9-V29 ±2 weeks for annual on- site visits, ±2 months for phone visits.

l) Reduction of eGFR by 50% from the baseline value (pre-randomisation) that is confirmed by a second serum creatinine value obtained at least 4 wks after the initial halving.

7.4 Chest x-ray (CXR)

A CXR screening in a *posteroanterior* view will be performed at screening (Visit 1) in countries with a high prevalence of tuberculosis or individuals considered to be at high risk, except for those individuals who have undergone chest radiography in the 1 month prior to screening. The main aim of CXR screening is to exclude asymptomatic infection e.g. tuberculosis. Interpretation of the tracing must be made by a qualified physician and documented on the CXR section of the eCRF. The CXR report should be labeled with the study number, patient initials, patient number, date, and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the relevant medical history/Current medical conditions eCRF page.

7.5 Laboratory evaluations

Laboratory evaluation of all specimens will be performed in each nephrology unit.

- Renal endpoints that need determined by serum creatinine including 40% decrease of eGFR, 50% reduction in eGFR, and ESRD have to be confirmed by two measurements at least 4-weeks apart. For this purpose, patients may need to attend an unscheduled visit one month after the study visit.
- Laboratory values that exceed the boundaries of a notable laboratory abnormality should be evaluated by the investigator and additional evaluations should be performed if judged appropriate by the investigator. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the criteria for a Serious Adverse Event, then the procedure for notification of serious adverse events must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study or from treatment, then the patient must be followed until the abnormality resolves or until it is judged to be permanent.

7.6 Haematology

Hemoglobin, white blood cell count, lymphocyte and platelet count will be measured at Visits 1, 4, 6, 7, 9 and then at yearly intervals until the end of the study.

7.7 Blood chemistry

Blood chemistry: Blood urea, creatinine, total bilirubin, SGPT, alkaline phosphatase, sodium, potassium, calcium, phosphorous, total protein, albumin, glucose and uric acid will be measured at Visits 1, 4, 6, 7, 9, and then at yearly intervals until the end of the study. Blood urea, creatinine, sodium, potassium, uric acid will be measured on Visit 2, 3.

Electrolyte measurement (sodium, potassium) as well as Blood Urea Nitrogen (BUN) and creatinine values, will be obtained from patients at every visit where a complete laboratory test is not done.

7.8 Creatinine Calibration

In China, a national central laboratory has been established at the Peking University First Hospital Central Laboratory, where serum creatinine levels will be measured using enzymatic method in a single laboratory. For other countries, the serum creatinine will be measured in the local laboratory of the study sites.

All the clinical laboratories will use a creatinine method that has calibration traceable to an IDMS (isotope dilution mass spectrometry) reference measurement procedure according to the recommendations of NKDEP's Laboratory Working Group in collaboration with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Communities Confederation of Clinical Chemistry (now called the European Federation of Clinical Chemistry and Laboratory Medicine). Methods based on either enzymatic or Jaffe method principles should have calibration traceable to IDMS.

7.9 Urinary analysis

A qualitative microscopic determination - white blood cells per high power field (WBCs/HPF) and red blood cells per high power field (RBCs/HPF) will be performed at each visit.

7.10 24-hour urine protein excretion

24 hour urine collection for protein excretion will be performed at Visit 1,2,3,4,6,7,9 and then at a yearly intervals until the end of the study. Creatinine will also be measured as a marker of completeness of collection

7.11 24-hour urine sodium

24 hour sodium excretion will be measured on all 24 hour urine specimens at randomisation V4, V6, V13, V21 and final visit

7.12 Glycosylated haemoglobin (HbA1C)

HbA1C will be measured in patients with diabetes at Visits 4, 7, 9 and then at yearly interval until the end of the study.

7.13 Lipid profile

Lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C) will be measured at Visits 4, 7 and 9 then the final visit.

Total cholesterol will also be measured at Visit 1

7.14 Scoring of histological lesions

The renal biopsy will receive at least immunomicroscopy (Immunohistochemistry or Immunofluorescence) and lightmicroscopy. The renal biopsy material or electronic images with PAS (periodic acid Schiff) stain will be collected from the study sites. The histological lesions will be reviewed at Visit 4 and graded according to the Oxford Classification (*see appendix 1*)

7.15 Pregnancy

All female patients of childbearing potential will have a urine pregnancy test screening performed at Visit 1 to evaluate eligibility for the trial.

7.16 Health-related Quality of Life

Health outcomes will be measured at V4, V6, V9 and then at yearly interval until the end of the study using the EuroQol EQ-5D (EQ-5D) questionnaire which generates a composite index score representing the preference for a given health state (i.e., health utilities). The instrument includes a visual analog scale and 5 questions covering the following dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. There are 3 possible responses to each question (no problem; some problem; severe problem), thus enabling estimation for 243 possible health states.

The working hypothesis is that there will be no decrease in patient reported outcomes in the control arm relative to the active treatment arm of the study. The data from this study will be the first in terms of health utility for patients with IgA nephropathy taking methylprednisolone/steroids. The EQ-5D questionnaire should be completed by patient who should sign and date the questionnaire.

7.17 Early Withdrawal from the Trial

Patients who discontinue study drug or withdraw early from this study should return for the assessments regularly as indicated by **Table 7**. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to ask if any of the primary or secondary endpoints have occurred, at the foreseen visit dates, for the remaining duration of the study.

7.18 Biobanking

All participants will be invited to contribute baseline blood, urine and DNA specimens for biobanking to allow subsequent study of IgA nephropathy, and the response to therapy.

In participating centres, consenting individuals will contribute sequential urine and/or blood samples (24 hour urine or random urine or plasma) at 0, 1st, 3rd, 6th, 12th and then every 12 month.

The samples to be collected are described in Appendix 8.

7.19 Data Handling & Management

The procedures for data review and query management are described in the Data Management Document and Monitoring Plan. Data will be reviewed throughout the study according to these documents.

Data for this study will be captured via a Web-based Electronic Data Capture system using the electronic Case Report Forms (eCRFs). The investigator should ensure the accuracy, completeness and timeliness of the data reported to the Coordinating Centre in the eCRF and in all required reports.

For each subject enrolled, an eCRF must be completed. It will be transcribed by the site from the paper source documents onto the eCRF. The participants will be identified only by initials and a participant ID number/identification code on the eCRF. The name and any other identifying detail will NOT be included in any study data electronic file.

Data will be validated for accuracy and reliability using two methods:

1. A comprehensive validation check program will centrally verify the data according to the Data Management Document and automatically generate discrepancies for resolution by the investigator. Manual discrepancies can also be raised if necessary.

2. Verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification) according to the Monitoring Plan, and the maintenance of a medication–dispensing log by the investigator.

An electronic audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person who made the change.

8 Assessment of Efficacy

8.1 Primary Efficacy Parameters

Progressive kidney failure, which is a composite of a persistent 40% decrease in eGFR, the development of end stage kidney disease, or death due to kidney disease. The outcomes will be defined as below:

- **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.

- **End stage kidney disease**: situations that need renal replacement therapy includes kidney transplantation, maintenance dialysis therapy, or situations where a patient dies due to kidney disease

- **Death due to kidney disease**: death due to kidney failure that need dialysis, and the death could be avoided by timely dialysis.

8.2 Secondary Efficacy Parameters

Secondary outcomes are each of eGFR reduction by 40%, 50%, end stage of kidney disease, as well as a composite outcome comprising both of these as well as death due to any cause.

In addition, the mean annual slope in eGFR during follow-up will be obtained by fitting a straight line through the calculated GFR using linear regression and the

principal of least squares. Proteinuria reduction will be evaluated by time-average proteinuria during follow-up time.

8.3 Procedures for Assessing Efficacy Parameters

Serum Creatinine:

Serum creatinine to determine eligibility or endpoints will be conducted in the morning by the local laboratory centre of each nephrology unit included in this trial. If possible, patients should present for lab evaluations in a fasted state

Estimated Glomerular Filtration Rate (eGFR):

The eGFR to determine eligibility for enrolment into the trial will be calculated from the serum creatinine concentration at Visit 1.

The eGFR to determine the incidence of study endpoints will be confirmed by two measurements at least 4-weeks apart

The eGFR calculation will use the equation of *CKD-EPI* (Levey AS 2009) (Summarized in table 6) .

Urine protein excretion (proteinuria):

24-hour urine protein excretion (g/day) will be determined during run-in phase (visit 1,2,3) baseline (visit 4) , 3 month (visit 6), 6 month (visit 7), and 12 month (visit 9) and then every 12 month to the final visit (summarized in table 7)

9. Assessment of Safety

9.1 Definitions

Adverse events (AEs)

According to the International Conference of Harmonization [ICH], an AE is any untoward medical occurrence in a patient or clinical investigation 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 or symptom, or disease temporally associated with the use of a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product. Pre-existing conditions which worsen during a study are AEs.

All reportable AEs encountered during the clinical study will be reported on the AE electronic form (eform) of the eCRF. Intensity of AEs will be graded on a three point scale [mild, moderate, severe] and reported in detail on the eCRF.

Mild	discomfort noticed but no disruption of normal daily activity.
Moderate	discomfort sufficient to reduce or affect daily activity.
Severe	inability to work or perform normal daily activity

Serious adverse events (SAEs)

Serious adverse events are defined as any untoward medical occurrence that meets one of more of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

The classification of ‘serious adverse event’ is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria.

If there is any doubt whether an event constitutes an SAE, this event should be considered a SAE.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR is defined as a serious adverse event for which the nature and severity of the event is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for products with a marketing authorisation.

9.2 Study specific reportable adverse events

9.2.1 Reportable serious adverse events

All SAEs should be reported during the first dose of the study drugs through the 28 days after discontinuation of the study drugs. For other study period, reporting of serious adverse events will be restricted to serious adverse events that are considered to be related to study treatment (possibly, probably or definitely) and SAEs of special interest per the protocol- severe infection requiring hospitalisation, gastrointestinal bleeding requiring hospitalisation, cardiovascular events.

For purposes of reporting serious adverse events in this study, non-fatal endpoint events that are adjudicated to be components of the primary endpoint (e.g. ESKD) will not be subjected to immediate or expedited serious adverse events reporting requirements.

Serious adverse events will be grouped by body system as defined by the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), following classification of investigator assessments into MedDRA preferred terms. Treatments will be compared with respect to the incidence of events by body system.

9.2.2 Reportable adverse events

For this trial, reporting of adverse events will be restricted to study treatment-related adverse events-new onset of diabetes mellitus, clinically evident fracture of osteonecrosis.

9.3 Safety alert terms for expedited reporting

In addition, if any of the following study treatment-related adverse events (serious or non-serious) occur in a subject in this study, they will be documented in the AE/SAE form of the eCRF and reported to the Coordinating Centre, using the procedure for serious adverse events, even if the criteria for seriousness are not fulfilled:

Reportable Adverse events:

- New onset of diabetes mellitus (for criteria of diabetes mellitus see Appendix 3)
- Severe Infection requiring hospitalization
- Clinically evident fracture or osteonecrosis
- Gastrointestinal bleeding requiring hospitalization
- Major cardiovascular event (non-fatal stroke, nonfatal myocardial infarction, heart failure requiring admission, and cardiovascular death)

These reportable adverse events are of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the investigators to the Coordinating Centre may be appropriate. Such events may require further investigation in order to characterize and understand them.

Pregnancy

Adequate human reproductive studies have not been conducted with corticosteroids (SmPC), therefore pregnancies occurring in female patients exposed to the study treatment must be reported within one working day to the coordinating centre.

A female patient must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. Study treatment will be permanently discontinued but the patient will remain in the study until study completion. Monitoring of the patient should be continued at least until conclusion of the pregnancy.

The investigator should counsel and discuss with the patient the risks of continuing with the pregnancy and the possible effects of early exposure to study medication on the fetus. Pregnancies occurring up to 90 days after the completion of the study treatment must also be reported to the investigator.

Where a SAE occurs in the pregnant female patient (irrespective of whether the SAE is pregnancy-related or not), the SAE must be collected separately.

Significant Overdose

In addition, cases in which a "significant overdose" (accidental or intentional) of the study treatment was taken, whether or not an adverse event occurred, are to be reported to the Sponsor in an expedited manner in the AE form of the eCRF. For purposes of this study, a "significant overdose" is defined as a subject's taking on the same day 5 or more times the planned daily dose for that day.

In the cases of significant overdose in which no adverse event occurred, the diagnosis on the AE log should be recorded as "overdose without adverse event", and the "overdose" criteria on the AE log should be ticked. For cases in which an adverse event occurred with overdose, the event description should be recorded as the diagnosis, and the "overdose" criteria should be ticked.

9.4 Period of Observation

For the purposes of this study, the period of observation for collection of treatment-related serious adverse events will commence from the time of the first dose of study treatment until the end of the study. Serious Adverse events that occur intermittently should be recorded as one AE.

If the investigator detects a serious adverse event in a study subject after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the coordinating centre to determine how the adverse event should be documented and reported.

9.5 Documentation and Reporting of Adverse Events

All reportable adverse events that occur during the observation period set in this protocol will be reported by the Investigator to the coordinating centre, The George Institute for Global Health, on the AE log of the eCRF. Instructions for reporting adverse events are provided in the investigator's study file.

Serious adverse events and adverse events that fulfill a reason for expedited reporting to the Coordinating Centre must be documented in the eCRF within 24 hours of the site becoming aware of the event and an email notification will be sent automatically to a specified list of Coordinating Centre representatives (including the medical monitor).

The investigator must also inform the study monitor in all cases. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study treatment. The Investigator will submit reportable adverse events to the relevant ethics committees in accordance with local ethics committee reporting requirements.

The coordinating centre will be responsible for reporting in an expedited manner, all SAEs that are both unexpected and at least reasonably related to study treatment (Suspected Unexpected Serious Adverse Reactions) to the Regulatory Authorities, IECs/IRBs as appropriate and to the Investigators within 7 days with an additional report within 8 days, and reporting of SUSARs to the study drug manufacturer within 3 working days of being notified of the adverse event. Any SAE not listed as an expected event in the SmPC will be considered as unexpected.

The George Institute will provide an Emergency 24 Hour Medical Coverage for study related medical emergencies outside regular business hours to allow for the provision of advice to investigators or research staff. Contact numbers will be distributed to all participating investigators in a separate document.

The study will adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 and comply with local regulatory requirements.

10. Statistics

10.1Statistical analyses:

Comparison will be made of the primary outcomes, comparing all those allocated methylprednisolone versus all those allocated control arm, on an intention to treat (ITT) basis. Cox proportional hazards analysis and Kaplan-Meier plots will be used to compare event rates among the two groups. Analysis will be stratified by proteinuria (<3.0g/day, ≥3.0g/day), renal function (eGFR<50 versus ≥50ml/min per 1.73m^2), histological lesion scoring (E1 or E0) and race (Asian, Caucasian).

10.2Sample size calculation and reasoning

This trial has good power to detect clinically important effects. A sample size of 750 patients will provide more than 90% power (α=0.05) to detect a 30% risk reduction with a steroid based treatment approach after an average follow-up of 5 years, equating to a 33% actual effect incorporating a 10% treatment drop out. We also have 80% power to detect a 26% RRR, equating to a 28% RRR due to the treatment after accounting for 10% treatment dropout

The sample size calculations have been performed using the log-rank test and assuming an annual combined rate of 40% decline in eGFR or ESKD of 12% in the placebo arm. The study is event driven, and will therefore continue until at least 335 primary endpoints have been observed. However the sample size might be adjusted based on the actual event rate.

A study including up to 15 years of follow-up (including 293 cases) showed that the ESKD incidence was 6.7% per person-year (Lv J 2008) in patients with eGFR>20ml/min.1.73m^2. Based on a prospective Chinese Cohort with IgA nephropathy including 650 patients and 4 years follow-up, the composite endpoint of 40% eGFR decline and ESKD was nearly 10% per person-year in patients with eGFR20-120ml/min.1.73m^2 and persistent proteinuria >1g/d after 3 month RAS inhibition therapy. The prospective randomised controlled trial from Manno C. et al.

(2009) showed the incidence of GFR halving or ESKD was 6% in patients with ramipril therapy and preserved renal function, (eGFR>50ml/min/1.73m^2). As this trial includes a higher-risk group (eGFR: 20-120ml/min/1.73m^2), the incidence of ESKD is likely to be increased two-fold or more, supporting the conservative nature of the annual event rate estimate of 12%.

The meta-analysis described above suggests that methylprednisolone might reduce the risk of the primary endpoint by 64%, i.e. a relative risk (RR) of 0.36. This trial is conservatively powered to detect a risk reduction of 30%, which is equivalent to the upper limit of the 95% confidence interval obtained in the meta analysis of previous trials.

10.3 Interim analysis

The trial DSMC will monitor safety data on an ongoing basis, and will also perform two unblinded interim analyses for the primary outcome, based on a comparison of the primary endpoint in the two treatment groups with the use of a normal approximation for a two-sided test, when one third and two thirds of the events have occurred. A group sequential approach (O'Brien Fleming method) will be utilised.

The analyses will be performed by an independent statistician from the George Institute for Global Health, who is not involved in managing the trial. The DSMC can recommend the Central Executive Committee of the TESTING-Trial should

- Adjust the duration of follow-up;
- Terminate the study early if there is clear and substantial evidence of benefit;
- Terminate the study early if the data suggests the risk of adverse events substantially outweighs the potential benefits

11. Participant Confidentiality & Record Keeping

11.1 Participant Confidentiality

The investigator and trial staff must ensure that subjects' anonymity will be maintained, that their identities are protected from unauthorized parties and take measures to prevent accidental or premature destruction of these documents. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

The investigator should keep a subject enrollment log showing codes, names and addresses. The investigator should maintain subjects' written consent forms documents in strict confidence.

When archiving or processing data pertaining to the investigator and/or to the patients, the co-ordinating centre shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.2. Investigator's Files / Source Documents/ Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (1) investigator's Study File, and (2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition, at the end of the study the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in readable format on CD which also has to be kept with the Investigator's Study File.

For this trial, electronic data entered into the eCRF will serve as source data, but some hard-copy source data must also be maintained as shown in appendix 6. Subject clinical source documents could include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrollment logs. The Investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, the Coordinating Centre must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Coordinating Centre to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

11.3 Direct Access to Source Documents

The investigator shall supply the coordinating centre on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor of the Study, the

Coordinating Centre, or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

12. Quality Assurance Procedures

The study will be conducted in accordance with the current approved protocol, ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 (ICH GCP), Declaration of Helsinki, relevant regulations and standard operating procedures.

12.1 Obtaining Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they require to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

If the subject is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to subjects must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the subject or by a local legally recognized alternative (e.g. the subject's thumbprint or mark). The witness

and the person conducting the informed consent discussions must also sign and personally date the consent document.

The investigator should inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

12.2 Delegation of Investigator Duties

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments, and their trial-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 Ethics and Regulatory Approvals

Before the start of the study, the protocol, informed consent document, any proposed advertising material and any other appropriate documents will be submitted to the appropriate Human Research Ethics Committee (HREC) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all subsequent and substantial amendments to the original approved documents. If applicable, the documents will also be submitted to the Regulatory Authorities where the trial is taking place for Clinical Trial Authorization, in accordance with local legal requirements.

Study medication can only be supplied to the investigator after documentation on **all** ethical and regulatory requirements for starting the study has been received by the Coordinating Centre.

Safety reports, annual progress reports and a final report at conclusion of the trial will be submitted to the Regulatory Authorities, research ethics committees and if applicable, to the study treatment manufacturer within the timelines defined in the Regulations.

12.4 Management of Protocol Deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The investigator should not implement any deviation from or changes of the protocol without agreement by the study management committee and documented approval from the Independent Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants the Investigator may implement any medical procedure deemed appropriate.

Deviations from the protocol must be documented and promptly reported to the study management committee and the Independent Ethics Committee (if applicable). The report should summarise the event and action taken.

12.5 GCP Training and Site Monitoring

Study monitors from the Coordinating Centre will conduct a site initiation visit prior to the start of the study to ensure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and ensure that acceptable facilities are available to conduct the study.

In addition, periodic site monitoring will be performed according to ICH GCP, the Coordinating Centre's SOP and Monitoring Plan. For each site, a minimum of one site monitoring visit per year must be performed. The monitors will verify that the clinical trial procedures are being conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and the applicable regulatory requirements. Data recorded in the eCRF will be evaluated for compliance with the protocol and accuracy in relation to source documents.

On completion of all patient treatments and evaluations, the monitor will conduct a closure visit at the site.

12.6 Audits and Inspections

The Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performance of the audits and inspections.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor (or Coordinating Centre) and authorize the Sponsor (or Coordinating Centre) to participate in this inspection. Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor (or Coordinating Centre). The Investigator shall take appropriate measures required by the Sponsor (or Coordinating Centre) to take corrective actions for all problems found during the audit or inspections.

12.7 Trial Executive Committee

The study will be conducted under leadership of a central executive committee (CEC) that has overall responsibility for protocol design, study conduct and publication. The members of the executive committee have great experience in managing patients with IgA nephropathy or chronic kidney diseases, and have demonstrated experience and expertise in designing, conducting and analysing clinical studies. The CEC will also oversee a national executive committee (NEC) in some participating countries/regions during the conduct of the study.

The NEC will facilitate the conduct of the trial in the countries that participate in this study, ensuring that the study is enrolled expeditiously and that data collection is performed according to Good Clinical Practice (GCP) guidelines.

Investigator proposed sub-studies will be evaluated by the CEC on scientific merit and must be approved by the CEC prior to being conducted.

12.8 Data and Safety Monitoring Committee (DSMC)

An independent DSMC will be established to review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate.

The DSMC will consist of physicians and a statistician experienced in clinical studies. The committee will be supported by an unblinded statistician at an independent research group. The independent DSMC will review safety data on an ongoing basis and may recommend the CSC/NSC to stop or amend the study based on safety findings.

12.9 Termination of the Study

The study must be closed at the site on completion of all participant treatment and evaluations. Furthermore, the study may be closed at any time at the request of the study steering committee, the Investigator, or a regulatory authority, with proper and timely notification of all parties concerned. As far as possible, early closure should occur after mutual consultation.

The Independent Ethics Committee will be informed and the Coordinating Centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements.

13 Publication Policy

The study will be conducted in the name of the TESTING study investigators.

- The principal publication from the study will be in the name of the TESTING study Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where an individuals' name is required for publication it will be that of the writing committee, with the study physician and/or chairs of the writing committee listed first and last, and subsequent authors listed alphabetically. All the study investigators will be listed at the end of main reports.
- It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

14 Property Rights

All the results, data and documents, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Investigator shall not mention any information in any application for any intellectual property rights.

15 Finance and Insurance

Participating Centre agreements will be signed between the George Institute for Global Health, Peking University Institute of Nephrology participating institutions and principal investigators and cover:

- Trial work and duration
- Obligations of the Principal Investigator
- Payment and withdrawal of funding
- Confidentiality
- Intellectual property
- Liability & Indemnity

The coordinating centre certifies that it has taken out a liability insurance policy. This insurance policy is in accordance with local laws and requirements. The insurance of the Coordinating Centre does not relieve the Investigator or manufacturers of the study interventions of any obligation to maintain their own liability insurance policy as required by applicable law. Liability and insurance provisions for this study are given in separate agreements.

Appendix 1 The Oxford Classification of IgA nephropathy

(Kidney Int 2009;76:534)

Table A1.1 Definitions of pathological variables used in the oxford classification of IgA nephropathy

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0 4–5 Mesangial cells/mesangial area=1 6–7 Mesangial cells/mesangial area=2 >8 Mesangial cells/mesangial area=3 The mesangial hypercellularity score is the mean score for all glomeruli	M0 ⩽0.5 M1 >0.5[a]
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 – absent S1 – present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 – absent E1 – present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0–25% – T0 26–50% – T1 >50% – T2

[a]Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.

Table A1.2: Recommended elements in renal biopsy report for a case of IgA nephropathy

Detailed description of the features present on
- Light microscopy
- Immunohistochemistry
- Electron microscopy

Summary of four key pathological features
- Mesangial score ⩽0.5 (M0) or >0.5 (M1)
- Segmental glomerulosclerosis absent (S0) or present (S1)
- Endocapillary hypercellularity absent (E0) or present (E1)
- Tubular atrophy/interstitial fibrosis ⩽25% (T0), 26–50% (T1), or >50% (T2)

Total number of glomeruli

Number of glomeruli with endocapillary hypercellularity, extracapillary proliferation, global glomerulosclerosis, and segmental glomerulosclerosis

Appendix 2 Equation for estimating GFR in this study

Race/Sex	Serum creatinine (mg/dl)	Equation
Black (CKD-EPI formula)		
Female	≤0.7	$GFR=166\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$
	>0.7	$GFR=166\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
Male	≤0.9	$GFR=163\times (Scr/0.9)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=163\times (Scr/0.9)^{-1.209}\times(0.993)^{Age}$
White or Others (CKD-EPI formula)		
Female	≤0.7	$GFR=144\times (Scr/0.7)^{-0.329}\times(0.993)^{Age}$
	>0.7	$GFR=144\times (Scr/0.7)^{-1.209}\times(0.993)^{Age}$
Male	≤0.9	$GFR=141\times (Scr/0.9)^{-0.411}\times(0.993)^{Age}$
	>0.9	$GFR=141\times (Scr/0.9)^{-1.209}\times(0.993)^{Age}$

Appendix 3 Criteria for the diagnosis of diabetes

1. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
   OR
2. Symptoms of hyperglycaemia and a casual plasma glucose ≥200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycaemia include polyuria, polydipsia, and unexplained weight loss.
   OR
3. 2-h plasma glucose ≥200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

* In the absence of unequivocal hyperglycaemia, these criteria should be confirmed by repeat testing on a different day.

Reference: American Diabetes Association 2009

Appendix 4 Criteria for the diagnosis of obesity

Body mass index (BMI) is a simple index of weight-for-height that is commonly used in classifying overweight and obesity in adult populations and individuals. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m2).

As for the Asian population, overweight is defined as a BMI equal to or more than 23, and obesity defined as BMI equal to or more than 25.

As for other population, it defines "overweight" as a BMI equal to or more than 25, and "obesity" as a BMI equal to or more than 30.

Table A4.1 WHO criteria for classification of adults according to BMI

Classification	BMI
Underweight	< 18.50
Normal range	18.50-24.99
Overweight	≥25.00
preobese	25.00-29.99
Obese class I	30.00-34.99
Obese class II	35.00-39.99
Obese class III	I 40

Table A4.2 Criteria for classification of Asian adults according to BMI

Classification	BMI
Underweight	< 18.50
Normal range	18.50-22.99
Overweight	≥23.00
Preobese	23.00-24.99
Obese class I	25.00-29.99
Obese class II	I 30

Appendix 5 Contraception Protection

Women of childbearing potential must use an acceptable method of contraception to prevent pregnancy. Acceptable methods of contraception include the following:

- Barrier type devices (e.g. female condom, diaphragm and contraceptive sponge) used ONLY in combination with a spermicide.
- Intra-uterine devices.
- Oral contraceptive agents started at least 90 days before start of study.
- Depo-Provera (medroxyprogesterone acetate).
- Levonorgestrel implants.
- Naturally or surgically sterile (amenorrheic for at least 1 year and no record of child birth for naturally sterile persons).
- Male partner is sterile and is the only sexual partner

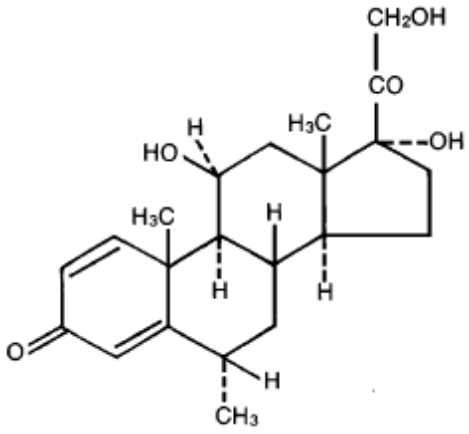
NB: True or periodic abstinence, the rhythm method or contraception by the partner only are NOT acceptable methods of contraception.

Appendix 6: Specification of Source data

Assessment	What will function as Source Data
Informed consent form	Individual consent form
In/exclusion criteria	eCRF
Med History/ Demography	eCRF, and copies of documents/letters where available to be filed in patient file
Renal biopsy report	Report filed in patient file
Height and Weight(W)	eCRF
Vital signs	eCRF
Physical Exam	eCRF
Short physical exam	eCRF
Screening log	Screening log maintained at each site
Randomisation	eCRF
Chest X-ray(CXR)	X-ray report in the patient file
Urinary analysis[a]	eCRF
24-hour urine protein	Lab report – filed in the patient file signed and dated by the responsible clinician
24-hour urine sodium	eCRF
HBV screening	eCRF
Pregnancy urine tests	eCRF
Hematology	eCRF
Blood chemistry panel-1[c]	Lab report – filed in the patient file signed and dated by the responsible clinician
Blood chemistry panel-2[d]	Lab report – filed in the patient file signed and dated by the responsible clinician
Fast blood glucose	eCRF
HbA1C (if diabetic)	eCRF
Lipid profile[e]	eCRF
Study drug dispensation	Drug accountability logs maintained at each site
Study drug accountability	Drug accountability logs maintained at each site
Co-Med	eCRF and referral letters or past med history information from medical records if available – to be filed in the patient file
Serious and reportable Adverse events	Written information on diagnosis, hospital discharge summaries etc. – filed in the patient file
Endpoints	Written information on diagnosis, hospital discharge summaries etc. – filed in the patient file
EQ-5D	Completed questionnaire

Appendix 7: Medrol Product information:

DRUG CLASS AND MECHANISM: Methylprednisolone is a synthetic (man-made) corticosteroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located adjacent to the kidneys. Corticosteroids affect metabolism in various ways and modify the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.
The chemical name for methylprednisolone is pregna - 1,4 - diene - 3,20-dione, 11, 17, 21-trihydroxy-6-methyl-, (6α, 11β)-and the molecular weight is 374.48. The structural for-mula is represented below:



STORAGE: Tablets should be kept at room temperature, between 20° and 25°C (68-77°F).
PRESCRIBED FOR: Methylprednisolone is used to achieve prompt suppression of inflammation. Examples of inflammatory conditions for which methylprednisolone is used include rheumatoid arthritis, systemic lupus erythematosus, acute gouty arthritis, psoriatic arthritis, ulcerative colitis, and Crohn's disease. Severe allergic conditions that fail conventional treatment also may respond to methylprednisolone. Examples include bronchial asthma, allergic rhinitis, drug-induced dermatitis, and contact and atopic dermatitis. Chronic skin conditions treated with methylprednisolone include dermatitis herpetiformis, pemphigus, severe psoriasis and severe seborrheic dermatitis. Chronic allergic and inflammatory conditions of the uvea, iris, conjunctiva and optic nerves of the eyes also are treated with methylprednisolone.
DOSING: Dosage requirements of corticosteroids vary among individuals and the diseases being treated. In general, the lowest effective dose is used. The initial oral dose is 4-48 mg daily depending on the disease. The initial dose should be adjusted based on response. Corticosteroids given in multiple doses throughout the day are more effective but also more toxic than the same total daily dose given once daily, or every other day. Methylprednisolone should be taken with food.

DRUG INTERACTIONS: Troleandomycin (TAO), an infrequently used macrolide antibiotic, reduces the liver's ability to metabolize methylprednisolone (and possibly other

corticosteroids). This interaction can result in higher blood levels of methylprednisolone and a higher probability of side effects. Erythromycin and clarithromycin (Biaxin) are likely to share this interaction, and ketoconazole (Nizoral) also inhibits the metabolism of methylprednisolone. Estrogens, including birth control pills, can increase the effect of corticosteroids by 50% by mechanisms that are not completely understood. For all of the above interactions, the dose of methylprednisolone may need to be lowered. Cyclosporin reduces the metabolism of methylprednisolone while methylprednisolone reduces the metabolism of cyclosporin. When given together, the dose of both drugs may need to be reduced to avoid increased side effects. Methylprednisolone may increase or decrease the effect of blood thinners [for example, warfarin (Coumadin)]. Blood clotting should be monitored and therapy adjusted in order to achieve the desired level of blood thinning (anti-coagulation).

Phenobarbital, phenytoin (Dilantin), and rifampin (Rifadin, Rimactane) may increase the metabolism of methylprednisolone and other corticosteroids, resulting in lower blood levels and reduced effects. Therefore, the dose of methylprednisolone may need to be increased if treatment with phenobarbital is begun.

PREGNANCY: Methylprednisolone has not been adequately evaluated in pregnant women.

NURSING MOTHERS: Methylprednisolone has not been adequately evaluated in nursing mothers.

SIDE EFFECTS: Adverse effects of methylprednisolone depend on dose, duration and frequency of administration. Short courses of methylprednisolone are usually well-tolerated with few, mild side effects. Long term, high doses of methylprednisolone may produce predictable and potentially serious side effects. Whenever possible, the lowest effective doses of methylprednisolone should be used for the shortest length of time to minimize side effects. Alternate day dosing also can help reduce side effects.

Side effects of methylprednisolone and other corticosteroids range from mild annoyances to serious irreversible bodily damage. Side effects include fluid retention, weight gain, high blood pressure, potassium loss, headache, muscle weakness, puffiness of the face, hair growth on the face, thinning and easy bruising of the skin, glaucoma, cataracts, peptic ulceration, worsening of diabetes, irregular menses, growth retardation in children, convulsions, and psychic disturbances. Psychic disturbances may include depression, euphoria, insomnia, mood swings, personality changes, and even psychotic behavior.

Prolonged use of methylprednisolone can depress the ability of the body's adrenal glands to produce corticosteroids. Abruptly stopping methylprednisolone in these individuals can cause symptoms of corticosteroid insufficiency, with accompanying nausea, vomiting, and even shock. Therefore, withdrawal of methylprednisolone usually is accomplished by gradually lowering the dose. Gradually tapering methylprednisolone not only minimizes the symptoms

of corticosteroid insufficiency, it also reduces the risk of an abrupt flare of the disease being treated.

Methylprednisolone and other corticosteroids can mask signs of infection and impair the body's natural immune response to infection. Patients on corticosteroids are more susceptible to infections and can develop more serious infections than individuals not on corticosteroids. For example, chickenpox and measles viruses can produce serious and even fatal illnesses in patients on high doses of methylprednisolone. Live virus vaccines, such as smallpox vaccine, should be avoided in patients taking high doses of methylprednisolone since even vaccine viruses may cause disease in these patients. Some infectious organisms, such as tuberculosis (TB) and malaria, can remain dormant in patients for years. Methylprednisolone and other corticosteroids can allow these infections to reactivate and cause serious illness. Patients with dormant TB may require anti-TB medications while undergoing prolonged corticosteroid treatment.

By interfering with the patient's immune response, methylprednisolone can prevent vaccines from being effective. Methylprednisolone also can interfere with the TB skin test and cause falsely negative results in patients with dormant TB infections.

Methylprednisolone impairs calcium absorption and new bone formation. Patients on prolonged treatment with methylprednisolone and other corticosteroids can develop osteoporosis and an increased risk of bone fractures. Supplemental calcium and vitamin D are encouraged to slow this process of bone thinning. In rare individuals, destruction of large joints can occur while undergoing treatment with methylprednisolone or other corticosteroids (aseptic necrosis). These patients experience severe pain in the joints involved, and can require joint replacement. The reason behind such destruction is not clear. Methylprednisolone can be used in pregnancy, but is generally avoided.

Reference: FDA Prescribing Information

Appendix 8: Biobanking

All participants will be invited to contribute baseline blood, urine and DNA specimens for biobanking to allow subsequent study of IgA nephropathy, and the response to therapy. The samples to be collected stored in the each participating country for future study. Informed consent must be obtained before drawing blood or urine.

1. Urine

24 hour urine collection processing, shipping and storing

The preparation of a properly mixed aliquot from the 24-hour urine collection is key to the correct measurement of the analyte. Therefore the following procedure must be followed closely:

- 24 hour urine may be measured by thoroughly mixing and pouring the sample into a 2 Litter graduated cylinder. A clean graduated cylinder must be used for each specimen.
- Be sure to record the volume on the requisition and aliquot container.
- Affix pre-printed labels to the10mL cryovials.
- Transfer urine into aliquots of 9mL.
- Store the aliquots at -20°C or -80 °C in a plastic rack or cardboard freezer box in an upright position within 4 fours.
- Label the racks or cardboard boxes with permanent marker or an adhesive label that says “TESTING 24 Hr Urine Refrigerated”

Random midstream urine collection processing, shipping and storing (for Proteomics)

- Encourage participants to stay hydrated even while fasting for the visit. However, do not collect samples after acute fluid load (>24 ounces) or after participant exertion. Collection will be random and, therefore, considered a “spot” urine collection.
- Place the sample on ice immediately after it is collected.
- Affix pre-printed labels to 2 airtight 10mL cryovials
- Transfer 9mL of urine into the 10mL cryovials.
- Store the aliquots at -20°C or -80 °C in a plastic rack or cardboard freezer box in an upright position within 4 fours.
- Label the racks or cardboard boxes with permanent marker or an adhesive label that says “TESTING Random Urine Refrigerated”

2. Blood collection: participant should remain fasted

DNA collection

- Participant remains fasted
- 5mL EDTA (purple top) tubes
- Blood Mixing During Venipuncture
- DO NOT SHAKE TUBES
- Centrifuge at 2100 g for 15 minutes.
- Separate the serum and extract the buffy coat and placed in a 2.5 ml cryovial
- Label with permanent marker or an adhesive label that says “TESTING DNA Refrigerated”
- Store the Genomic DNA at -20°C or -80 °C

3. Serum collection

- Participant remains fasted
- 5mL (red top) tubes
- The drawn blood must be stored at room temperature for at least 30 minutes for complete clotting to occur.
- The serum must be separated from the clotted blood by centrifugation. Centrifuge at 2100 g for 15 minutes.
- Affix labels to aliquot cryovials
- Transfer all serum into one tube
- Label with permanent marker or an adhesive label that says “TESTING Serum Refrigerated”

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TESTING Study Protocol

Therapeutic Evaluation of STeroids in IgA Nephropathy Global low dose study

V8.0 31 October 2018

GI-R-01-2011

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"A collaboration between the Peking University Institute of Nephrology, the George Institute for Global Health and renal researchers around the world"

GENERAL INFORMATION

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Minghui Zhao (Peking University Institute of Nephrology, China)

Executive and Steering Committee Signature

I have read and approve this protocol. I assure that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality.

Name (print):	
Signature:	
Date of Signature:	

Participating Centre Investigator Signature

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make all reasonable efforts to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Steering Committee to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study. I understand that the study may be terminated or enrolment suspended at any time by the Steering Committee, with or without cause, or by me if it becomes necessary to protect the best interests of the study participants.
I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Investigator's Name (print):	
Investigator's Signature:	
Date of Signature:	

TABLE OF CONTENTS

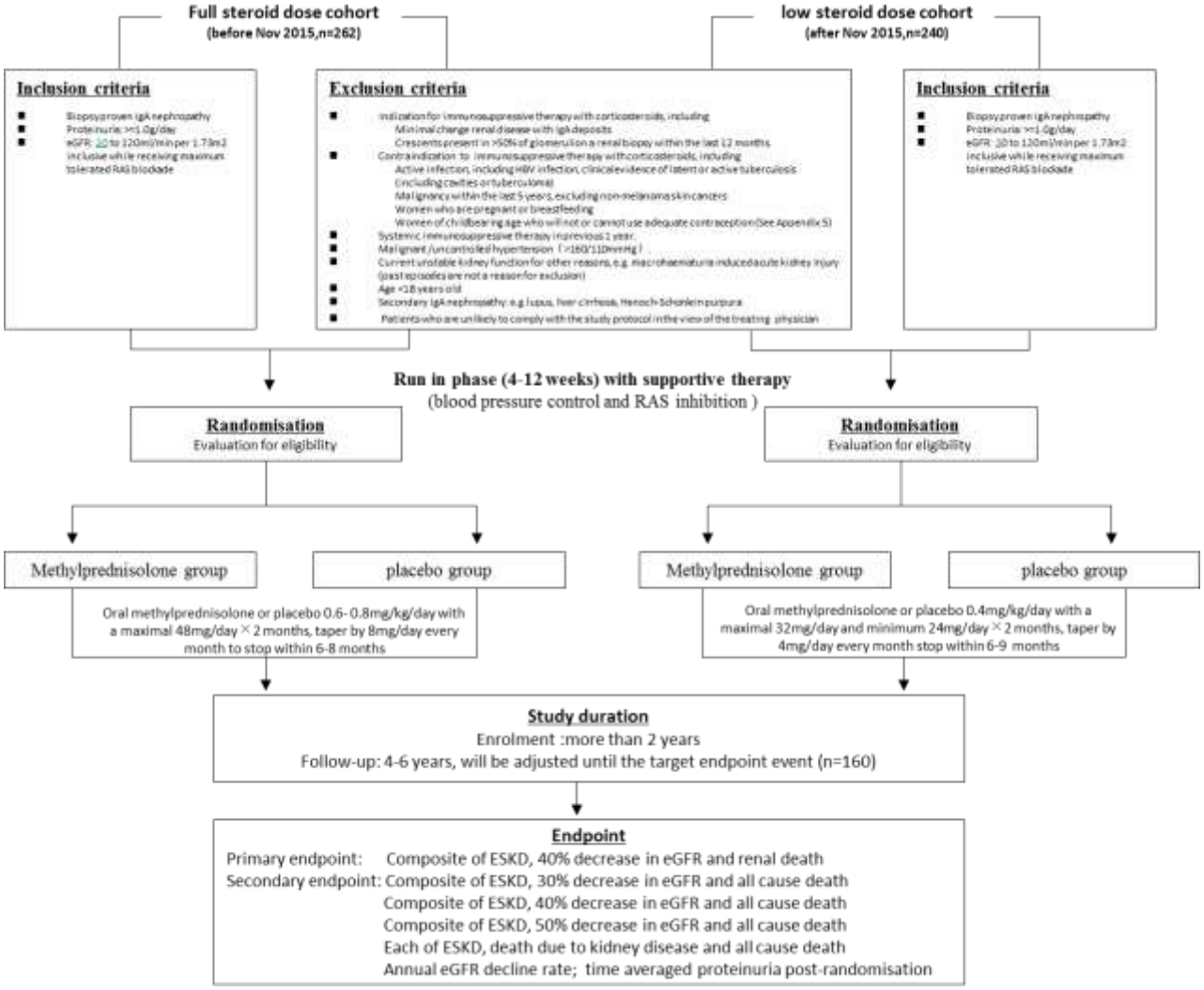
ACE	Angiotensin-Converting-Enzyme
AIPRI study	Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study
ARB	Angiotensin-II-Receptor Blocker
AZA	Azathioprine
BP	Blood Pressure
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CARI	Caring for Australians with Renal Impairment
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CYCLO	Cyclophosphamide
CXR	Chest X-ray
DSMC	Data Safety Monitoring Committee
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
eGFR	estimated Glomerular Filtration Rate
EQ-5D	EuroQoL EQ-5D
ESKD	End Stage Kidney Disease
GCP	Good Clinical Practice
HbA1c	Glycosylated Haemoglobin
HDL-C	High-density Lipoprotein Cholesterol
HPF	High Power Field
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IgAN	IgA Nephropathy
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
JNC-7	Seventh Joint National Committee Guidelines for the Management of Hypertension
KDIGO	Kidney Disease: Improving Global Outcomes
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDL-C	Low-density Lipoprotein Cholesterol
MDRD	Abbreviated Modification of Diet in Renal Disease Study Equation
MMF	Mycophenolate Mofetil
MOH	Ministry of Health
RAS	Renin-Angiotensin-System
RBC	Red Blood Cell
REIN Study	Ramipril Efficacy in Nephrology study
SAE	Serious Adverse Event
SCr	Serum Creatinine
SGPT	Serum Glutamic Pyruvic Transaminase
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
WBC	White Blood Cell

1. Overview of the study

Title	TESTING low dose study- Therapeutic Evaluation of STeroids in IgA Nephropathy Global low dose study
Study Purpose	This study will evaluate the long-term efficacy and safety of low dose oral methylprednisolone compared to matching placebo, on a background of routine RAS inhibitor therapy, in preventing kidney events in patients with IgA nephropathy and features suggesting a high risk of progression
Study Outcomes	Overall Primary outcome for combined TESTING and TESTING low-dose cohorts Progressive kidney failure, which is a composite of a 40% decrease in eGFR, the development of end stage kidney disease (ESKD) defined as a need for maintenance dialysis or kidney transplantation, and death due to kidney disease Overall Secondary outcomes for combined cohorts ▪ The composite of ESKD, 30% decrease in eGFR and all cause death ▪ The composite of ESKD, 40% decrease in eGFR and all cause death ▪ The composite of ESKD, 50% decrease in eGFR and all cause death ▪ Each of ESKD, death due to kidney disease and all cause death ▪ Annual eGFR decline rate ▪ Time averaged proteinuria post-randomisation Primary outcome specifically for the low-dose cohort ▪ Change in proteinuria from baseline at 6th and 12th months ▪ Mean change in eGFR at 6th and 12th months Safety outcomes ▪ Serious infections requiring hospitalisation ▪ New onset diabetes mellitus ▪ Clinically apparent gastrointestinal haemorrhage requiring hospitalisation ▪ Clinically evident fracture or osteonecrosis ▪ Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease
Population	The target population will consist of patients with primary IgA nephropathy who are at high risk of progression to kidney failure.
Inclusion Criteria	▪ IgA nephropathy proven on renal biopsy

	▪ Proteinuria: ≥ 1.0g/day while receiving maximum tolerated dose of RAS blockade following the recommended treatment guidelines of each country where the trial is conducted. ▪ eGFR: 30 to 120ml/min per 1.73m2(inclusive) while receiving maximum tolerated RAS blockade.
Exclusion criteria	▪ Indication for immunosuppressive therapy with corticosteroids, such as: o Minimal change renal disease with IgA deposits o Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months. ▪ Contraindication to immunosuppressive therapy with corticosteroids, including o Active infection, including HBV infection (HBsAg-positive, or HBeAg-positive, or serum detectable HBV-DNA) or clinical evidence of active tuberculosis (nodules, cavities, tuberculoma, etc.) o Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (i.e. squamous or basal cell carcinoma) o Current or planned pregnancy or breastfeeding o Women of childbearing age who are not able or willing to use adequate contraception (See Appendix 5) ▪ Systemic immunosuppressive therapy in the previous 1 year. ▪ Malignant/uncontrolled hypertension >160 mmHg systolic or 110 mmHg diastolic. ▪ Current unstable kidney function for other reasons, e.g. macrohaematuria induced acute kidney injury (past episodes are not a reason for exclusion) ▪ Age <18 years old ▪ Secondary IgA nephropathy: e.g. due to lupus, liver cirrhosis, Henoch-Schonlein Purpura ▪ Patients who are unlikely to comply with the study protocol in the view of the treating physician ▪ Participation in another trial (current or within the last month)
Investigational and reference therapy	Individuals will be randomised 1:1 to oral methylprednisolone or matching placebo. All participants will also receive standard guideline based care, without steroid therapy. Prophylactic trimethoprim/sulfamethoxazole (a single strength tablet daily or half a double strength tablet daily) will be used during the first 3 months

	after randomisation, for the prevention of severe PJP infection, unless there is a documented sulfa allergy.
Study design	This is a randomised, parallel-group, two-arm, double-blind, long-term study. The initial study cohort was randomised to oral methylprednisolone 0.6-0.8 mg/kg/day, with a reducing dose regimen over 6-8 months. Due to a higher than expected risk of adverse events, this second cohort was commenced that will randomise participants to a lower dose regimen (0.4mg/kg/day initially, maximal dose of 32mg/day, minimum dose of 24mg/day and then reducing over 6-9 months), compared to matching placebo.
Efficacy assessments	▪ Persistent reduction in eGFR by 40%, defined as an eGFR, which is persistently reduced by more than 40% for a period of at least 4 weeks ▪ End stage kidney disease requiring ongoing maintenance dialysis or renal transplantation ▪ Death due to kidney disease ▪ Annual rate of eGFR decline ▪ Proteinuria reduction ▪ EQ-5D questionnaire (Quality Of Life (QOL) questionnaire)
Safety assessments	▪ All Serious Adverse Events ▪ Adverse Events of Special Interest
Sample size	The sample size calculations have been performed by using the log-rank test and assuming an annual combined event rate for the primary endpoint (40% eGFR decrease, ESKD and death due to kidney disease) of 12% in the placebo arm. An overall sample size of 500 participants will provide 90% power (α=0.05) to detect a 40% risk reduction with methylprednisolone and 80% power for a 35% risk reduction, after an expected average follow-up of 4 years in each cohort. This corresponds to a total of 160 and 170 events for a 40% and 35% risk reduction, respectively. These calculations assume that 15% of participants will have outcome information unavailable after 4 years (i.e. 3.2% per year). 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.


Full steroid dose cohort
(before Nov 2015,n=262)
low steroid dose cohort
(after Nov 2015,n=240)
Inclusion criteria
Biopsy proven IgA nephropathy
Proteinuria: >=1.0g/day
eGFR: 30 to 120ml/min per 1.73m2 inclusive while receiving maximum tolerated RAS blockade
Exclusion criteria
Indication for immunosuppressive therapy with corticosteroids, including
Minimal change renal disease with IgA deposits
Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months
Contraindication to immunosuppressive therapy with corticosteroids, including
Active infection, including HBV infection, clinical evidence of latent or active tuberculosis (including cavities or tuberculomas)
Malignancy within the last 5 years, excluding non-melanoma skin cancers
Women who are pregnant or breastfeeding
Women of childbearing age who will not or cannot use adequate contraception (See Appendix 5)
Systemic immunosuppressive therapy in previous 1 year.
Malignant /uncontrolled hypertension (>160/110mmHg)
Current unstable kidney function for other reasons, e.g. macrohaematuria induced acute kidney injury (past episodes are not a reason for exclusion)
Age <18 years old
Secondary IgA nephropathy: e.g. lupus, liver cirrhosis, Henoch-Schonlein purpura
Patients who are unlikely to comply with the study protocol in the view of the treating physician
Inclusion criteria
Biopsy proven IgA nephropathy
Proteinuria: >=1.0g/day
eGFR: 30 to 120ml/min per 1.73m2 inclusive while receiving maximum tolerated RAS blockade
Run in phase (4-12 weeks) with supportive therapy
(blood pressure control and RAS inhibition)
Randomisation
Evaluation for eligibility
Randomisation
Evaluation for eligibility
Methylprednisolone group
placebo group
Methylprednisolone group
placebo group
Oral methylprednisolone or placebo 0.6- 0.8mg/kg/day with a maximal 48mg/day × 2 months, taper by 8mg/day every month to stop within 6-8 months
Oral methylprednisolone or placebo 0.4mg/kg/day with a maximal 32mg/day and minimum 24mg/day × 2 months, taper by 4mg/day every month stop within 6-9 months
Study duration
Enrolment :more than 2 years
Follow-up: 4-6 years, will be adjusted until the target endpoint event (n=160)
Endpoint
Primary endpoint: Composite of ESKD, 40% decrease in eGFR and renal death
Secondary endpoint: Composite of ESKD, 30% decrease in eGFR and all cause death
Composite of ESKD, 40% decrease in eGFR and all cause death
Composite of ESKD, 50% decrease in eGFR and all cause death
Each of ESKD, death due to kidney disease and all cause death
Annual eGFR decline rate; time averaged proteinuria post-randomisation

2. Background & Rationale

2.1 Epidemiology

Immunoglobulin a (IgA) nephropathy is an immune-complex mediated glomerulonephritis defined immuohistologically by the presence of glomerular IgA accompanied by a variety of histopathologic lesions (Berger J 1968, Donadio JV 2002). It may occur at any age, but the clinical onset is most commonly in the second and third decades of life.

IgA nephropathy is recognized as one of, if not, the most common primary glomerular disease worldwide, especially in young adults (D'Amico G 1987). IgA nephropathy is a histological diagnosis; few epidemiologic studies have examined the incidence in different populations around the world. Data from autopsy and renal allograft donors suggest that 1-2% of the population are affected by IgA nephropathy (Varis J 1993, SuzukiK 2003). The reported incidence varies from 15-40 new cases per million population per year in Europe, to 42.9 in Australia and 12 in USA (Table 1).

In most reports of cohort studies from referral based centres or renal biopsy registries, prevalence rates have been expressed as the proportion of cases of glomerulonephritis, or as a percentage of a total series of renal biopsies. IgAN is highly prevalent in Asia and Australia, accounting for 30-40% of cases of glomerulonephritis, compared with about 20% in Europe and the USA (Summarized in Table 1). IgA nephropathy is also the most common cause of end stage of kidney disease (ESKD) in young adult Caucasians (Nair R 2006). The reason for this wide variance in incidence is partly attributable to indications for renal biopsy.

2.2 Pathogenesis

Although the pattern of glomerular IgA/IgG deposits has long suggested an immune complex-mediated mechanism, this remained a largely unproven assertion. Recent studies have established the crucial role of aberrantly glycosylated IgA1 and autoantibodies to the abnormal IgA1 in the pathogenesis of IgA nephropathy (Novak J 2008, Glassock RJ 2009). These breakthrough studies have considerably clarified the likely pathogenesis of IgA nephropathy (Figure 1). The IgA deposits in the mesangial zones of the patients with IgA nephropathy are mainly of the IgA1 subclass (Conley ME 1980). IgA1 is one of the very few serum proteins to possess O-linked glycans (containing N-acetylgalactosamine, galactose and sialic acid, Figure 1) in the hinge region. It is now firmly established that serum IgA1 molecules are poorly O-galactosylated in patients with IgA nephropathy, and more importantly, mesangial IgA eluted directly from glomeruli predominantly comprises aberrant galactosylated IgA1 (Hiki Y 1995, Allen AC 1995, Xu LX 2005, Moldoveanu Z 2007).

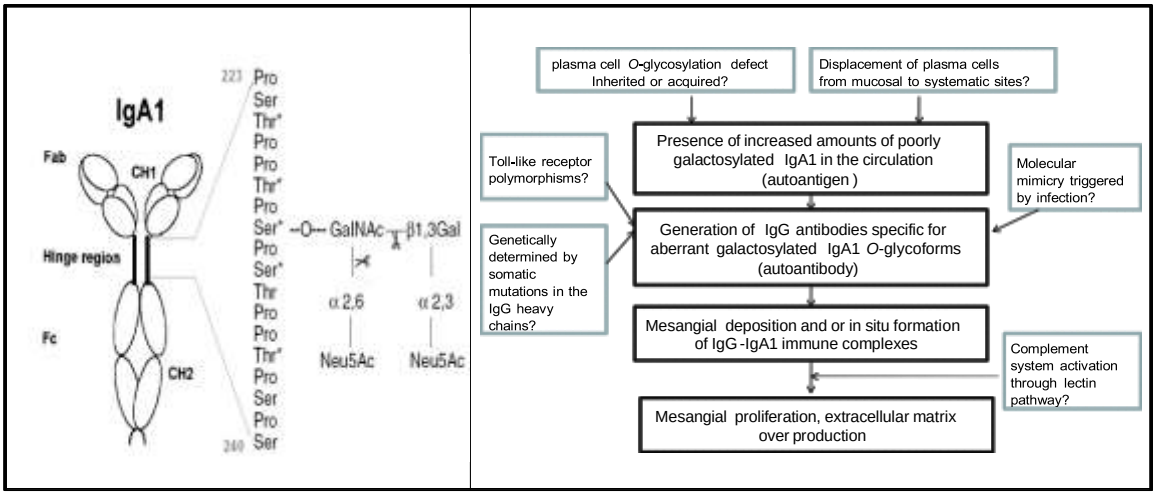


Figure 1a:Molecular structture of IgA1

Figure 1b: Model of pathogenesis of IgA nephropathy (revised from Barrat J 2009)

2.3 Risk factors and outcomes

IgA nephropathy is characterized by a highly variable clinical course ranging from a totally benign incidental condition to rapidly progressive renal failure, although most affected individuals develop chronic, slowly progressive renal injury and many patients will develop ESKD (Nachman PH 2007). It is estimated that 1% to 2% of all patients with IgA nephropathy will develop ESKD each year from the time of diagnosis (Nachman PH 2007). In a study of 3620 patients derived from 18 separate series, the 10-year ESKD-free survival rate was estimated to be 80% and 85% overall in most of the European, Asian and Australian studies, but it was lower in the United States (57% to 78%) (D'Amico G 2004).

The risk of developing ESKD has been shown to be higher in people with particular clinical and laboratory features. Studies using multivariate survival analysis have shown that impaired renal function, sustained hypertension, persistent proteinuria (especially proteinuria over 1 gram per day) and the nephrotic syndrome constitute poor prognostic markers (D'Amico G 2004, Manno C 2007, Lv J 2008) (summarized in Table 2). A recent report from the Toronto Glomerulonephritis Registry revealed that proteinuria and blood pressure levels during follow-up were the most important predictor of the rate of GFR decline, which underscored the importance of proteinuria remission and blood pressure management (Reich HN 2008, Figure 2). The Oxford classification of IgA nephropathy has established specific pathological features as independent predictors of renal progression. Factors found to be important include mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity and tubular atrophy/interstitial fibrosis (Cattran DC 2009). Extensive crescentic disease also confers a worse short-term prognosis, often accompanied by a rapidly progressive loss of renal function. This new Oxford classification emphasizes the importance of proliferative lesions in the prognosis of IgA nephropathy.

Another breakthrough in the past two years is a consequence of the cloning and immortalization of B cells from patients with IgA nephropathy. Novak and his colleagues have clearly demonstrated that a B cell abnormality involving premature enzymatic sialylation and/or reduced galactosylation of the O-linked serine residues at the hinge region of IgA1 is the basis for the production of aberrantly glycosylated IgA1 (Suzuki H 2008); furthermore, IgG produced by the B cells binds to poorly galactosylated IgA1 and is capable of triggering the formation of IgA1-IgG immune complexes (Suzuki H 2009). Thus, B cells in IgA nephropathy are programmed to manufacture both the autoantigen and the autoantibodies (*a situation unique in autoimmune disease*) for forming immune complexes (Glassock RJ 2009). These findings offer new sights into the disease pathogenesis, and suggest a possible rationale for immunosuppressive therapy in the management of IgA nephropathy.

Table 1. Epidemiological data regarding the frequency IgA nephropathy

Country	Author (year)	Study population (number of renal biopsy)	Proportion of primary GN (%)	Proportion of all GN (%)	Incidence (per 1 million person-years)
Asia					
China	Zhou FD (2009)	Single Centre-north China (5714)	58.2		
	Li LS (2004)	Single Centre-south China (13,519)	45.6		
Japan	1999	National Survey (1850)	47.3		
Korea	Chang JH (2009)	Single Centre (1818)	28.3		
Singapore	Woo KT (1999)	Review	45		
Oceania					
Australia	Briganti EM (2001)	Population-based (2030)	48.3	34.1	42.9
Europe					
CzechRepublic	Rychlík I (2004)	National Registry of Renal Biopsies (4004)	34.5		
Italy	Schena FP (1997)	National Registry of Renal Biopsies (13835)	36.9		
	Stratta P 1996	Population based survey			14.7
Spain	Rivera F (2002)	National Registry of Renal Biopsies (7016)		17	7.9
UK	Hanko JB (2009)	Regional biopsy registry (1844)	38.8		3.4 (1976 to 1985) to 17.9 (1996-2005)
Netherland	Tiebosch AT (1987)	Population based survey			19
France	Simon P (2004)	Population based survey			28
Americas					

USA	Nair R (2006)	Nephropathology Associates from 24 states (4504)		22	
	Wyatt RJ (1998)	Population-based survey			5(1975-1979) to 12 (1990- 1994)
Brazil	M. G. Polito (2010)	National biopsy data	20.1		

Table 2: Clinical and Histological Prognostic Factors in IgA Nephropathy

Clinical§	Histological¶
<u>Strong predictors*</u>	
Elevated serum creatinine or reduced eGFR level	Mesangial hypercellularity
Severe proteinuria	segmental glomerulosclerosis
Higher BP levels	endocapillary hypercellularity
	tubular atrophy/interstitial fibrosis
<u>Weak predictors#</u>	
Older age at presentation	
Male sex	
Absence of history of recurrent macroscopic hematuria	

¶ Oxford classification of IgA nephropathy (Cattran D C 2009)

§ revised from D'Amico G 2004

* Significant by multivariate analysis in most studies

Significant only by univariate analysis in many studies.

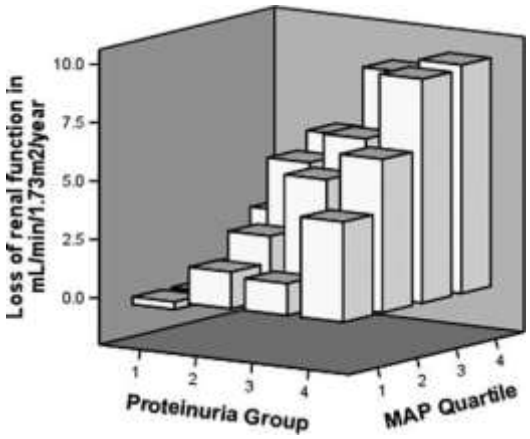


Figure 2: Relationship between proteinuria and MAP during follow-up, and loss of GFR. Group 1, time average proteinuria <1 g/d; group 2, 1 to 2 g/d; group 3, 2 to 3 g/d; group 4, >3 g/d. (Reich HN 2008)

2.4 Current therapy for IgA nephropathy- RAS inhibition and blood pressure management

Blood pressure lowering and RAS inhibition remain the cornerstone of management in people with IgA nephropathy. A series of randomised controlled trials, including the Angiotensin-Converting-Enzyme Inhibition in Progressive Renal Insufficiency Study (AIPRI) study and the Ramipril Efficacy in Nephrology (REIN) study, have established the role of ACE inhibitors in the management of glomerular disease (Maschio G 1996; Ruggenenti P 1998). In the AIPRI study, which included 192 patients with glomerulonephritis, an ACE inhibitor (Benazepril) reduced the risk of ESKD or doubling SCr by 53% (95%CI, 27%-70%). The REIN study involved 160 participants with glomerular disease, including 75 with IgA nephropathy, and showed that ramipril compared with conventional treatment decreased the rate of change in GFR by approximately 30%, and the risk for progression to ESKD by almost 50%. These effects have been suggested to be independent of their blood pressure lowering ability. Pooled results from 11 randomised controlled trials (including data from the AIPRI and REIN studies) indicated that risk of kidney failure or doubling SCr was reduced by about 33% (95% CI 0.16 to 0.47) with an ACE inhibitor compared with other classes of antihypertensive drugs in patients with chronic kidney disease and proteinuria greater than 0.5 g per day (Jafar TH 2003). Several studies have been conducted using ACE inhibitors (enapril, benazapril) or ARBs (valsartan) in IgA nephropathy aiming to slow the progression of renal failure. Most of the studies enrolled patients with proteinuria> 0.5-1.0g/day. In 2003, A Spanish group first reported the effects of enalapril in 44 patients with IgA nephropathy. During long-term follow-up (74-78months), 13% (3/23) in the ACE inhibitor group and 57% (12/21) of the patients in the control group reached the end point of 50% increase in serum creatinine from baseline (OR, 0.18; 95% CI, 0.03 to 0.87; P =0.04) (Praga M 2003). More recently, the IgACE study, a European multicentre, randomised, double-blind trial, examined the effect of benazepril in 66 children or young people with IgA nephropathy. After a mean follow-up of 38 months, more placebo-treated patients experienced the end point of a 30% decrease of GFR (5 vs. 1, 14.7% vs. 3.1%). Because of the small sample size and short follow-up period, the difference did not reach statistical significance (p=0.182) (Coppo R 2007). A randomised controlled trial in 109 Chinese adults with IgA nephropathy showed that valsartan reduced proteinuria and slowed the rate of renal function decline (Li PK 2006). A meta-analysis of the eleven RCTs, including 585 IgA nephropathy patients, concluded that the use of ACE inhibitors or ARBs produced a significant decrease in proteinuria and renal progression (Cheng J 2009). There is currently no strong evidence to suggest that the combination of ACE inhibitors and ARBs are superior to monotherapy with either class of agent alone for renal protection in proteinuric or non-proteinuric renal diseases, including IgA nephropathy (Kunz R 2008). Based on these studies, the current recommended approach to IgA nephropathy with proteinuria and/or hypertension emphasizes rigorous BP control with maximal renin- angiotensin system blockade using either an ACEI or an ARB to minimize proteinuria (Barratt J 2006, MOH guidelines on glomerulonephritis 2007).

2.5 Corticosteroids in IgA nephropathy

The use of corticosteroids in IgA nephropathy remains controversial. Breakthroughs in the understanding of pathogenesis of IgA nephropathy, including identification of specific auto

antigen/autoantibody (characteristic in autoimmune disease, *as discussed in the Pathogenesis section*), immune-complex mediated glomerulonephritis and complement activation through lectin pathway, have provided a clear potential rationale for immunosuppressive therapy with corticosteroids in the management of progressive IgA nephropathy. Recently reported RCTs have tested interventions intended to slow immune and inflammatory events implicated in progressive IgA nephropathy with corticosteroids. There are two situations where the use of steroid therapy is often considered indicated, and they are (1) in patients with the nephrotic syndrome and minimal change lesions on renal biopsy (detected by electron microscopy) and (2) in patients with crescentic glomerulonephritis (MOH Singapore guidelines 2007)

The currently available data from randomised trials of steroids in IgA nephropathy are summarised in Table 3.

Lai KN et al (1986) examined the effects of corticosteroid therapy in 34 Chinese people with documented IgA nephropathy and nephrotic syndrome. In the steroid arm, patients received 4-months of prednisone (40-60mg/day for 2 months, then ½ dose during the subsequent 2 months). During a mean study period of 38 months (range 12-106), corticosteroid treatment resulted in remission of nephrotic syndrome in 80% of patients with mild glomerular histopathological changes, but with no impact on kidney function.

In 1999, an Italian study first suggested that steroid therapy with methylprednisolone might protect kidney function in IgA nephropathy. In this randomised controlled trial, 86 proteinuric IgA nephropathy patients with preserved renal function (urine protein excretion 1-3g/day, serum creatinine<1.5mg/dl) were randomised to either a corticosteroid group (Methylprednsolone1g × 3days at 1st, 3rd, 5th month; then 0.5mg/kg on alternate day ×6months), or a control group (supportive therapy). After 5- years of follow-up, nine of the participants randomised to steroids (9/43, 21%) and 14 in the control group (14/43, 33%) reached the primary endpoint of 50% SCr increase (p=0.048) (Pozzi C 1999). In a post-trial 10-year extension of follow-up, steroid therapy significantly reduced proteinuria and prevented kidney failure with 13 patients reaching doubling of SCr in the control group compared to only 1 in the steroid group. Renal survival was significantly better in the steroid group (97% vs. 53%, p=0.003) (Pozzi C 2004). Since this study was conducted between 1987 and1999, RAS blockade was used in only a minority of patients, (equally distributed between groups), and the achieved BP level was not in line with current recommendations. The ability of corticosteroids to achieve additional benefits on top of adequate BP control and full dosage RAS inhibitors was, therefore, questioned (Barratt J 2005).

In 2009, two randomised controlled trials reported the effects of corticosteroids on top of ACE inhibitors, suggesting this treatment could reduce proteinuria and preserve renal function better than ACE inhibitors alone in patients with IgA nephropathy (Lv J 2009, Mann 2009). The first was a pilot study from China, randomly allocating 63 Chinese patients (Proteinuria 1-5g/day and GFR>30ml/min

per 1.73m2) to prednisone on a background of cilazepril (n=33) or to a control group (cilazepril alone, n=30). After 27-months of follow-up, the combination of steroids and ACE inhibitors significant reduced proteinuria and preserved renal function compared to ACE inhibitors alone; only one patient (1/33, 3%) progressed to the end point of a 50% increase in SCr in the corticosteroids group while 7(7/30, 23%) in the ACE inhibitors group reached this endpoint (p=0.001). Similar results were reported from a larger Italian multicentre RCT involving 97 patients and a median follow-up of 5 years. In this study, corticosteroids significantly reduced the risk of doubling of SCr or ESKD (2/49, 4.2% *vs.* 13/49, 26.5% p=0.003) as compared to the control arm. These two trials strengthen the evidence that corticosteroid therapy in patients with proteinuric IgA nephropathy may be beneficial when used in combination with ACE inhibitors. However both trials did not achieve a full dosage of ACE inhibitors (in the Manno study, the average dose of ramipril was 6.5mg/day and Lv J study 3.75mg/day), leading to persisting uncertainty about the value of corticosteroids after supportive therapy has been optimized. Another limitation of available trials is that participants with impaired kidney function (eGFR<50ml/min per 1.73m2) were excluded from most studies, so currently there are no data of efficacy and safety of steroids in this population

A search of Medline, EMBASE and CCRT database identified 7 small, randomised controlled trials, which evaluated the role of corticosteroids in IgA nephropathy (Lv J 2012). Nearly all studies observed a significant reduction in proteinuria with corticosteroids, however in four trials, the effects on kidney function did not reach statistical significance likely due to the relatively small sample size, short follow-up (Lai 1986, Julian 1993, Shoji 2000,Ronald 2006) and possibly the modest dosage of steroids (Katafuchi 2003). A meta-analysis of these data (Figure 3) shows that corticosteroids significantly reduced the risk of doubling SCr or ESKD by 74% (RR 0.26, 95% confidence interval [CI] 0.1 to 0.71) and ESKD alone by 64% (RR 0.36, 95%CI, 0.15 to 0.91). Subgroup analysis suggested that high dose oral steroids are more effective than low dose (greater vs. less than 30 mg/day, p=0.032, Figure 4)

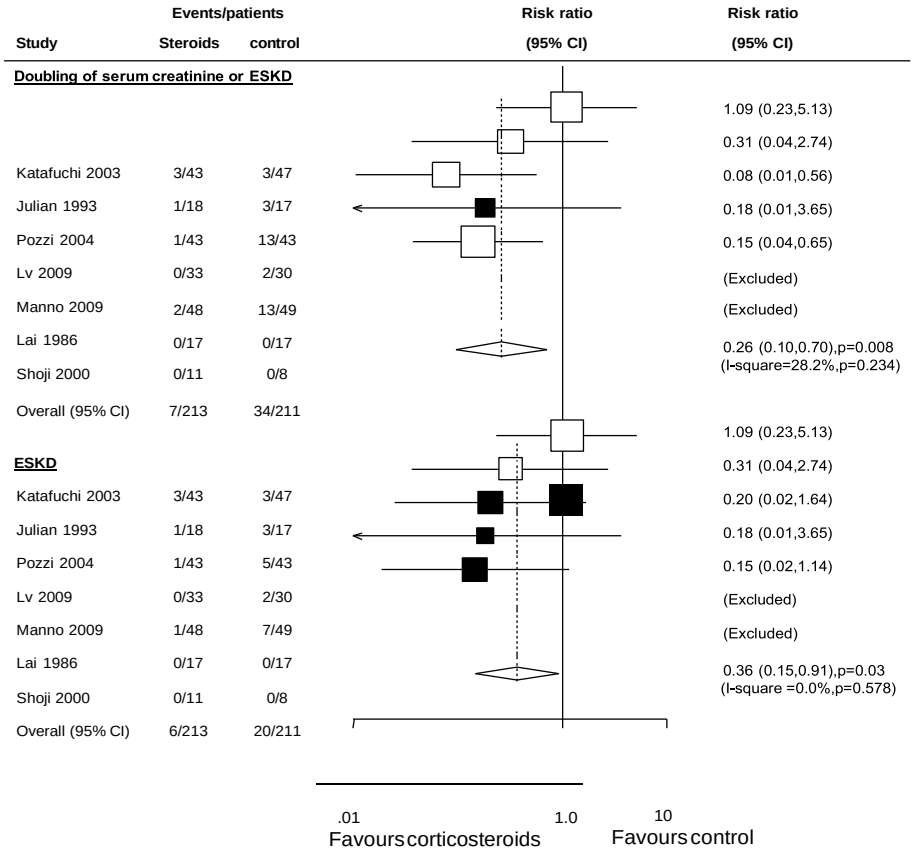


Figure 3: corticosteroids therapy on the outcomes of doubling of serum creatinine or ESKD

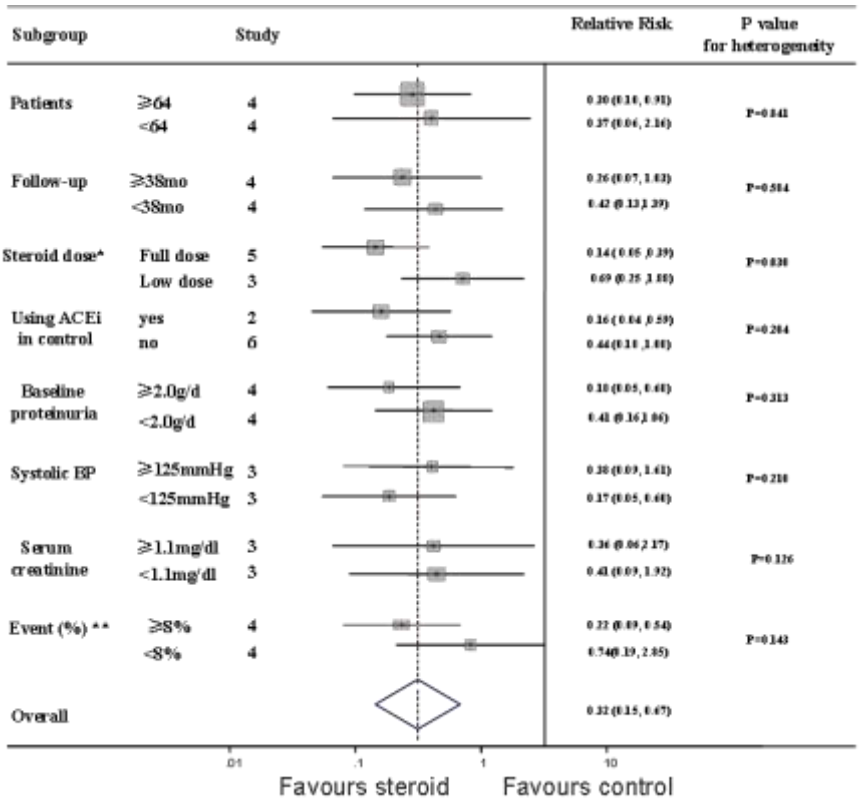


Figure 4: subgroup analysis of steroids on the outcome of doubling serum creatinine or ESKD

*Full dose: prednisone>30mg/d or methylprednisolone pulse therapy; Low dose: prednisone<30mg/d

**Percentage of patients progressed to composite renal endpoints in each trial CI, confidence intervals; RR, relative risk.

Table 3: Characteristics of the participants, interventions, comparisons and outcomes in the included randomised controlled trials

Study	Patients	No. Patients	Steroids group	Control	Follow-up (mths)	Event number				Benefits
						Doubling SCr		ESKD		
						Steroids	Control	Steroids	Control	
Lai 1986	IgA nephropathy with nephrotic syndrome	34 (17/17)	Pred 40-60 mg/d	No treatment	28	0 (-)	0 (-)	0 (-)	0 (-)	Reduced proteinuria No effect on the GFR
Julian 1993	CCr >25ml/min per 1.73m	35 (18/17)	Pred 60 mg/god	No treatment	6-24	1(-)	2(-)	1(-)	2(-)	No effect on change of Proteinuria; a trend to preserve renal function (defined by 1/SCr, p=0.06)
Shoji 2000	Proteinuria <1.5g/d Scr<1.5mg/dl	19 (11/8)	Pred 0.8 mg/kg/d	Dypiridamole 300 mg/d	12	0 (-)	0 (-)	0 (-)	0 (-)	Reduced proteinuria, no effect on the GFR; Reducing renal lesion in histology
Katafuchi 2003	Scrn<1.5mg/dl	90 (43/47)	Pred 20 mg/d	Dypiridamole 150-300 mg/d	65	3 (1.3%)	3 (1.2%)	3 (1.3%)	3 (1.2%)	Reduced proteinuria. No effect on the renal survival (Defined as ESKD)
Pozzi 2004	Scr<1.5mg/dl Proteinuria 1- 3.5g/day	86 (43/43)	MP 1g × 3 days, then 0.5mg/kg/day	Supportive care	82	1 (0.3%)	13 (4.3%)	1 (0.3%)	5 (1.7%)	Reduced proteinuria. Improved renal survival (defined as doubling of SCr)
Hogg* 2006	Proteinuria(UP/C) >1.0 or >0.5 with renal lesions at risk; GFR>50	64 (33/31)	Pred 60 mg/god	Placebo	24	_	_	_	_	No effect on the Proteinuria reduction or renal survival (defined as 60% decrease of GFR)
LV JC 2009	Proteinuria 1-5g/day GFR>30ml/min.1.73 m2	63 (33/30)	Pred 0.8-1mg/kg/d	Cilazapril mean dosage 3.75mg/d	27.3	0 (-)	2 (3.0%)	0 (-)	2 (3.0%)	Reduced Proteinuria and improved renal survival (50% increase of SCr)
Manno 2009	Proteinuria>1g/day GFR>50ml/min.1.73 m2	97 (48/49)	Pred 1mg/kg/day	Ramipril mean dosage 7.5mg/d	60	2 (0.9%)	13 (5.7%)	1 (0.4%)	7 (3.0%)	Reduced Proteinuria and improved renal survival (defined as doubling of SCr and or ESKD)
Rauen T (2015)	Proteinuria>0.75g/day GFR 30-90ml/min.1.73m2	109 (55/54)	MP 1g × 3 days;then 0.5mg/kg/day	Supportive care	36	_	_	_	_	Increased clinical remission while no effect on kidney function

SCr: serum creatinine; ESKD: end stage kidney disease; GFR: glomerular filtration rate; CCr: creatinine clearance rate;

Pred: prednisone; MP: methylprednisone

***** Ronald study including 3 trial arms: corticosteroids group (n=33),O3FA group (n=32) and placebo group (n=31)

The supportive versus immunosuppressive therapy of progressive IgA nephropathy (STOP IgAN) (Eitner F 2008) is a multi-centre trial aiming to evaluate whether corticosteroids alone or combined with cyclophosphamide/azathioprine may improve proteinuria remission rates as compared with current supportive therapy. The recently published results showed individuals randomised to immunosuppression had a higher rate of proteinuria remission, but with more adverse effects, and no significant change in the rate of decrease in the eGFR in either group (Rauen T 2015). Although well designed, it is a smaller trial (n=162) with short follow-up (3 yrs) and is powered on a relatively soft endpoint: full clinical remission (proteinuria <0.2g/day and stable renal function) or GFR loss>15ml/min per 1.73m2. The stability of kidney function in the placebo group also made it very unlikely that any benefit on kidney function could be demonstrated. Therefore, uncertainty persists regarding the risks and benefits in higher risk individuals with IgAN.

2.6 Current guidelines and meta-analysis of corticosteroids in IgA nephropathy

KDIGO (Kidney Disease: Improving Global Outcomes) suggest that patients with persistent proteinuria >1 g/d, despite 3–6 months of optimized supportive care (including ACE inhibitors or ARBs and blood pressure control), and GFR >50 ml/min per 1.73m2, receive a 6-month course of corticosteroid therapy. Available national guidelines from CARI (Caring for Australians with Renal Impairment) and the Singaporean MOH have both addressed the potential benefits of steroids in patients with IgAN and persistent proteinuria, and suggest they may have a role.

A recent meta-analysis also revealed that steroids reduced proteinuria and renal progression (Cheng J 2009, Samuels JA 2003). However current recommendations from guidelines are based on small, single-centre trials and there is still much uncertainty on the use of steroids in patients with IgA nephropathy. For example, the guideline from CARI notes that there is no evidence to suggest patients with IgA nephropathy and established renal impairment (< 60mL/min) benefit from steroid therapy (CARI 2006); the Singaporean MOH guideline for glomerulonephritis pointed out that although steroids are of likely benefit in selected IgA patients, it is unknown if the immunosuppressive regimens would still be beneficial if optimal blood pressure control is achieved with the use of ACE inhibitors and/or ARBs (MOH clinical guideline 2007); The recent KDIGO guideline for glomerulonephritis states that 'there is low low-quality evidence that corticosteroids provide additional benefit to optimized supportive care', however 'there is no evidence to suggest the use of corticosteroids in patients with GFR<50ml/min.

2.7 Rationale for a large clinical trial of corticosteroids in patients with IgA nephropathy

IgA nephropathy is one of most common reasons for kidney failure in young adults. Decreased kidney function, hypertension and persistent proteinuria are the strongest risk factors for progressive loss of kidney function and kidney failure. Current established therapies include full RAS inhibition and

optimal blood pressure control for patients with proteinuria and/or hypertension, but a substantial risk of progression remains even when these therapies are employed.

The available evidence also suggests that corticosteroids may be effective in patients with IgA nephropathy at risk for progression. The completed studies have important shortcomings, which have limited their implementation into guidelines and clinical practice. These include:

1. The completed studies were mostly conducted at a single centre, leading to uncertainty about the balance of benefits and risks when applied across multiple centres with varying expertise in this area. STOP-IgAN was a notable exception, but participants in that trial had very stable kidney function limiting power
2. The studies generally used an intermediate primary endpoint, leading to uncertainty about the clinical importance of the findings
3. Many of the available studies were of suboptimal quality
4. The completed studies were not adequately powered to detect moderate treatment benefits on hard outcomes, making them susceptible to type 1 errors and publication/reporting bias
5. Data regarding the potential harms of corticosteroid therapy were not collected in a systematic and consistent fashion from most studies
6. Supportive therapies were often sub-optimally provided
7. The participants chosen were not necessarily those at highest risk of progressive loss of kidney function and kidney failure

These limitations have led to reluctance to implement steroid therapy into guidelines and clinical practice in many parts of the world, and therefore a large well-designed and adequately powered multi-centre randomised trial is required to resolve these persistent uncertainties, and allow the role of steroid therapy in IgAN to be defined.

Although IgA nephropathy is the most common glomerular disease worldwide, there are still no RCTs with adequate power and quality to reliably inform clinical practice (Leaf DE 2010, Strippoli GF 2009). The TESTING study is an international double-blinded randomised controlled trial, which was initiated in 2012. In this study, 750 participants were planned to receive 0.6-0.8mg/kg/day of methylprednisolone (maximal 48mg/d) for two months, tapered subsequently and stopped within 6-8 months, a similar regimen as suggested by the KDIGO guidelines for IgA nephropathy.

2.8 Dose effect of steroids in IgA nephropathy

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 substantial benefits for steroids on kidney outcomes with a modest number of events, 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 and the results to date, the Steering Committee decided to discontinue treatment with the dose of methylprednisolone being used at the time due to the safety concerns, to analyse and report the results given their clinical importance to people being treated with steroids around the world. As significant renal 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.

Each of the original and the low-dose cohorts in TESTING will have separate power to detect reductions in proteinuria and effects on average eGFR, along with effects on important safety outcomes with the steroid regimens used. Participants will undergo long term follow-up for an average of 4 years in each cohort, and the effects of both regimens on the risk of the composite kidney outcome will be assessed on the study population as a whole, stratified for treatment regimen so long as there is no evidence of significant heterogeneity in the efficacy at reducing the primary outcome.

2.9 Health significance of the proposed study

IgA nephropathy is the most common glomerular disease worldwide and also the most common reason for end stage of kidney disease in young adults (Nair R 2006). IgA nephropathy accounts for 44% of patients with ESKD due to glomerulonephritis in Australia (Briganti FM 2001) and it is estimated that IgA nephropathy accounts for up to 10% of all patients in need of renal replacement therapy in western countries. The percentage is even higher (up to 15% to 20%) in developing countries. In China, 50% of ESKD are due to glomerular disease (Wang HY 2005), and patients with IgA nephropathy pose a particularly important health care problem because the patients are usually relative young when they reach ESKD and have a relatively good life expectancy. Therefore, renal replacement therapy carries a substantial social, emotional and financial burden. In Australia, the number of people with ESKD due to IgAN is estimated to be about 1700, generating an annual cost for renal replacement therapy of $426 to 452M. The trial we propose will provide reliable evidence regarding the benefits and harms of a preventive strategy for individuals with IgA nephropathy at high risk of reaching ESKD.

There is a dearth of high quality evidence for such clinical decisions, and an international consensus on this question is still lacking. This will be the largest trial in glomerular disease; through the successful completion of the present study, the research team will provide evidence that will form the basis of future treatment guidelines for IgA nephropathy.

3. Trial Hypotheses and Objectives

3.1 Trial hypotheses

A 6-9 month regimen of tapering corticosteroid therapy compared to matching placebo will reduce the risk of kidney failure in participants with high-risk IgA nephropathy

3.2 Trial objectives

This study aims to evaluate the long-term efficacy and safety of oral methylprednisolone compared to matching placebo, on a background of routine RAS inhibitor therapy, in participants with IgA nephropathy and features suggesting a high risk of progression.

3.2.1 Primary objective for combined analysis of TESTING and TESTING low-dose cohorts

To determine if adding oral methylprednisolone to best available standard care for 6-9 months reduces the risk of the composite outcome of persistent 40% reduction in eGFR, end stage kidney disease (ESKD) and death due to kidney disease, compared to matching placebo, in participants with progressive IgA nephropathy.

3.2.2 Secondary objectives for combined cohorts

To determine if adding oral methylprednisolone to optimal background care, compared to placebo:

1) Reduces the risk of the composite outcome comprising ESKD, persistent 30% reduction in eGFR and death due to any cause.
2) Reduces the risk of the composite outcome comprising ESKD, persistent 40% reduction in eGFR and death due to any cause.
3) Reduces the risk of the composite outcome comprising ESKD, persistent 50% reduction in eGFR and renal death.
4) Reduces the risk of each of ESKD and death due to kidney disease
5) Reduces proteinuria, defined as time-averaged proteinuria post-randomisation,
6) Stabilises kidney function, as defined by average yearly slope of eGFR post randomisation
7) Is safe, with particular reference to the risk of:
    - Serious infections requiring hospitalisation
    - New onset diabetes mellitus
    - Clinically apparent gastrointestinal haemorrhage requiring hospitalisation
    - Clinically evident fracture or osteonecrosis
    - Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease.

3.2.3 Primary objective specifically for low dose cohort

To determine if adding oral low dose methylprednisolone to optimal background care have benefits on proteinuria reduction or GFR decline, compared to placebo:

1) Change in proteinuria from baseline at 6th and 12th months
2) Mean change in eGFR at 6th and 12th months

In order to allow more detailed comparison of the effects on the kidney for each of the two doses of steroids being used, given the limited power to do this for the main primary outcome these outcomes were added after the completion of the full dose arm.

4. Trial Design

This trial will include over 500 participants with IgA nephropathy (262 in the original dose cohort, and at least 240 in the low dose cohort) who are at high risk for renal progression. Following randomisation participants will undertake a 6-9 month intervention and then be followed-up regularly until at least 160 primary endpoints are observed, which is expected to require average 4-year follow-up. Each cohort will be followed for an average of at least 4 years to allow comparisons of effects

This is a double blind, randomised, parallel-group, two-arm, long-term study that comprises 3 study phases.

4.1 Pre-randomisation period (4 to 12 weeks)

During a 4 to 12 week screening period, the participant's eligibility for randomisation into the trial will be evaluated. The participant should receive 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 (see Table 5 for guidelines on the recommended maximum labelled dose for ACE inhibitor and ARB, noting that the maximum dose may be zero in those participants who cannot tolerate ACE Inhibitors or ARBs). For participants that have already received ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks, while for participants that haven't received such therapy, the run-in will be 12 weeks, so all participants have been on RAS blockade for at least 12 weeks prior to study entry. Other BP lowering agents should be adjusted or added during this stage to achieve guideline based targets. In subjects who whom ACE inhibitor or ARB is medically contraindicated e.g. angioedema, the subject's eligibility should be discussed with medical monitor on a case by case basis.

For participants that fail the screening period, but are still willing to be part of the study and the investigator thinks will be a feasible participant, re-screening can occur. The participant should be treated as a new subject, though the prior consent form can be used, if the re-screening is no more than 6 months since the original consent. The Trial Coordinating Centre and/or Medical Monitor should be approached if a site wishes to re-screen a participant to discuss the logistics of re-screening.

4.2 Study treatment period

At randomisation, participants who fulfil all eligibility criteria and no exclusion criteria will be randomised to either the steroid therapy or matching placebo in a double-blind fashion.

Low dose regimen used in this protocol (after Nov 30 2015): Participants will 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 will then be tapered by 4 mg daily/month, for a total treatment period of 6-9 months.

For reference, the original protocol 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.

Prophylactic treatment with trimethoprim/sulfamethoxazole (a single strength tablet daily or half a double strength tablet daily) is recommended by the Steering Committee during the first 12 weeks (+/- 4 days) after randomisation, as prophylaxis against life-threatening Pneumocystis Jirovecii pneumonia (PJP) observed in

the Chinese participants using the original protocol. For patients with known sulfa allergy, pentamidine or atovaquone can be used as an alternative at the discretion of the treating physician. For countries or regions with very low incidence of pneumocystis Jirovecii where PJP prophylaxis is not routinely recommended by the local guidelines in patients treated with steroids therapy, PJP prophylaxis can be exempted after notifying the Study Chairs in patients with a documented sulfa allergy.

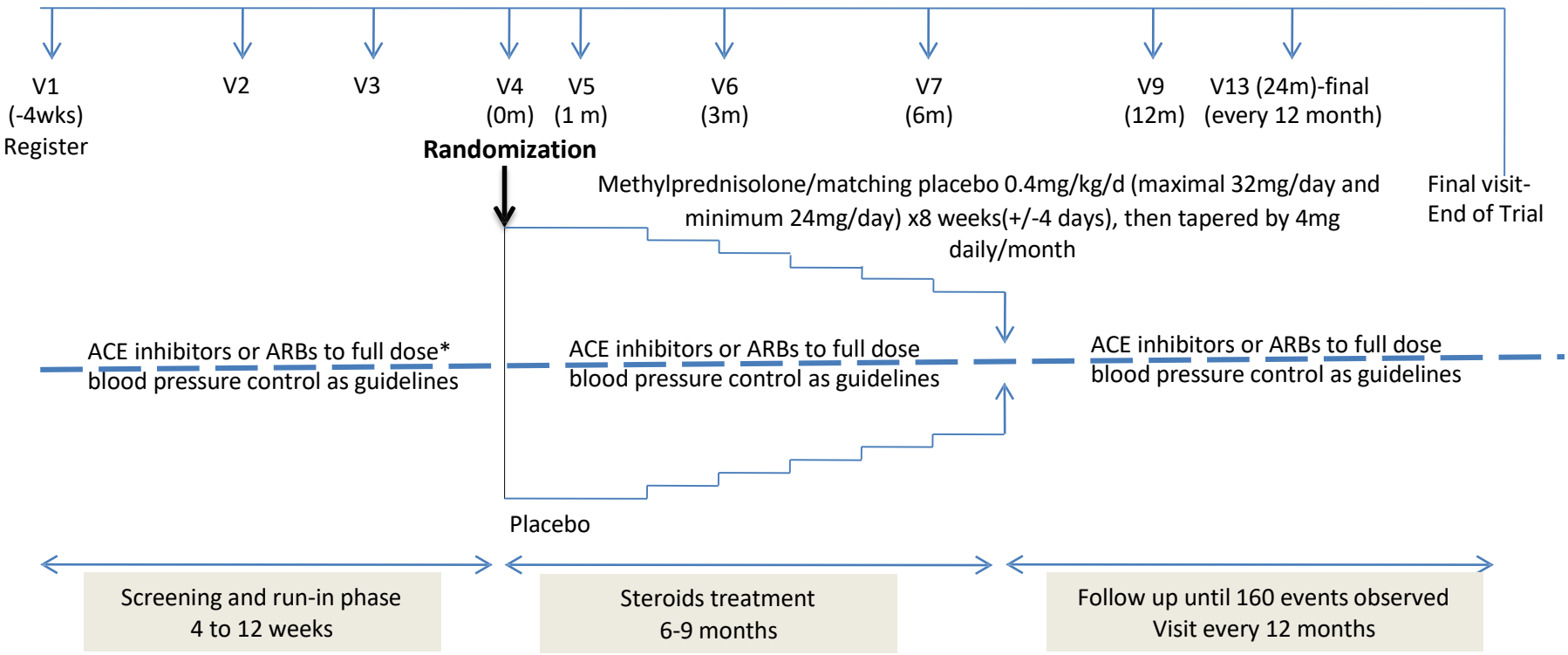
Throughout the trial investigators should strive to manage BP and other background therapies according to relevant local guidelines. 24-hour creatinine clearance will be measured at baseline and trimethoprim/sulfamethoxazole stopping time. This should coincide with Visit 6, but may have to be arranged separately.

4.3 Follow up phase

Participants will continue to be followed at regular intervals (see section '7.1 By Visit' below) for a planned average of 4 years in each cohort. Of note, the study is event driven and will be continued until 160 primary endpoints have occurred, so the final follow up duration may be longer or shorter depending on the event rate.

An overview of the study design is shown in Figure 5.

Figure 5：Study period of low-dose regimen



Note:

1. The intervals between v1 and v4 should be at least 4 weeks.
2. For participants that are already receiving the maximum tolerated or labeled dose of ACE inhibitors or ARBs for more than 8 weeks, the run-in phase is at least 4weeks and the patient only receive a second visit (V3). If all inclusions are fulfilled on the two visits, the participant can be randomised.
3. For participants that have received RAS inhibition for less than 8 weeks, the patients will receive 2 additional visits (V2 and V3) during the 4-12 weeks. If all inclusions are fulfilled on both V1 and V3, the participant can be randomised.
4. Full-dose regimen (before Nov 2015): Methylprednisolone/matching placebo 0.6-0.8mg/kg/d (maximal 48mg/d) x8 weeks (+/-4 days), tapered by 8mg/day every month and stopped at 6-8 months
   Low-dose regimen (after Nov 2015): Methylprednisolone/matching placebo 0.4mg/kg/d (maximal 32mg/d and minimum 24mg/d) x 8 weeks (+/- 4days), then tapered by4mg/day each month, and stopped within 6-9months.
5. For ACE inhibitors (or ARB if intolerant to ACE inhibitors) titrate to full dose as guidelines recommend.

5. Trial Medication

5.1 Investigational Medicinal Product

Study Medication will be administered in the following forms:

Table 4: study medication		
Drug/Ingredient	Methylprednisolone/Medrol	Matching Placebo
Formulation	Methylprednisolone/Medrol tablets 4mg/tablet	Tablets containing excipient, identical in appearance to methylprednisolone/Medrol but without the active ingredient
Manufacturer	Pfizer Pharmaceuticals	PPP for Australia, Canada, India, Malaysia; Shanghai Xinyi for China, Hong

Medrol will be used where provided by Pfizer including in China, but other agents of equivalent dosage may be used where Medrol is not provided.

The study treatment will be packaged and supplied by a manufacturer. Blister cards or bottles will be used in this study. There will be extra tablets to be used in case of loss during treatment.

The study treatment will contain information on the labels that will include: protocol number, batch number, kit number, storage information, and the investigational product caution statement. The labels will have space to write in the participant number. Additional statements will be printed on the label as required by local regulations.

All clinicians involved in the prescription of study treatment must read the Summary of Product Characteristics (SmPC)/Product Information which provides detailed information about the composition, indications, side effects, suggested dosage and contraindications of the study treatments.

5.2 Dosing Regimen

Participants will be required to take study drug each morning with food to reduce the risk of gastrointestinal side effects. All participants will receive conventional therapy for managing optimal blood pressure control that is in line with the current guidelines and maximal tolerated dose of ACE inhibitors or ARBs.

Given a relative high incidence of pneumocystis Jiroveci pneumonia (PJP) was observed in the initial participants enrolled in the TESTING study and randomised to full dose steroids, prophylactic trimethoprim/sulfamethoxazole (a single strength tablet daily or half a double strength tablet daily) will be used during the first 3 months after randomisation, for the prevention of severe PJP infection, unless there is a documented sulfa allergy. Inclusion of these patients may still occur, after notifying the Study Chairs, so long as the site rate of PJP is documented to be very low.

Diet: All participants will have standard dietary recommendations for CKD, e.g. Low-salt 3-6g/day (50-100mmol/day) and high calcium diet as per local country-based guidelines as part of standard care.

Participants will be advised to quit smoking and limit alcohol intake to safe levels during the study as per local country-based guidelines as part of standard care.

5.3 Drug Accountability

The trained authorized/delegated study staff will inventory and acknowledge receipt of all shipments of the study treatments by emailing the signed investigator product receipt form contained in the shipment to the Trial Coordinating Centre. The study treatments must be kept in a locked area with restricted access. The study treatments must be stored and handled in accordance with the manufacturer's instructions. The investigator or pharmacist will also keep accurate records of the quantities of the study treatments dispensed, used, and returned by each participant using an accountability form.

The study monitor will periodically check the supplies of study treatments held by the investigator or pharmacist to verify accountability of all study treatments used.

For reasons of safety, institutional regulations and storage capacity at sites, at the conclusion of the study, all used and unused study treatments at the site will be destroyed by investigational site staff according to local guidelines following monitoring inspection unless prior arrangements have been approved by the Trial Coordinating Centre in writing. Documentation of destruction with a complete and accurate account of study treatments destroyed must be available for verification by the study monitor and filed in the investigator site file.

5.4 Participant Compliance

Study medications will be distributed by the investigator or appropriately qualified designee.

Participants will be instructed to bring their unused study treatment to every visit. Compliance will be assessed by tablet counts with regard to the total number of tablets taken over the entire treatment period. Details will be recorded in the electronic case report form (eCRF). Investigators and their study personnel will be instructed to be sure that all participants take their prescribed number of

tablets each month. If a participant forgets to take the tablets on a particular day she/he should be instructed to continue as planned on the next day. The participant should not try to catch up by increasing the dose on the next day.

5.5 Concomitant Medication

Background care

Participants in this study, whether in the intervention or control arm, will all receive standard care for IgA nephropathy. The investigator should strive to control the blood pressure according to current guidelines. Throughout the trial, all participants should receive ACE inhibitors or ARBs adjusted to the maximal labelled or tolerated dose (whichever is reached first; noting that the maximum dose may be zero in those participants who cannot tolerate ACE Inhibitors or ARBs) aiming at achieving proteinuria <1g/d. The recommended maximum dose of ACE inhibitors or ARBs from K/DOQI or JNC 7 is summarized in Table 5

Table 5. Recommended maximum labelled dose for ACE inhibitor and ARB

ACEIs	**Proposed Max Dose (mgs per day)**	**Frequency per day**
captopril	75	2
cilazapril	5	1
benazepril	40	1
delapril	120	2
enalapril	20	1-2
fosinopril	40	1
imidapril	10	1
lisinopril	40	1
moexipril	15	1
perinodopril	8 or 10	1
quinapril	80	1
ramipril	10	1
trandolapril	4	1
zofenopril	60	1
ARBs	**Proposed Max Dose (mgs per day)**	**Frequency per day**
candesartan	16	1
eprosartan	600	1-2
fimasartan	120	1
irbesartan	300	1
losartan	100	1-2
olmesartan	40	1
telmisartan	80	1
valsartan	320	1

Permitted concomitant medications

The goal of blood pressure treatment in IgAN should be <130/80mmHg in participants with proteinuria. Any other antihypertensive medications, including diuretics, calcium channel blockers and beta-

blockers can be used at any time point or can be added when ACE inhibitors or ARBs are not adequate to achieve blood pressure targets. Diuretics such as hydrochlorothiazide (SCr<1.5mg/day) or loop diuretics (SCr>1.5mg/day) will be recommended as second line therapy. Dual RAS blockade is discouraged, but not prohibited. Other therapies such as statins or aspirin will be recommended for people fulfilling the required criteria according to local guidelines.

Chinese traditional medicine including Chinese herbs and acupuncture are a common treatment in China. These treatments are permitted and will be recorded on the eCRF.

Prohibited concomitant medications

Any other immunosuppressive therapies e.g. Mycophenolate Mofetil (MMF), cyclophosphamide (CYCLO) or azathioprine (AZA) are not permitted in this study, unless there are other definite indications for using these drugs.

Rifampin is also prohibited from this study as it interacts with methylprednisolone and makes the study drug less effective. The investigator should consult the product information of Medrol (Methylprednisolone) in appendix 7 for other prohibited concomitant medication.

6. Selection and Withdrawal of Participants

6.1 Target population

The target population will consist of participants 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 renal function, proteinuria and hypertension. This trial will include participants with eGFR 20 to 120 ml/min per 1.73m2 (original higher dose cohort) or 30-120 ml/min per 1.73m2 (lower dose cohort) and proteinuria ≥1.0g/day, with or without hypertension. Participants with indications for the use of steroids (e.g. crescentic glomerulonephritis (percentage of crescents >50%), or nephrotic syndrome and minimal change lesions on renal biopsy (as detected on electron microscopy) are excluded from this study (MOH Singapore guidelines 2007). Data from the Peking University IgA Nephropathy Database (www.renal-online.org) suggest that approximately 62% of individuals with renal biopsy proven IgA nephropathy will qualify for participation in this study.

6.2 Inclusion criteria

1) IgA nephropathy, proven on renal biopsy
2) Proteinuria (on most recent test): ≥1.0g/day while receiving maximum tolerated dose of RAS blockade
   - ≥1.0g/day on most recent available lab tests on Visit 1
   - ≥1.0g/day while receiving maximum tolerated dose of RAS blockade on Visit 3

3）eGFR (on most recent test): 20 to 120ml/min per 1.73m2 for participants in the full-dose arm; 30 to 120ml/min per 1.73m2 for participants in the low-dose arm (inclusive)

- The diagnosis of IgA nephropathy will be based on the demonstration of IgA deposits on direct immunofluorescence examination or immunohistochemistry, with typical histological findings and no other likely explanation for the individuals kidney disease
- Serum creatinine and proteinuria evaluation for eligibility will be determined on at least two visits during run-in phase (see section 6.5)
- Estimated GFR will be calculated using the equation of CKD-EPI (summarised in Table 6)
- Participants with eGFR >120 ml/min per 1.73m2 at screening who subsequently have an eGFR less than 120 ml/min per 1.73m2 after RAS inhibition therapy at visit 3 are eligible for this study

6.3 Exclusion Criteria

Participants 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 renal disease with IgA deposits
   - Crescents present in >50% of glomeruli on a renal 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 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 (See Appendix 5)

3) Systemic immunosuppressive therapy in the previous 1 year
4) Malignant /uncontrolled hypertension（>160 mmHg systolic or 110 mmHg 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 <18 years old
7) Secondary IgA nephropathy: e.g. due to lupus, liver cirrhosis, Henoch-Schonlein Purpura
8) Participants 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)

Table 6. Equations for estimating GFR in this study

Basis of equation and sex	Serum creatinine (mg/dl)	Equation for estimating GFR
Female	≤0.7	144×(SCr/0.7)−0.329×0.993Age [×1.159 if black]
Female	>0.7	144×(SCr/0.7)−1.209×0.993Age [×1.159 if black]
Male	≤0.9	141×(SCr/0.9)−0.411×0.993Age [×1.159 if black]
Male	>0.9	141×(SCr/0.9)−1.209×0.993Age [×1.159 if black]

SCr is serum creatinine

Reference: N Engl J Med 2012; 367:20-9.

6.4 Selection of Participants

This study will be international and conducted in up to 70 centres in a number of countries, including China (including Hong Kong Special Administrative Region), Australia, Canada, India and Malaysia.

6.5 Screening and Run-in phase

All eligible participants who provide informed consent will be invited to enter the run-in phase. The aim of 4- to 12- week run-in phase is to evaluate eligibility for the trial, identify potential non–compliance and optimise background therapies. Participants will not receive any study treatment during the run-in period.

All participants will be on RAS blockade for at least 3 months prior to randomisation, e.g.

1) For participants who have received treatment with ACE inhibitors or ARBs for more than 8 weeks, the run-in phase will be 4 weeks;
2) For those not previously receiving RAS blockade therapy, the run-in phase will be 12 weeks.
3) For those who have received RAS blockade therapy for less than 8 weeks, the run-in phase will be adjusted to ensure that all the participants will be on RAS inhibition for at least 12 weeks before randomisation.

During the whole study period including run-in phase, participants will receive standard background therapy for IgA nephropathy, including RAS inhibitors and blood pressure control according to current guidelines. All participants will receive ACE inhibitors (or ARBs if intolerant to ACE inhibitors) titrated to the maximum labelled or tolerated dose (whichever is reached first) according to local or national guidelines. The recommended dose of ACE inhibitors or ARBs from K/DOQI or JNC-7 is summarized in Table 5. Additional blood pressure lowering medications should be used to achieve treatment targets as per local guidelines.

For participants that fail the screening period, but are still willing to be part of the study and the investigator thinks will be a feasible participant, re-screening can occur. The participant should be treated as a new subject, though the prior consent form can be used. The Trial Coordinating Centre and/or Medical Monitor should be approached if a site wishes to re-screen a participant to discuss the logistics of re-screening.

Run-in phase study visits:

There will be 2-3 study visits during the run-in period.

Visit 1: The participant will be provided with information regarding the trial and offered an opportunity to consider and discuss this information. Those individuals who provide written informed consent will have eligibility for enrolment into the trial assessed. The screening procedures to be performed are described in Table 7.

Visit 2-3: If all inclusion and no exclusion criteria are fulfilled, participants will attend the second or the third visits to confirm eligibility based on renal function (eGFR) and 24-hour proteinuria.

a. For participants that are already receiving the maximum tolerated or labelled dose of ACE inhibitors or ARBs for more than 8 weeks, the run-in phase is at least 4 weeks and the participant only attends a second visit (V3). If all inclusions are fulfilled on the two visits, the participants are randomised.
b. For participants that have received RAS inhibition less than 8 weeks, the participants will receive 2 additional visits (second and third visits-V2 and V3) during the 4-12 weeks at least 2 weeks apart. The third visit will be within 2 weeks before randomisation. If all inclusions are fulfilled on the both V1 and V3, the participants are randomised.

6.5.1 Screening Log

The screening log is designed to monitor participant recruitment at the study centre. A screening log of all participants evaluated for enrolment in the study will be compiled regularly by research coordinators at each study site. The log will record all screened participants, whether they are randomised into the study or considered ineligible for the study. Additionally, the reason participants were excluded or the reasons eligible participants were not enrolled will be recorded in the log. A copy of the log should be retained in the investigator's study files. The Trial Coordinating Centre will compile a cumulative screening log during the recruitment period, using information from each study site.

6.6 Randomisation Procedure / Code Break

All participants meeting inclusion and exclusion criteria and providing informed consent for whom all baseline data has been collected will be randomised to either the methylprednisolone group or matching placebo group in a 1:1 ratio using a web based randomisation system developed and maintained by Data Management at The George Institute for Global Health. Randomisation will be achieved using a minimisation algorithm via a password-protected encrypted website interface. The randomisation schedule will be generated by the randomisation code administrator at The George Institute for Global Health. This password-protected and/or encrypted electronic Master Randomisation List is kept by Data Management in their secure system and is only accessible to the authorised senior staff.

Participants should be randomised within 2 weeks after completion of Visit 3

Every participant who participates in any study related procedure will be assigned a unique participant number via the web-based randomisation system. This system will be available 24 hours a day, 7 days a week.

Randomisation will be stratified using a minimisation method according to participating region, proteinuria (<3g/day or ≥3g/day), estimated GFR (<50ml/min/1.73m2 or ≥50ml/min/1.73m2) and kidney biopsy findings (endocapillary proliferation according Oxford classification, E1 or E0).

Randomisation data are kept confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the members of the DSMC and the independent biostatistician who will perform the interim analysis. Unblinding of participants should only be performed when knowledge of the treatment allocation will influence the participant's management in a significant fashion. The precise reason for unblinding must always be provided, together with details of the name of the clinician making the decision, the date and time the decision was made and any supporting documentation that supports the decision (such as laboratory reports). In any case of unblinding, the follow-up schedule of data collection should be maintained to enable full analysis of all participant data on an intention-to-treat basis.

The investigator will contact the Trial Coordinating Centre if they consider there is a need for unblinding and this will be adjudicated by members of the Steering Committee.

As per regulatory reporting requirement, the Trial Coordinating Centre will unblind the identity of the study medication for all unexpected serious adverse events that are considered by the investigator to be related to study drug.

Unblinding for ongoing safety monitoring by the DSMC will be performed according to adequate procedures in place to ensure integrity of the data as outlined in a separate DSMC charter.

6.7 Blinding

This is a double blind prospective randomised controlled trial. Both the participant and study personnel at each site will be blinded to treatment assignment, as will individuals serving on the Endpoint Adjudication Committee.

6.8 Withdrawal of Participants

Participants have the right to refuse treatment (allowing follow-up for safety) or completely withdraw from the study at any time for any reason. The investigator also has the right to withdraw participants from the study treatment if they believe that is in the best interests of the participant due to intercurrent illness, SAE, treatment failure, protocol violations, non- compliance, administrative reasons or other reasons. Due to the risks associated with abrupt withdrawal of steroid therapy, withdrawal of the study medication for any reason requires medical supervision and should follow local clinical practice guidelines established for steroid tapering.

Individuals withdrawing from study treatment will be asked to consent to phone contact according to the original protocol schedule. This will allow endpoint events or safety outcomes to be captured for the entire duration of the study. Participants will have the right to withdraw consent to any follow-up if they so wish.

If the reason for removal of a participant from the study is an AE or an abnormal laboratory test result, the principal specific event or test will be recorded on the eCRF.

Should a participant decide to withdraw consent or if they are withdrawn by the investigator for reasons mentioned above, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible. A complete final evaluation at the time of the participant's withdrawal should be made with an explanation of why the participant is withdrawing from the study.

An excessive rate of withdrawals may make study interpretation difficult; therefore, unnecessary withdrawal of participants should be avoided.

6.9 Expected Duration of Trial

This is an event driven trial, and will continue until at least 160 primary endpoint events are observed across the entire study population. The total duration of this study is expected to be at least 6 years with recruitment of at least 4 years and a subsequent follow up of at least 2 years, i.e. for the first participant, the follow-up is at least 6 years and for the last participant, the follow-up is 2 years or more. All randomised participants will participate in the active treatment phase of up to 12 months duration and will be followed up for at least 2 years post-treatment until the earliest of any of the following:

- Completion of the follow-up period (final visit)
- Death or ESKD
- Withdrawal of consent, by the participant or legal surrogate, or withdrawal by the investigator due to reasons mentioned above
- Premature study termination as defined in Section 12

The actual overall study duration or participant recruitment period may vary.

7. Trial Procedures

7.1 By visit

Table 7 lists all of the assessments and indicates with an "X" the visits (data collection) when they are performed. The participants randomised to full-dose and low-dose methylprednisolone should undertake study visits according to Table 7. During follow-up, participants will continue to receive routine clinical care with visits at least 3-monthly as per current standard clinical practice.

In the first year all the scheduled visits are conducted face-to-face, with the exception of visit 8 which is primarily a telephone visit, but may be conducted face-to-face. If a face-to-face visit is conducted – any blood or urine or other test results collected are for clinical decision making only and not required for the trial. The follow-up visits are scheduled as face to face visits at 12 month-intervals and telephone or face-to-face (at the choice of the investigator) visits at 3-month intervals (labelled ☏).

Participants who discontinue study drug, should be encouraged to attend scheduled study visits for the duration of the follow-up. At a minimum, they will be contacted for safety evaluations during the 30 days following the last dose of study drug, including final contact at the 30-day point. Documentation of attempts to contact the participant will be recorded in the participant record.

An eCRF should be completed for every scheduled assessment. If participants do not attend, this will be captured on the eCRF.

All data obtained from the assessments listed in Table 7 must be supported in the participant's source documentation (e.g. medical charts, participant notes or electronic data). Assessments that generate data for database entry and which are recorded on eCRFs are listed using the eCRF name. Assessments that are transferred to the database electronically (e.g. laboratory data) are listed by test name. For the purpose of this trial certain information entered into the eCRF can act as source data as specified in Appendix 6

Whenever possible, study assessments will be made by the same person, at the same time of day, at each study visit. For face-to-face visits, each evaluation will be conducted in the morning wherever possible. Please note that if circumstances exist where the study participant is unable to attend morning site visits (i.e. evening shift worker, etc.), afternoon evaluations are permitted. Some lab evaluations may require participants to present in a fasted state (see Table 7 for details). Scheduled visit dates should be adhered to as closely as possible.

If one visit is postponed, brought forward or missed, it should not result in the next visit being postponed or brought forward. The next visit, if at all possible, should adhere to the original time schedule. On occasion, a visit will be missed and this will be captured in the eCRF.

7.2 Physical examination & Vital signs

A complete physical examination will be performed at Visit 1 (Table 7) and the last End of Trial Visit. It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, and extremities, vascular and neurological. Additional physical examinations may be performed whenever clinically indicated.

Information about the all physical examinations must be present in the eCRF, which will act as source data for the purpose of this study. Significant findings that are present prior to the start of study drug must be included in the Relevant Medical History/Current Medical Conditions screen on the participant's eCRF. Significant findings made after the start of study drug, which meet the definition of a suspected, unexpected serious adverse reaction must be recorded on the Serious Adverse Event screen of the participant's eCRF.

Vital signs – Blood Pressure and Heart rate will be measured at Visits 1 (Screening), 2 (Run-in 1), 3 (Run-in 2), 4 (Randomisation), 6 (3 months), 7 (6 months), 9 (12 months) and then every 12 months as listed in table 7.

7.3 Height and weight

Height in centimetres (cm) will be measured at Visit 4 (randomisation).
Body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured at Visit 4 (randomisation), at 6 months, 12 months and then every 12 months as listed in table 7.

7.4 Chest x-ray (CXR)

A CXR screening in a *posteroanterior* view will be performed at screening (Visit 1) in countries with a high prevalence of tuberculosis or individuals considered to be at high risk, except for those individuals who have undergone chest radiography in the 1 month prior to screening. The main aim of the CXR screening is to exclude active infection e.g. tuberculosis. Interpretation of the image must be made by a qualified physician and documented on the CXR section of the eCRF. The CXR report should be labelled with the study number, participant initials, participant number, date and kept in the source documents at the study site. Clinically significant abnormalities should also be recorded on the relevant medical history/Current medical conditions eCRF page.

Screening for Latent tuberculosis

As there is a high prevalence of latent tuberculosis in India, QuantiFERON®-TB Gold (*Immune Release Gamma Assay: IGRA*) will be performed at screening in that country to detect latent tuberculosis. Those detected positive for latent TB will be offered INH prophylaxis as per standard practice at the participating trial sites.

7.5 Laboratory evaluations

Laboratory evaluation of all specimens will be performed locally, no more than 2 weeks prior to a scheduled study visit in the first 12 months from randomisation, and no more than 4 weeks for subsequent visits.

- Renal endpoints that need to be determined by serum creatinine, including 40% decrease of eGFR, 30% reduction in eGFR, 50% reduction in eGFR and ESKD have to be confirmed by two measurements at least 4-weeks apart. For this purpose, participants may need to attend an unscheduled visit one month after the study visit.
- Laboratory values that exceed the boundaries of a notable laboratory abnormality should be evaluated by the investigator and additional evaluations should be performed if judged appropriate by the investigator. If the laboratory abnormality is the primary reason for an unforeseen hospitalisation or otherwise fulfils the criteria for a Serious Adverse Event, then the procedure for notification of serious adverse events must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study or from treatment, then the participant must be followed until the abnormality resolves or until it is judged to be permanent.

7.6 Haematology

Haemoglobin, white blood cell count, lymphocyte and platelet count will be measured at Visits 1, 4, 6, 7, 8 (if a clinic visit), 9 and then at yearly intervals until the end of the study.

7.7 Blood chemistry

Blood chemistry: Blood Urea Nitrogen, creatinine, total bilirubin, SGPT, alkaline phosphatase, sodium, potassium, calcium, phosphorous, total protein, albumin, glucose and uric acid will be measured at Visits 1, 4, 6, 7, 8 (if a clinic visit), 9, and then at yearly intervals until the end of the study. Blood Urea Nitrogen, creatinine, sodium, potassium, and uric acid will be measured on Visit 2, 3. Electrolyte measurement (sodium, potassium) as well as Blood Urea Nitrogen and creatinine values will be obtained from participants at every visit where a complete laboratory test is not done.

7.8 Creatinine calibration

In China, a national central laboratory has been established at the Peking University First Hospital Central Laboratory, where serum creatinine levels will be measured using enzymatic method in a single laboratory. For other countries, the serum creatinine will be measured in the local laboratory of the study sites.

All the clinical laboratories will use a creatinine method that has calibration traceable to an IDMS (isotope dilution mass spectrometry) reference measurement procedure, according to the recommendations of NKDEP's Laboratory Working Group in collaboration with the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) and the European Communities Confederation of Clinical Chemistry (now called the European Federation of Clinical Chemistry and Laboratory Medicine). Methods based on either enzymatic or Jaffe method principles should have calibration traceable to IDMS.

7.9 Urinary analysis

A qualitative microscopic determination - white blood cells per high power field (WBCs/HPF) and red blood cells per high power field (RBCs/HPF) will be performed at each clinic visit.

7.10 24-hour urine protein excretion

24-hour urine collection for protein excretion will be performed at Visit 1,2,3,4,6,7,8 (if a clinic visit), 9 and then at yearly intervals until the end of the study. 24-hour urine creatinine will also be measured as a marker of completeness of collection.

7.11 24-hour urine sodium

24-hour sodium excretion will be measured on all 24-hour urine specimens at randomisation V4, V6, V13, V21 and the final visit.

7.12 Glycosylated haemoglobin (HbA1C)

HbA1C will be measured in participants with diabetes at Visits 4, 7, 9 and then at yearly interval until the end of the study.

7.13 Fasting Lipid profile

Lipid profile (total cholesterol, triglycerides, HDL-C, LDL-C) will be measured at Visits 4, 7 and 9 then the final visit. Total cholesterol will also be measured at Visit 1.

7.14 Scoring of histological lesions

Whenever possible, renal biopsy scoring should be performed centrally in countries with established expertise and facility. The central pathology centre will review and score either the actual stained slides or captured electronic images. Slides or electronic images of periodic acid stained Schiff (PAS) staining are essential for histology scoring centrally. For sites or countries without such facilities, local pathologist report will be used for the histology scoring. Information required to be entered into the eCRF include mesangial hypercellularity (Absent (M0) or present (M1)), Segmental glomerulosclerosis (absent (S0) or present (S1)), Endocapillary hypercellularity (absent (E0) or present (E1)), and tubular atrophy or interstitial fibrosis (T0: 0-25% (mild), T1:25-50% (Moderate) or T2: >50% (Severe). This information is required at visit 4 to be eligible for randomisation (*refer to appendix 1*).

7.15 Pregnancy

All female participants of childbearing potential will have a urine pregnancy test screening performed at Visit 1 to evaluate eligibility for the trial.

7.16 Health-related Quality of Life

Health outcomes will be measured at V4, V6, V9 and then at yearly intervals until the end of the study using the EuroQol EQ-5D (EQ-5D) questionnaire, which generates a composite index score representing the preference for a given health state (i.e., health utilities). The instrument includes a visual analog scale and 5 questions covering the following dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. There are 3 possible responses to each question (no problem; some problem; severe problem), thus enabling estimation for 243 possible health states.

The working hypothesis is that there will be no decrease in participant reported outcomes in the control arm relative to the active treatment arm of the study. The data from this study will be the first in terms of health utility for participants with IgA nephropathy taking methylprednisolone/steroids. The EQ-5D questionnaire should be completed by participant who should sign and date the questionnaire, unless site policy does not allow this, in which case it must be clearly documented that the participant self-completed the questionnaire.

7.17 Early withdrawal from the trial

Participants who discontinue study drug or withdraw early from this study should return for the assessments regularly as indicated by Table 7. If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to ask if any of the primary or secondary endpoints have occurred, at the foreseen visit dates, for the remaining duration of the study. Vital status will be obtained at every scheduled visit time point.

7.18 Unscheduled visits

The eCRF will have the capacity to capture data for unscheduled visits that may occur at the discretion of the site investigator or at the request of the Steering Committee. Unscheduled visits should not replace regular scheduled visits.

7.19 Biobanking (optional)

All participants will be invited to contribute baseline blood, urine and DNA specimens for biobanking to allow subsequent study of IgA nephropathy, and the response to therapy. In participating centres, consenting individuals will contribute sequential urine and/or blood samples (24 hour urine or random urine or plasma) at 0, 1st, 3rd, 6th, 12th and then at yearly intervals. The samples to be collected are described in Appendix 8. In Canada, a different procedure will be followed, using a locally established plan.

7.20 Data Handling & Management

The procedures for data review and query management are described in the Data Management Plan and Monitoring Plan. Data will be reviewed throughout the study according to these documents. In Canada, a locally developed Monitoring Plan will be followed.

Data for this study will be captured via a Web-based Electronic Data Capture system using the electronic Case Report Forms (eCRFs). The investigator should ensure the accuracy, completeness and timeliness of the data reported to the Trial Coordinating Centre in the eCRF and in all required reports.

For each participant enrolled, an eCRF must be completed. It will be transcribed by the site from the paper source documents onto the eCRF. The participants will be identified only by initials and a participant ID number/identification code on the eCRF. The name and any other identifying detail will NOT be included in any study data electronic file.

Data will be validated for accuracy and reliability using two methods:

1. A comprehensive validation check program will centrally verify the data according to the Data Management Document and automatically generate discrepancies for resolution by the investigator. Manual discrepancies can also be raised if necessary.
2. Verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification) according to the Monitoring Plan, and the maintenance of a medication–dispensing log by the investigator.

An electronic audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person who made the change.

Table 7. Schedule of Study Tests, Procedures and Clinic Visits

Background therapy (ACE inhibitors or ARBs)																														
Phase	Screening and run-in			Study Drug Treatment						Follow-up																				
Years	Year 1									Year 2				Year 3				Year 4				Year 5				Year 6+[a]				
Time	-12 to -4g			0	1	3	6	9	12	15 ☎	18 ☎	21 ☎	24	27 ☎	30 ☎	33 ☎	36	39 ☎	42 ☎	45 ☎	48	51 ☎	54 ☎	57 ☎	60	63 ☎	66 ☎	69 ☎	Every 3 months	End of study
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29+	
Informed consent form	x																													
Vital status					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
In/exclusion criteria	x	x	x	x																										
Medical history/ demography	x																													
Height				x																										
Weight				x			x		x				x				x				x				x					x
Vital signs	x	x	x	x		x	x		x				x				x				x				x					x
Physical examination	x																													x
Screening log	x	x	x																											
Randomisation				x																										
Chest X-ray[b]	x																													
Urinary analysis[c]	x			x		x	x		x				x				x				x				x					x
24-hour urine protein	x	x	x	x		x	x		x				x				x				x				x				x	x
24-hour urine creatinine	x	x	x	x		x	x		x				x				x				x				x					x
24-house urine sodium				x		x							x								x									X

Table 7. Schedule of Study Tests, Procedures and Clinic Visits

Background therapy (ACE inhibitors or ARBs)																														
Phase	Screening and run-in			Study Drug Treatment					Follow-up																					
Years	Year 1								Year 2				Year 3				Year 4				Year 5				Year 6+[a]				
Time	-12 to -4g			0	1	3	6	9	12	15 ☎	18 ☎	21 ☎	24	27 ☎	30 ☎	33 ☎	36	39 ☎	42 ☎	45 ☎	48	51 ☎	54 ☎	57 ☎	60	63 ☎	66 ☎	69 ☎	Every 3 months	End of study
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29+	
Urine volume	x			x		x	x		x				x				x				x				x					x
HBV screening	X																													
Pregnancy urine tests	x																													
Haematology [d]	x			x		x	x		x				x								x									x
Blood chemistry (fasting)[e]	x			x		x	x		x				x				x				x				x					x
Blood chemistry[f]		x	x																											
HbA1c (if diabetic)				x			x		x				x								x									x
Lipid profile[g]				x			x		x																					
Pathology scoring[h]				x																										
Study drug dispensation				x	x	x	x																							
Study drug accountability				x	x	x	x	x																						
Concomitant medications				x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Prophylactic trimethoprim /sulfamethoxazole				x																										
Adverse events					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Endpoints					x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
EQ-5D				x		x			x				x				x				x				x					x

a	Full-dose participants will have follow-up beyond 6 years
b	Only in countries with a high prevalence of tuberculosis or individuals considered to be at high risk
c	Urinary analysis: qualitative microscopic determination
d	Haematology: haemoglobin, WBC, lymphocyte, platelet count
e	Blood chemistry 1: blood urea nitrogen, creatinine, total bilirubin, ALT alkaline phosphatase, sodium, potassium, calcium, phosphorous, total protein, albumin, glucose, uric acid, total cholesterol
f	Blood chemistry 2: blood urea nitrogen, creatinine, sodium, potassium, uric acid
g	Fasting lipid profile: total cholesterol, triglycerides, HDL-C, LDL-C
h	Pathology scoring according to Oxford classification (see appendix 1)

8. Assessment of Efficacy

8.1 Overall Primary Efficacy Parameters for combined TESTING and TESTING low-dose cohorts

Progressive kidney failure, which is a composite of a persistent 40% decrease in eGFR, the development of end stage kidney disease, or death due to kidney disease.

The outcomes will be defined as below:

- 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.
- End stage kidney disease: situations that need renal replacement therapy includes kidney transplantation, maintenance dialysis therapy, or situations where a participant dies due to kidney disease
- Death due to kidney disease: death due to kidney failure that need dialysis, and the death could be avoided by timely dialysis.

8.2 Secondary Efficacy Parameters for combined cohorts

Secondary outcomes are each of eGFR reduction by 30%, 40%, 50%, end stage of kidney disease, as well as a composite outcome comprising both of these as well as death due to any cause.

In addition, the mean annual slope in eGFR during follow-up will be obtained by fitting a straight line through the calculated eGFR using linear regression and the principal of least squares. Proteinuria reduction will be evaluated by time-average proteinuria during follow-up

Outcomes for each dose cohort: Change in proteinuria from baseline at 6 and 12months； Mean change in eGFR at 6 and 12 months.

Primary Efficacy parameters specifically for low dose cohort

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

8.3 Procedures for Assessing Efficacy Parameters

Serum Creatinine:

Serum creatinine to determine eligibility or endpoints will be conducted in the morning by the local laboratory centre of each nephrology unit included in this trial. If possible, participants should present for lab evaluations in a fasted state.

Estimated Glomerular Filtration Rate (eGFR):

- The eGFR to determine eligibility for enrolment into the trial will be calculated from the serum creatinine concentration at Visit 1.

- The eGFR to determine the incidence of study endpoints will be confirmed by two measurements at least 4-weeks apart.
- The eGFR calculation will use the equation of CKD-EPI (Summarized in Table 6).

Urine protein excretion (proteinuria):

24-hour urine protein excretion (g/day) will be determined during run-in phase (visits 1, 2, 3) baseline (visit 4), 3 month (visit 6), 6 month (visit 7), and 12 month (visit 9) and then every 12 months to the final visit (summarized in Table 7)

9. Assessment of Safety

9.1 Definitions

Adverse Events (AEs)

According to the International Conference of Harmonization [ICH], an AE is any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign or symptom, or disease temporally associated with the use of a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product. Pre-existing conditions, which worsen during a study, are AEs.

All reportable AEs encountered during the clinical study will be reported on the AE electronic form (eform) of the eCRF. Intensity of AEs will be graded on a three point scale [mild, moderate, severe] and reported in detail on the eCRF.

Mild	discomfort noticed but no disruption of normal daily activity
Moderate	discomfort sufficient to reduce or affect daily activity
Severe	inability to work or perform normal daily activity

Serious Adverse Events (SAEs)

Serious adverse events are defined as any untoward medical occurrence that meets one of more of the following criteria:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defects

The classification of 'serious adverse event' is not related to the assessment of the severity of the adverse event. An event that is mild in severity may be classified as a serious adverse event based on the above criteria. If there is any doubt whether an event constitutes an SAE, this event should be considered a SAE.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

SUSAR is defined as a serious adverse event for which the nature and severity of the event is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for products with a marketing authorisation.

9.2 Study specific reportable adverse events

9.2.1 Reportable serious adverse events

All SAEs should be reported from the first dose of the study drugs through to 30 days after discontinuation of the study drugs. For other study periods, reporting of serious adverse events will be restricted to serious adverse events that are considered to be related to study treatment (possibly,

probably or definitely) and SAEs of special interest per the protocol- severe infection requiring hospitalisation, gastrointestinal bleeding requiring hospitalisation, cardiovascular events.

For purposes of reporting serious adverse events in this study, non-fatal endpoint events that are adjudicated to be components of the primary endpoint (e.g. ESKD) will not be subjected to immediate or expedited serious adverse events reporting requirements.

Serious adverse events will be grouped by body system as defined by the latest version of the Medical Dictionary for Regulatory Activities (MedDRA), following classification of investigator assessments into MedDRA preferred terms. Treatments will be compared with respect to the incidence of events by body system.

9.2.2 Reportable adverse events

For this trial, reporting of non-serious adverse events will be restricted to the study treatment-related adverse events of special interest e.g. new onset of diabetes mellitus, clinically evident fracture and osteonecrosis.

9.3 Safety alert terms for expedited reporting

In addition, if any of the following study treatment-related adverse events (serious or non-serious) occur in a participant in this study, they will be documented in the AE/SAE form of the eCRF and reported to the Trial Coordinating Centre, using the procedure for serious adverse events, even if the criteria for seriousness are not fulfilled:

Reportable Adverse events:

- New onset of diabetes mellitus (for criteria of diabetes mellitus see Appendix 3)
- Severe Infection requiring hospitalisation
- Clinically evident fracture or osteonecrosis
- Gastrointestinal bleeding requiring hospitalisation
- Major cardiovascular event (non-fatal stroke, nonfatal myocardial infarction, heart failure requiring admission, and cardiovascular death)

These reportable adverse events are of scientific and medical concern specific to the study treatment, for which ongoing monitoring and rapid communication by the investigators to the Trial Coordinating Centre may be appropriate. Such events may require further investigation in order to characterize and understand them.

Pregnancy

Adequate human reproductive studies have not been conducted with corticosteroids (SmPC). Therefore, pregnancies occurring in female participants exposed to the study treatment must be reported within one working day to the Trial Coordinating Centre.

A female participant must be instructed to stop taking the study medication and immediately inform the

investigator if she becomes pregnant during the study. Study treatment will be permanently discontinued, but the participant will remain in the study until study completion. Monitoring of the participant should be continued at least until conclusion of the pregnancy.
The investigator should counsel and discuss with the participant the risks of continuing with the pregnancy given her underlying renal disease and the possible effects of early exposure to study medication on the fetus, which might include a slightly increased risk of cleft palate. Pregnancies occurring up to 90 days after the completion of the study treatment must also be reported to the investigator.

Where a SAE occurs in the pregnant female participant (irrespective of whether the SAE is pregnancy-related or not), the SAE must be collected separately.

Significant Overdose

Cases in which a "significant overdose" (accidental or intentional) of the study treatment was taken, whether or not an adverse event occurred, are to be reported to the Sponsor in an expedited manner in the AE form of the eCRF. For purposes of this study, a "significant overdose" is defined as a participant's taking on the same day 5 or more times the planned daily dose for that day.

In the cases of significant overdose in which no adverse event occurred, the diagnosis on the AE log should be recorded as "overdose without adverse event", and the "overdose" criteria on the AE log should be ticked. For cases in which an adverse event occurred with overdose, the event description should be recorded as the diagnosis, and the "overdose" criteria should be ticked.

9.4 Period of Observation

For the purposes of this study, the period of observation for collection of treatment-related serious adverse events will commence from the time of the first dose of study treatment until the end of the study. Serious Adverse events that occur intermittently should be recorded as one AE.

If the investigator detects a serious adverse event in a study participant after the end of the period of observation, and considers the event possibly related to prior study treatment, he or she should contact the Trial Coordinating Centre to determine how the adverse event should be documented and reported.

9.5 Documentation and Reporting of Adverse Events

All reportable adverse events that occur during the observation period set in this protocol will be reported by the Investigator to the Trial Coordinating Centre on the AE log of the eCRF. Instructions for reporting adverse events are provided in the investigator's study file.
Serious adverse events and adverse events that fulfil a reason for expedited reporting to the Trial Coordinating Centre must be documented in the eCRF within 24 hours of the site becoming aware of the event and an email notification will be sent automatically to a specified list of Trial Coordinating Centre representatives (including the medical monitor).

The investigator must also inform the study monitor in all cases. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the study treatment. The Investigator will submit reportable adverse events to the relevant ethics committees in accordance with local ethics committee reporting requirements.

The Trial Coordinating Centre will be responsible for reporting in an expedited manner, all SAEs that are both unexpected and at least reasonably related to study treatment (Suspected Unexpected Serious Adverse Reactions) to the Regulatory Authorities, IECs/IRBs as appropriate and to the Investigators within 7 days with an additional report within 8 days, and reporting of SUSARs to the study drug manufacturer within 3 working days of being notified of the adverse event. Any SAE not listed as an expected event in the SmPC will be considered as unexpected.

The George Institute for Global Health will provide Emergency 24 Hour Medical Coverage for study related medical emergencies outside regular business hours to allow for the provision of advice to investigators or research staff. Contact numbers will be distributed to all participating investigators in a separate document.

The study will adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 and comply with local regulatory requirements.

10. Statistics

10.1 Statistical analyses

Comparison will be made of the primary outcomes, comparing all those allocated methylprednisolone versus all those allocated control arm, on an intention to treat (ITT) basis. Cox proportional hazards analysis and Kaplan-Meier plots will be used to compare event rates among the two groups. Subgroup analysis to check consistency of effect will be performed according to the following factors: randomised steroid dose (*full-dose* versus *lower-dose*), baseline proteinuria (<3.0g/day, ≥3.0g/day), baseline renal function (eGFR<50 versus ≥50ml/min per 1.73m2), baseline histological lesion scoring (E1 or E0) and race (Asian, Caucasian).

10.2 Sample size calculation and reasoning

A sample size of 500 participants will provide 90% power (α=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 have been performed using the log-rank test and assuming an annual combined rate of 40% decline in eGFR or ESKD of 12% in the placebo arm and 10% of participants lost to follow-up over 4 years. The study is event driven, and will therefore continue until at least 160 primary endpoints have been observed. However, the sample size might be adjusted based on the actual event rate.

The effects of methylprednisolone compared to placebo on these outcomes will initially be analysed separately for the high and low-dose cohorts, and combined if the results are statistically consistent.

A study, including up to 15 years of follow-up (including 293 cases), showed that the ESKD incidence was 6.7% per person-year (Lv J 2008) in participants with eGFR>20ml/min.1.73m2. Based on a prospective Chinese Cohort with IgA nephropathy including 650 patients and 4 years follow-up, the composite endpoint of 40% eGFR decline and ESKD was nearly 10% per person-year in patients with eGFR 20-120ml/min/1.73m2 and persistent proteinuria >1g/d after 3 month RAS inhibition therapy. The prospective randomised controlled trial from Manno C. et al. (2009) showed the incidence of GFR halving or ESKD was 6% in patients with ramipril therapy and preserved renal function, (eGFR>50ml/min/1.73m2). As this trial includes a higher-risk group (eGFR: 30-120ml/min/1.73m2), the incidence of ESKD is likely to be increased two-fold or more, supporting the conservative nature of the annual event rate estimate of 12%.

The meta-analysis described above suggests that methylprednisolone might reduce the risk of the primary endpoint by 64%, i.e. a relative risk (RR) of 0.36. This trial is conservatively powered to detect a risk reduction of 40%.

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.

10.3 Interim analysis

The trial DSMC will monitor safety data on an ongoing basis, but will not perform any formal interim analyses for efficacy for the primary outcome. As the TESTING Low Dose study is unlikely to have adequate, separate power to detect a significant effect on the primary outcome, and will assess the primary outcome in combination with the original dose group, the DSMC will not stop the Low Dose study early for efficacy, but can review efficacy data to consider the balance of risks and benefits.

As the DSMC identified a serious imbalance in serious adverse events between the high-dose methylprednisolone and placebo arms of the original trial, the main focus will be to monitor rates of serious adverse events, and to advise the trial leadership if a serious imbalance was to occur. The DSMC will therefore continue to review data from the Low Dose cohort on a regular basis.

The DSMC analyses will be performed by an independent statistician from The George Institute for Global Health, who is not involved in managing the trial. The DSMC can recommend the Steering Committee of the TESTING Trial should:

- Adjust the duration of follow-up; or other study design characteristics
- Terminate the study early if the data suggests the risk of adverse events substantially outweighs the potential benefits

11. Participant Confidentiality & Record Keeping

11.1 Participant Confidentiality

The investigator and trial staff must ensure that participants' anonymity will be maintained, that their identities are protected from unauthorized parties, and take measures to prevent accidental or premature destruction of these documents. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act, which requires data to be anonymised as soon as it is practical to do so.

The investigator should keep a participant enrolment log showing codes, names and addresses. The investigator should maintain participant' written consent forms documents in strict confidence.

When archiving or processing data pertaining to the investigator and/or to the participants, the co-ordinating centre shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

11.2 Investigator's Files / Source Documents/ Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories (1) investigator's Study File, and (2) participant clinical source documents.

The Investigator's Study File will contain the protocol/amendments, schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorisation forms and other appropriate documents/correspondence, etc. In addition, at the end of the study the investigator will receive the participant data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes which will be kept with the Investigator's Study File.

For this trial, electronic data entered into the eCRF will serve as source data, but some hard-copy source data must also be maintained as shown in appendix 6. Participant clinical source documents could include hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and participant screening and enrolment logs. The Investigator must keep these two categories of documents (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, the Trial Coordinating Centre must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and the Trial Coordinating Centre to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the participant, appropriate copies should be made for storing outside of the site.

11.3 Direct Access to Source Documents

The investigator shall supply the Trial Coordinating Centre on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that participant confidentiality is protected.

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Sponsor of the Study, the Trial Coordinating Centre or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

12. Quality Assurance Procedures

The study will be conducted in accordance with the current approved protocol, ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 (ICH GCP), Declaration of Helsinki, relevant regulations and standard operating procedures.

12.1 Obtaining Informed Consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as they require to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

If the participant is unable to read, oral presentation and explanation of the written informed consent form and information to be supplied to participants must take place in the presence of an impartial witness. Consent must be confirmed at the time of consent orally and by the personally dated signature of the participant or by a local legally recognized alternative (e.g. the participant's thumbprint or mark). The witness and the person conducting the informed consent discussions must also sign and personally date the consent document.

The investigator should inform the participant's primary physician about the participant's participation in the trial if the participant has a primary physician and if the participant agrees to the primary physician being informed.

12.2 Delegation of Investigator Duties

The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the study treatments and their trial-related duties and functions. The investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

12.3 Ethics and Regulatory Approvals

Before the start of the study, the protocol, informed consent document, any proposed advertising material and any other appropriate documents will be submitted to the appropriate Human Research Ethics Committee (HREC) for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all subsequent and substantial amendments to the original approved documents. If applicable, the documents will also be submitted to the Regulatory Authorities where the trial is taking place for Clinical Trial Authorisation in accordance with local legal requirements.

Study medication can only be supplied to the investigator after documentation on all ethical and regulatory requirements for starting the study has been received by the Trial Coordinating Centre.

Safety reports, annual progress reports and a final report at conclusion of the trial will be submitted to the Regulatory Authorities, research ethics committees and if applicable, to the study treatment manufacturer within the timelines defined in the Regulations.

12.4 Management of Protocol Deviations

A protocol deviation is an unanticipated or unintentional departure from the expected conduct of an approved study that is not consistent with the current research protocol or consent document. A protocol deviation may be an omission, addition or change in any procedure described in the protocol.

The investigator should not implement any deviation from or changes of the protocol without agreement by the Steering Committee and documented approval from the Independent Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to trial participants. In the event of an emergency intended to eliminate an apparent immediate hazard to participants, the Investigator may implement any medical procedure deemed appropriate.
Deviations from the protocol must be documented and promptly reported to the Steering Committee and the Independent Ethics Committee (if applicable). The report should summarise the event and action taken.

12.5 GCP Training and Site Monitoring

Study monitors from the Trial Coordinating Centre will conduct a site initiation visit prior to the start of the study to ensure that proper study-related documentation exists, assist in training investigators and other site personnel in study procedures and GCP guidelines, confirm receipt of study supplies, and ensure that acceptable facilities are available to conduct the study.

In addition, periodic site monitoring will be performed according to ICH GCP, the Trial Coordinating Centre's SOP and Monitoring Plan (local plan for Canada). The monitors will verify that the clinical trial procedures are being conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP and the applicable regulatory requirements. Data recorded in the eCRF will be

evaluated for compliance with the protocol and accuracy in relation to source documents.

On completion of all participant treatments and evaluations, the monitor will conduct a closure visit at the site.

12.6 Audits and Inspections

The Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities. The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The Investigator will make every effort to help with the performance of the audits and inspections.

As soon as the Investigator is notified of a planned inspection by the authorities, he/she will inform the Sponsor (or Trial Coordinating Centre) and authorize the Sponsor (or Trial Coordinating Centre) to participate in this inspection. Any result or information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor (or Trial Coordinating Centre). The Investigator shall take appropriate measures required by the Sponsor (or Trial Coordinating Centre) to take corrective actions for all problems found during the audit or inspections.

12.7 Executive Committee and Steering Committee

The study will be conducted under leadership of a Steering Committee that has overall responsibility for protocol design, study conduct and publication. The members of the Steering Committee have great experience in managing patients with IgA nephropathy or chronic kidney diseases, and have demonstrated experience and expertise in designing, conducting and analysing clinical studies.

The Executive Committee is a subset of the Steering Committee and has responsibility for coordinating protocol design, study conduct and publication.

Investigator proposed sub-studies will be evaluated by the Steering Committee on scientific merit and must be approved by the Steering Committee prior to being conducted.

The specific remits of these Committees are outlined in the Executive and Steering Committee Charter.

12.8 Data and Safety Monitoring Committee (DSMC)

An independent DSMC has been established to review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, complications and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate.

The DSMC will consist of physicians and a statistician experienced in clinical studies. The committee will be supported by an unblinded statistician from an independent research group. The independent DSMC will review safety data on an ongoing basis and may recommend the Steering Committee to stop or amend the study based on safety findings.

12.9 Termination of the Study

The study must be closed at the site on completion of all participant treatment and evaluations. Furthermore, the study may be closed at any time at the request of the Steering Committee, the Investigator, or a regulatory authority, with proper and timely notification of all parties concerned. As far as possible, early closure should occur after mutual consultation.

The Independent Ethics Committee will be informed and the Trial Coordinating Centre or the investigator will supply reason(s) for the termination or suspension as specified by the applicable regulatory requirements.

13. Publication Policy

The study will be conducted in the name of the TESTING study investigators.

- The principal publication from the study will be in the name of the TESTING study Investigators with full credit assigned to all collaborating investigators, research coordinators and institutions. Where an individuals' name is required for publication it will be that of the writing committee, with the study physician and/or chairs of the writing committee listed first and last, and subsequent authors listed alphabetically. All the study investigators will be listed at the end of main reports.
- It is intended that the results of the study will be reported and disseminated at international conferences and in peer-reviewed scientific journals.

14. Property Rights

All the results, data and documents, which arise directly or indirectly from the Clinical Trial in any form, shall be the immediate and exclusive property of the Sponsor. The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Investigator shall not mention any information in any application for any intellectual property rights.

15. Finance and Insurance

Participating Centre agreements will be signed between the George Institute for Global Health, Peking University Institute of Nephrology participating institutions and principal investigators and cover:

- Trial work and duration
- Obligations of the Principal Investigator
- Payment and withdrawal of funding
- Confidentiality
- Intellectual property
- Liability & Indemnity

The Trial Coordinating Centre certifies that it has taken out a liability insurance policy. This insurance policy is in accordance with local laws and requirements. The insurance of the Trial Coordinating Centre does not relieve the Investigator or manufacturers of the study interventions of any obligation to maintain their own liability insurance policy as required by applicable law. Liability and insurance provisions for this study are given in separate agreements.

Appendix 1: The Oxford Classification of IgA nephropathy

(Kidney Int 2009; 76:534)

Table A1.1 Definitions of pathological variables used in the oxford classification of IgA nephropathy

Variable	Definition	Score
Mesangial hypercellularity	<4 Mesangial cells/mesangial area=0 4–5 Mesangial cells/mesangial area=1 6–7 Mesangial cells/mesangial area=2 >8 Mesangial cells/mesangial area=3 The mesangial hypercellularity score is the mean score for all glomeruli	M0 ⩽0.5 M1 >0.5[a]
Segmental glomerulosclerosis	Any amount of the tuft involved in sclerosis, but not involving the whole tuft or the presence of an adhesion	S0 – absent S1 – present
Endocapillary hypercellularity	Hypercellularity due to increased number of cells within glomerular capillary lumina causing narrowing of the lumina	E0 – absent E1 – present
Tubular atrophy/interstitial fibrosis	Percentage of cortical area involved by the tubular atrophy or interstitial fibrosis, whichever is greater	0–25% – T0 26–50% – T1 >50% – T2

[a]Mesangial score should be assessed in periodic acid-Schiff-stained sections. If more than half the glomeruli have more than three cells in a mesangial area, this is categorized as M1. Therefore, a formal mesangial cell count is not always necessary to derive the mesangial score.

Table A1.2: Recommended elements in renal biopsy report for a case of IgA nephropathy

Detailed description of the features present on
Light microscopy
Immunohistochemistry
Electron microscopy
Summary of four key pathological features
Mesangial score ⩽0.5 (M0) or >0.5 (M1)
Segmental glomerulosclerosis absent (S0) or present (S1)
Endocapillary hypercellularity absent (E0) or present (E1)
Tubular atrophy/interstitial fibrosis ⩽25% (T0), 26–50% (T1), or >50% (T2)
Total number of glomeruli
Number of glomeruli with endocapillary hypercellularity, extracapillary proliferation, global glomerulosclerosis, and segmental glomerulosclerosis

Appendix 2: Equations for estimating GFR in this study

Basis of equation and sex	Serum creatinine (mg/dl)	Equation for estimating GFR
Female	≤0.7	144×(Scr/0.7)−0.329×0.993Age [×1.159 if black]
Female	>0.7	144×(Scr/0.7)−1.209×0.993Age [×1.159 if black]
Male	≤0.9	141×(Scr/0.9)−0.411×0.993Age [×1.159 if black]
Male	>0.9	141×(Scr/0.9)−1.209×0.993Age [×1.159 if black]

Scr is serum creatinine; Scys is serum cystatin C

Reference: N Engl J Med 2012;367:20-9.

Appendix 3: Criteria for the diagnosis of diabetes

1. FPG ≥126 mg/dl (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*

   OR

2. Symptoms of hyperglycaemia and a casual plasma glucose ≥ 200 mg/dl (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycaemia include polyuria, polydipsia, and unexplained weight loss.

   OR

3. 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

* In the absence of unequivocal hyperglycaemia, these criteria should be confirmed by repeat testing on a different day.

Reference: American Diabetes Association 2009

Appendix 4: Criteria for the diagnosis of obesity

Body mass index (BMI) is a simple index of weight-for-height that is commonly used in classifying overweight and obesity in adult populations and individuals. It is defined as the weight in kilograms divided by the square of the height in meters (kg/m2).

As for the Asian population, overweight is defined as a BMI equal to or more than 23, and obesity defined as BMI equal to or more than 25.

As for other population, it defines "overweight" as a BMI equal to or more than 25, and "obesity" as a BMI equal to or more than 30.

Table A4.1 WHO criteria for classification of adults according to BMI

Classification	BMI
Underweight	< 18.50
Normal range	18.50-24.99
Overweight	≥25.00
preobese	25.00-29.99
Obese class I	30.00-34.99
Obese class II	35.00-39.99
Obese class III	≥ 40

Table A4.2 Criteria for classification of Asian adults according to BMI

Classification	BMI
Underweight	< 18.50
Normal range	18.50-22.99
Overweight	≥23.00
Preobese	23.00-24.99
Obese class I	25.00-29.99
Obese class II	≥30

Appendix 5: Contraception protection

Women of childbearing potential must use an acceptable method of contraception to prevent pregnancy. Acceptable methods of contraception include the following:

- Barrier type devices (e.g. female condom, diaphragm and contraceptive sponge) used ONLY in combination with a spermicide
- Intra-uterine devices
- Oral contraceptive agents started at least 90 days before start of study
- Depo-Provera (medroxyprogesterone acetate)
- Levonorgestrel implants
- Naturally or surgically sterile (amenorrheic for at least 1 year and no record of child birth for naturally sterile persons)
- Male partner is sterile and is the only sexual partner

NB: True or periodic abstinence, the rhythm method or contraception by the partner only are NOT acceptable methods of contraception.

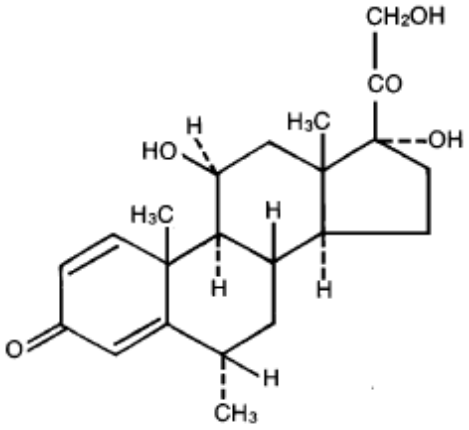
Appendix 6: Specification of source data

Assessment	What will function as Source Data
Informed consent form	Individual consent form
In/exclusion criteria	eCRF
Med History/ Demography	eCRF, and copies of documents/letters where available to be filed in participant file
Renal biopsy report	Report filed in participant file
Height and Weight(W)	eCRF
Vital signs	eCRF
Physical Exam	eCRF
Screening log	Screening log maintained at each site
Randomisation	eCRF
Chest X-ray(CXR)	X-ray report in the participant file
Urinary analysis	eCRF
24-hour urine protein	Lab report – filed in the participant file or electronic medical record
24-hour urine sodium	Lab report – filed in the participant file or electronic medical record
HBV screening	Lab report – filed in the participant file or electronic medical record
Pregnancy urine tests	Lab report – filed in the participant file or electronic medical record
Haematology	Lab report – filed in the participant file or electronic medical record
Blood chemistry panel-1	Lab report – filed in the participant file or electronic medical record
Blood chemistry panel-2	Lab report – filed in the participant file or electronic medical record
Fast blood glucose	Lab report – filed in the participant file or electronic medical record
HbA1C (if diabetic)	Lab report – filed in the participant file or electronic medical record
Lipid profile	Lab report – filed in the participant file or electronic medical record
Study drug dispensation	Drug accountability logs maintained at each site
Study drug accountability	Drug accountability logs maintained at each site
Co-Med	eCRF and referral letters or past med history information from medical records if available – to be filed in the participant file
Serious and reportable Adverse events	Written information on diagnosis, hospital discharge summaries etc. – filed in the participant file
Endpoints	Written information on diagnosis, hospital discharge summaries etc. – filed in the participant file
EQ-5D	Completed questionnaire

Appendix 7: Medrol product information

DRUG CLASS AND MECHANISM: Methylprednisolone is a synthetic (man-made) corticosteroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located adjacent to the kidneys. Corticosteroids affect metabolism in various ways and modify the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The chemical name for methylprednisolone is pregna - 1,4 - diene - 3,20-dione, 11, 17, 21-trihydroxy-6-methyl-, (6α, 11β)-and the molecular weight is 374.48. The structural for-mula is represented below:



STORAGE: Tablets should be kept at room temperature, between 20° and 25°C (68-77°F).
PRESCRIBED FOR: Methylprednisolone is used to achieve prompt suppression of inflammation. Examples of inflammatory conditions for which methylprednisolone is used include rheumatoid arthritis, systemic lupus erythematosus, acute gouty arthritis, psoriatic arthritis, ulcerative colitis and Crohn's disease. Severe allergic conditions that fail conventional treatment also may respond to methylprednisolone. Examples include bronchial asthma, allergic rhinitis, drug-induced dermatitis and contact and atopic dermatitis. Chronic skin conditions treated with methylprednisolone include dermatitis herpetiformis, pemphigus, severe psoriasis and severe seborrheic dermatitis. Chronic allergic and inflammatory conditions of the uvea, iris, conjunctiva and optic nerves of the eyes also are treated with methylprednisolone.
DOSING: Dosage requirements of corticosteroids vary among individuals and the diseases being treated. In general, the lowest effective dose is used. The initial oral dose is 4-48 mg daily depending on the disease. The initial dose should be adjusted based on response. Corticosteroids given in multiple doses throughout the day are more effective, but also more toxic than the same total daily dose given once daily or every other day. Methylprednisolone should be taken with food.
DRUG INTERACTIONS: Troleandomycin (TAO), an infrequently used macrolide antibiotic, reduces the liver's ability to metabolize methylprednisolone (and possibly other corticosteroids). This interaction can result in higher blood levels of methylprednisolone and a higher probability of side

effects. Erythromycin and clarithromycin (Biaxin) are likely to share this interaction, and ketoconazole (Nizoral) also inhibits the metabolism of methylprednisolone. Estrogens, including birth control pills, can increase the effect of corticosteroids by 50% by mechanisms that are not completely understood. For all of the above interactions, the dose of methylprednisolone may need to be lowered.
Cyclosporin reduces the metabolism of methylprednisolone while methylprednisolone reduces the metabolism of cyclosporin. When given together, the dose of both drugs may need to be reduced to avoid increased side effects. Methylprednisolone may increase or decrease the effect of blood thinners [for example, warfarin (Coumadin)]. Blood clotting should be monitored, and therapy adjusted in order to achieve the desired level of blood thinning (anti-coagulation).
Phenobarbital, phenytoin (Dilantin), and rifampin (Rifadin, Rimactane) may increase the metabolism of methylprednisolone and other corticosteroids, resulting in lower blood levels and reduced effects. Therefore, the dose of methylprednisolone may need to be increased if treatment with phenobarbital is begun.
PREGNANCY: Methylprednisolone has not been adequately evaluated in pregnant women.
NURSING MOTHERS: Methylprednisolone has not been adequately evaluated in nursing mothers.
SIDE EFFECTS: Adverse effects of methylprednisolone depend on dose, duration and frequency of administration. Short courses of methylprednisolone are usually well-tolerated with few, mild side effects. Long term, high doses of methylprednisolone may produce predictable and potentially serious side effects. Whenever possible, the lowest effective doses of methylprednisolone should be used for the shortest length of time to minimize side effects. Alternate day dosing also can help reduce side effects.
Side effects of methylprednisolone and other corticosteroids range from mild annoyances to serious irreversible bodily damage. Side effects include fluid retention, weight gain, high blood pressure, potassium loss, headache, muscle weakness, puffiness of the face, hair growth on the face, thinning and easy bruising of the skin, glaucoma, cataracts, peptic ulceration, worsening of diabetes, irregular menses, growth retardation in children, convulsions, and psychic disturbances. Psychic disturbances may include depression, euphoria, insomnia, mood swings, personality changes, and even psychotic behaviour.
Prolonged use of methylprednisolone can depress the ability of the body's adrenal glands to produce corticosteroids. Abruptly stopping methylprednisolone in these individuals can cause symptoms of corticosteroid insufficiency, with accompanying nausea, vomiting, and even shock. Therefore, withdrawal of methylprednisolone usually is accomplished by gradually lowering the dose. Gradually tapering methylprednisolone not only minimizes the symptoms of corticosteroid insufficiency, it also reduces the risk of an abrupt flare of the disease being treated.
Methylprednisolone and other corticosteroids can mask signs of infection and impair the body's natural immune response to infection. Patients on corticosteroids are more susceptible to infections and can develop more serious infections than individuals not on corticosteroids. For example, chickenpox and measles viruses can produce serious and even fatal illnesses in patients on high doses of methylprednisolone. Live virus vaccines, such as smallpox vaccine, should be avoided in patients taking high doses of methylprednisolone since even vaccine viruses may cause disease in

these patients. Some infectious organisms, such as tuberculosis (TB) and malaria, can remain dormant in patients for years. Methylprednisolone and other corticosteroids can allow these infections to reactivate and cause serious illness. Patients with dormant TB may require anti-TB medications while undergoing prolonged corticosteroid treatment.

By interfering with the patient's immune response, methylprednisolone can prevent vaccines from being effective. Methylprednisolone also can interfere with the TB skin test and cause falsely negative results in patients with dormant TB infections.

Methylprednisolone impairs calcium absorption and new bone formation. Patients on prolonged treatment with methylprednisolone and other corticosteroids can develop osteoporosis and an increased risk of bone fractures. Supplemental calcium and vitamin D are encouraged to slow this process of bone thinning. In rare individuals, destruction of large joints can occur while undergoing treatment with methylprednisolone or other corticosteroids (aseptic necrosis). These patients experience severe pain in the joints involved, and can require joint replacement. The reason behind such destruction is not clear. Methylprednisolone can be used in pregnancy, but is generally avoided.

Reference: FDA Prescribing Information

Appendix 8: Biobanking

All participants will be invited to contribute baseline blood, urine and DNA specimens for biobanking to allow subsequent study of IgA nephropathy, and the response to therapy. The samples are to be collected and stored in each participating country for future study. Informed consent must be obtained before drawing blood or urine.

1) Urine

24-hour urine collection processing, shipping and storing

The preparation of a properly mixed aliquot from the 24-hour urine collection is key to the correct measurement of the analyte. Therefore the following procedure must be followed closely:

- 24 hour urine may be measured by thoroughly mixing and pouring the sample into a 2 Litre graduated cylinder. A clean graduated cylinder must be used for each specimen;
- Be sure to record the volume on the requisition and aliquot container;
- Affix pre-printed labels to the10mL cryovials;
- Transfer urine into aliquots of 9mL;
- Store the aliquots at -20°C or -80 °C in a plastic rack or cardboard freezer box in an upright position within 4 fours;
- Label the racks or cardboard boxes with permanent marker or an adhesive label that says "TESTING 24 Hr Urine Refrigerated".

Random midstream urine collection processing, shipping and storing (for Proteomics):

- Encourage participants to stay hydrated even while fasting for the visit. However, do not collect samples after acute fluid load (>24 ounces) or after participant exertion. Collection will be random and, therefore, considered a "spot" urine collection;
- Place the sample on ice immediately after it is collected;
- Affix pre-printed labels to 2 airtight 10mL cryovials;
- Transfer 9mL of urine into the 10mL cryovials;
- Store the aliquots at -20°C or -80 °C in a plastic rack or cardboard freezer box in an upright position within 4 fours;
- Label the racks or cardboard boxes with permanent marker or an adhesive label that says "TESTING Random Urine Refrigerated".

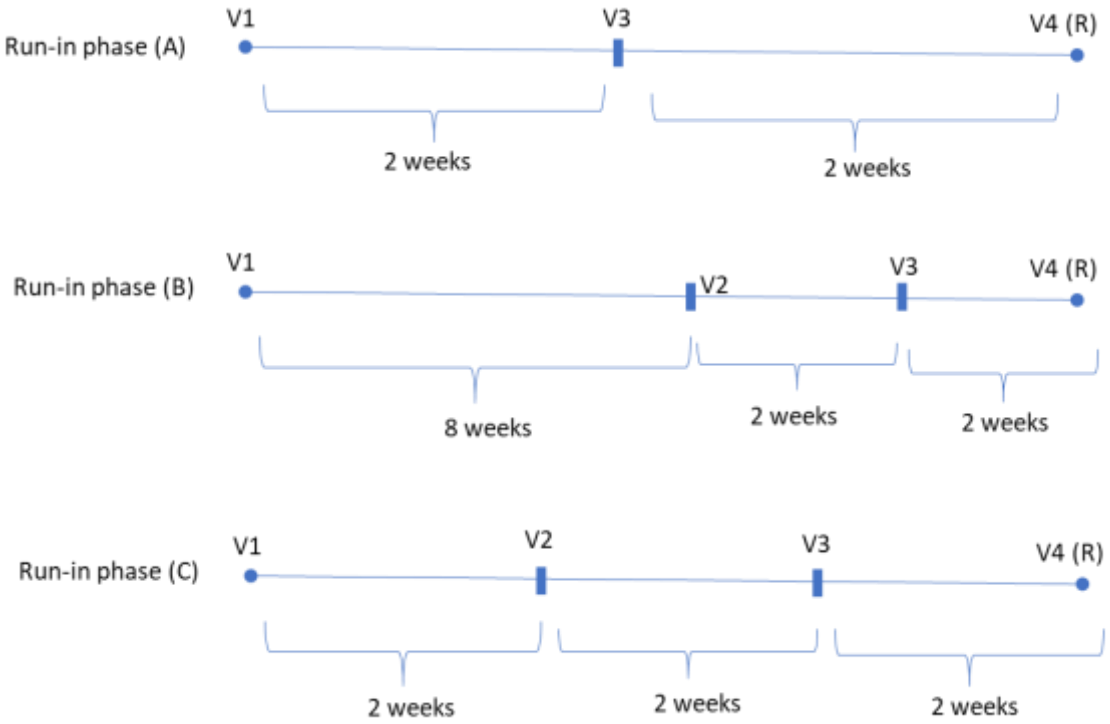
2) Blood collection: participant should remain fasted

DNA collection

- Participant remains fasted;
- 5mL EDTA (purple top) tubes;
- Blood Mixing During Venipuncture;
- DO NOT SHAKE TUBES;
- Centrifuge at 2100 g for 15 minutes;
- Separate the serum and extract the buffy coat and placed in a 2.5 ml cryovial;
- Label with permanent marker or an adhesive label that says "TESTING DNA Refrigerated";
- Store the Genomic DNA at -20°C or -80 °C.

3) Serum collection
   - Participant remains fasted;
   - 5mL (red top) tubes;
   - The drawn blood must be stored at room temperature for at least 30 minutes for complete clotting to occur;
   - The serum must be separated from the clotted blood by centrifugation. Centrifuge at 2100 g for 15 minutes;
   - Affix labels to aliquot cryovials;
   - Transfer all serum into one tube;
   - Label with permanent marker or an adhesive label that says “TESTING Serum Refrigerated”.

Appendix 9 - Diagrammatic representation of the different options during the run-in phase.



Run-in phase option (A)- Participants already received maximum labelled dose of ACE inhibitor or ARB for >8 weeks.

Run-in option (B) - Participants never on AEC inhibitor or ARB. Eight weeks for dose titration to maximum labelled dose follows by 4 weeks between V2-4, a total of 12 weeks or more.

Run-in option (C) - Participants had received AECi or ARB but not at its maximum labelled dose or less than 8 weeks (e.g 6 weeks at the time consent). An additional 2 weeks to make up a total of 8 weeks of stable ACEi and ARB dose, then follows by 4 weeks between V2-4.

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TESTING
Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study

Protocol Number: GI-R-01-2011

Statistical Analysis Plan

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Contents

1 Introduction

1.1 Study synopsis

The TESTING (**T**herapeutic **E**valuation of **ST**eroids in **I**gA **N**ephropathy **G**lobal) study is a multicenter, double-blinded, randomized placebo-controlled trial designed to evaluate the long-term efficacy and safety of oral methylprednisolone, on a background of maximal tolerated dose of 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.

In brief, after a 4 to 12 week run-in phase to ensure participants are receiving standard guideline based care (blood pressure control and the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) at the maximum tolerated/labelled dose), eligible patients will be randomised to methylprednisolone or matching placebo. All participants will continue to receive standard care throughout the trial.

1.2 Objectives

Protocol Primary objective

To determine if 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.

Protocol Secondary objectives

To determine if adding oral methylprednisolone to optimal background care, compared to placebo:

1. Reduces the risk of the composite outcome comprising ESKD, persistent 40% reduction in eGFR and death due to any cause.
2. Reduces the risk of the composite outcome comprising ESKD, persistent 50% reduction in eGFR and death due to any cause.
3. Reduces the risk of each of ESKD and renal death
4. Affect safety outcomes with special focus on:
    - Serious infections requiring hospitalisation
    - New onset diabetes mellitus
    - Clinically apparent gastrointestinal haemorrhage requiring hospitalisation
    - Clinically evident fracture or osteonecrosis
    - Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalisation or death due to cardiovascular disease.

2 Study Population

2.1 Target population

The target population will consist 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 renal function, proteinuria, and hypertension.

2.2 Inclusion Criteria

1) IgA nephropathy, proven on renal biopsy.

2）Proteinuria (on most recent test): ≥1.0g/day while receiving maximum tolerated dose of RAS blockade

- ≥1.0g/day on most recent available lab tests on Visit 1
- ≥1.0g/day while receiving maximum tolerated dose of RAS blockade on Visit 3

3）eGFR (on most recent test): 20 to 120ml/min per 1.73m^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 equation of CKD-EPI (Appendix A)
- Patients with eGFR >120 ml/min per 1.73m^2 at screening stage while reaching less than 120 ml/min per 1.73m^2 after tolerated RAS inhibition therapy at visit 3 are eligible for this study

2.3 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:
   - **a.** Minimal change renal disease with IgA deposits
   - **b.** Crescents present in >50% of glomeruli on a renal biopsy within the last 12 months.
2) Contraindication to immunosuppressive therapy with corticosteroids, including
   - **a.** 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.)
   - **b.** Malignancy within the last 5 years, excluding treated non-melanoma skin cancers (i.e. squamous or basal cell carcinoma)

c. Current or planned pregnancy or breastfeeding

d. Women of childbearing age who are not able or willing to use adequate contraception (See Appendix 5)

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)

3 Study Design

3.1 Aim & Hypothesis

This is a double blind, randomised, parallel-group, two-arm, long-term study that comprises 3 study phases i.e. Run-in phase, Treatment phase and Follow-up phase. This study aims to evaluate the long-term efficacy and safety of a 6-8 month regimen of tapering corticosteroid therapy i.e. oral methylprednisolone on a background of routine Renin Angiotensin System (RAS) inhibitor therapy in patients with IgA nephropathy and features suggesting a high risk of renal progression.

3.2 Study design and study drug dosing regimen

Patients with IgA nephropathy who are at high risk of progression to kidney failure are randomised in a 1:1 ratio to either methylprednisolone or matching placebo in a double-blind fashion.

After a 4-12 week run-in phase for background therapies optimization, participants randomised to the intervention group will receive oral methylprednisolone 0.6-0.8mg/kg/d (up to a maximum of 48 mg/day) for 2 months. The dose is then tapered by 8mg every month until the course is completed. Investigators will have the option of reducing the treatment dose from 8mg to 4mg for one month prior to cessation. Individuals randomised to the placebo group will follow an identical protocol using matching placebo tablets. The total treatment duration will therefore be 6-8 months for all participants. Patients were to be evaluated once every 1-3 months during methylprednisolone therapy as usual practice.

The third phase is post-treatment follow up.

3.3 Expected duration of trial

The total duration of this study was expected to be at least 6 years with recruitment of at least 2 years and a subsequent follow up of at least 4 years. All randomised subjects were expected to participate in the active treatment phase of up to 8 months duration and be followed up for at least 4 years post-treatment until the earliest of any of the following:

- Completion of the follow-up period (final visit)
- Death or ESKD
- Withdrawal of consent, by the subject or legal surrogate, or withdrawal by the investigator due reasons mentioned above
- Premature study termination as defined by study protocol Version 5 of 13 May 2015

3.4 Power Calculations

A sample size of 750 patients will provide more than 90% power (α=0.05) to detect a 30% risk reduction with a steroid based treatment approach after an average follow-up of 5 years, equating to a 33% actual effect incorporating a 10% treatment drop out. The study has 80% power to detect a 26% RRR, equating to a 28% RRR due to the treatment after accounting for 10% treatment dropout.

The sample size calculations were performed using the log-rank test and assume an annual combined rate of 40% decline in eGFR or ESKD of 12% in the placebo arm. The study was designed to continue until at least 335 primary endpoints had been observed.

3.5 Premature termination of the study

The study protocol specifies that the study could be closed at any time at the request of the study steering committee, the Investigator, or a regulatory authority, with proper and timely notification of all parties concerned. The Independent Ethics Committee will be informed and the Coordinating Centre or the investigator will supply reason(s) for the termination or suspension, as specified by the applicable regulatory requirements.

3.6 Outcome

3.6.1 Primary outcome

The primary, protocol-specified outcome is progressive kidney failure which is a composite of a persistent 40% decline in estimated glomerular filtration rate (eGFR), the development of end stage kidney disease (ESKD) as defined as a need for maintenance dialysis or kidney transplantation, and death due to kidney disease.

1) Persistent ≥ 40% reduction in eGFR

The baseline eGFR is defined as the mean of the two eGFRs from Visit 3 (pre-randomisation visit) and Visit 4 (randomization 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" ≥ 40% eGFR reduction is established by the occurrence of 2 consecutive follow-p 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 until the final available study visit.

2) End stage kidney disease

ESKD 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 renal death where criteria for ESKD has not previously been met. ESKD 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 ESKD will be the presence of either symptomatic or advanced asymptomatic uremia defined using the following criteria:

(i) eGFR <15 mL/min/1.73 m^2 on 2 blood tests at least 30 days apart AND the presence of symptoms ascribed to uraemia
(i) eGFR <8 mL/min/1.73 m^2 on two blood tests at least 30 days apart which may be with or without the presence of symptoms ascribed to uraemia

3) Renal death:

Patients with eGFR<15ml/min/1.73m^2 may die prior to initiating renal replacement therapy.

Such events will be classified as renal death when they satisfy the following 3 criteria

1. The patient with eGFR<15ml/min/1.73m^2 dies
   AND
2. The patient has refused RRT or dialysis is not available
   AND
3. The death cannot be attributed to a specific aetiology (e.g. CV death, Stroke, progression of cancer, violence)

The diagnosis of renal 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 RRT will be designated the cause of death.

3.6.2 Protocol-specified secondary outcomes

The protocol-specified secondary outcomes, which build on the protocol's objectives, are:

1. The composite of outcome of ESKD, persistent 40% decrease in eGFR and death due to any cause.
2. The composite outcome comprising ESKD, persistent 50% reduction in eGFR and death due to any cause.
3. The composite of outcome of ESKD and renal death
4. The individual components of the composite, i.e. persistent 40% decrease in eGFR, persistent 50% decrease in eGFR, ESKD, renal death and all cause death
5. Change in eGFR, considered using the following:
   - Rate of eGFR decline (ml/min/1.73m^2 per year)

     -Defined for each individual patient using the slope from least squares linear regression of all eGFR estimates over time
   - Rate of eGFR decline (ml/min/1.73m^2 per year) defined as above, but excluding the treatment period with highest steroid exposure (i.e. excluding eGFR values from month 1 (visit 5) and month 3 (visit 6).
   - Trajectory of eGFR over time using all available eGFR estimates, as outlined in section 5.2.1
6. Time average proteinuria, calculated as follows:
   - For each patient, the proteinuria measurements will be from visits V4, V6, V7, V9, V13, and then yearly thereafter during follow-up
   - Time average proteinuria for each patient will be the mean of (3*V4 + 3*V6 + 6*V7)/12, V9, V13, and each yearly measurement thereafter

7. Safety outcomes including:
   - All serious adverse events

     Definition: SAEs are reported by investigators using the following guidance: SAEs are defined as any untoward medical occurrence that meets one of more of the following criteria:
     - Results in death
     - Is life-threatening
     - Requires inpatient hospitalisation or prolongation of existing hospitalisation
     - Results in persistent or significant disability/incapacity
     - Is a congenital anomaly/birth defect
   - Serious infections requiring hospitalization
   - New onset diabetes mellitus
   - Clinically apparent gastrointestinal haemorrhage requiring hospitalization.

- Clinically evident fracture or osteonecrosis
- Pregnancy
- Cardiovascular events, defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalization or death due to cardiovascular disease**.**

3.6.3 Exploratory secondary outcomes

1. The composite outcome comprising ESKD, persistent 25% reduction in eGFR and death from any cause.

Definition of persistent 25% reduction in eGFR: a reduction to less than 25% of baseline eGFR that stays below this level on all subsequent eGFR measurements during follow-up

2. Individual component of persistent 25% decreased in eGFR
3. Proportion of patients in complete proteinuria remission (definition as 3.6.2 #6) AND stable renal function (eGFR loss of < 5 ml/min/1.73m^2 from baseline eGFR) evaluated at the following time points: 6, 12 and 24 months, and at the end of follow-up
4. 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

5. Disappearance microhaematuria –

   Defined as urine analysis of RBC < 5phf at the end of the study/ last available visit for those participants with micro or macrohaematuria at randomization visit.

6. Change in proteinuria, considered using the following:
   - Trajectory of proteinuria over time using all available proteinuria estimates, as outlined in section 5.2.3 #6
   - Achieving complete proteinuria remission (CR), partial proteinuria remission (PR) and total proteinuria remission (TR) (i.e. complete and partial remission combined), defined as follows:

     Complete proteinuria remission (CR) is defined as 24 hour urinary protein <200mg/day.

     Partial proteinuria remission (PR) is defined as proteinuria less than 50% of baseline by 24 hour urinary protein, AND <1gm/day.

   - Achieving proteinuria remission will be considered as follows (see section 5.2.3 #6 for more details)

   a) Time to achieving persistent CR, PR and total remission, with “persistent” defined as maintaining the CR or PR definition on all subsequent measurements of proteinuria until the end of follow-up
   b) Proportion of patients in proteinuria remission (CR, PR and TR) evaluated at the following time points: 6, 12 and 24 months, and at the end of follow-up. This considers only the proteinuria status at each given time point.

4. Analysis principles

4.1 General principles

Comparison will be made for all of the outcomes by comparing all those allocated to methylprednisolone versus all those allocated to the control arm on an intention to treat (ITT) basis. All randomized participants will be analysed in the group to which they were assigned regardless of protocol violations. Cox proportional hazards analysis and Kaplan-Meier plots will be used to compare time to events among the two groups. No adjustment will be made for multiple testing across the primary endpoints. However the outcomes are clearly categorized by degree of importance (primary, main secondary and exploratory secondary) and a limited number of subgroup analyses are pre-specified. All missing information will be treated as missing data without imputation. All statistical tests will be two-tailed and a 5% significance level maintained throughout the analyses. In case of borderline statistical significance for the primary endpoint (i.e. a p-value between 1.66% and 5%), results will be interpreted with caution. Heterogeneity across subgroups will be tested by adding an interaction term to the appropriate statistical model. Summaries of continuous variables which are normally distributed will be presented as means and standard deviations or medians and inter-quartiles for skewed data, while categorical variables will be presented as frequencies and percentages.

4.2. Blinding

The current statistical analysis plan has been developed by a group nominated by the TESTING Steering Committee which includes statisticians and clinical researchers with nephrology expertise. The group will not be unblinded until after the SAP has been fully signed off. The statistician(s) responsible for interim monitoring and liaising with the DSMB will not provide input to the SAP. The results will be unblinded to the rest of the team once the final statistical report has been completed.

4.3 Patient deposition

Flow of patients through the study will be displayed in a “CONSORT” diagram as in the appendix B. Numbers of patients who were registered, fulfilled eligibility criterion, together with reasons for exclusion, and number randomised by study centre will be summarised.

4.4. Patient follow up

A separate figure (Appendix C) will summarise the follow up method for randomized patients indicating the numbers of patients who withdrew consent (with follow up) and those true loss to follow up.

4.5 Characteristics of patients and baseline comparisons

Description of the following baseline characteristics will be presented by treatment group. Discrete variables will be summarized 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. In some instances, additional frequencies and percentage of patients in each category will be reported as indicated in the list below. Continuous variables will be summarized by use of standard measures of central tendency and dispersion using mean and standard deviation and/or quantile points at 0.25, 0.5 and 0.75 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 if appropriate at the discretion of the Study Director.

- Age
- Sex
- Ethnicity
    - Caucasian
    - Chinese
    - South-East Asian
- 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
- Medication
    - ACE/ARB
    - Proportion achieved maximum labelled dose of ACE/ ARB
    - Concomitant medications

4.6 Physical characteristics

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

4.7 Kidney biopsy parameter based on Oxford Classification for IgA nephropathy

- Mesangial hypercellularity
- Segmental glomerulosclerosis
- Endocapillary hypercellularity
- Tubular atrophy/ interstitial fibrosis
- Percentage of glomeruli with crescents in the kidney biopsy

4.8 Laboratory Results

Continuous variables will be summarized 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 (screening, randomization, 3, 6, 12 and 24 months) and by treatment group. To assess the treatment effect on laboratory

variables, a linear mixed effects model with a random intercept, with treatment and time (categorical) as fixed effects will be used. Whenever appropriate, a fully unstructured covariance model will be used at indicated time points at baseline, 3, 6, 12 and 24 months of follow-up.

4.8.1 Laboratory measures

- Haemoglobin
- Total white blood cell count
- Platelet count
- Lymphocytes
- Sodium
- Potassium
- Chloride
- Fasting blood sugar
- Reported Calcium
- Phosphate
- Uric acid
- Bicarbonate
- Urea
- Creatinine
- eGFR (CKD-Epi)
- Total protein
- Albumin
- Total bilirubin
- Alanine aminotransferase
- Alkaline phosphatase
- C-reactive protein
- Parathyroid Hormone
- Total cholesterol

4.8.2 Urinary Measures

- Urinary analysis
  - Red blood cell per HPF
  - White blood cells per HPF
- 24 hours urine protein* (g/24-hour)
- 24 hours urine creatinine§ (mmol/24-hour)

*Twenty-four hour urinary collections are considered incomplete if collections had 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.

5. Specific Analysis Methods

5.1 Primary outcomes

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. The primary outcome is time from randomization to the first instance of a 40% decline in eGFR, ESKD or death due to renal disease, censored at the date when patients died (for causes other than

renal disease), were lost to follow up, withdrew from study, or at the end of study visit, whichever occurred first.

Sensitivity analysis:
A sensitivity analysis will be done including or excluding patients who reached the primary endpoint but the endpoint is not confirmed yet (e.g. Patient commenced on dialysis but has not reached 30 days of confirmation, at the time of analysis)

Sub-group analysis:
The following protocol-specified subgroups will be performed for the primary endpoint for stratified analysis:

1. Degree of proteinuria (<3.0g/day, ≥3.0g/day) at baseline
2. eGFR <50 versus ≥50ml/min per 1.73m^2) at baseline
3. Histological lesion scoring (E1 or E0)

The following additional subgroup analysis will also be performed for the primary endpoint:

4. Baseline maximum tolerated dose of ACE or ARB (>80%, 50-79% and <50% achieved of maximum labelled dose)

Heterogeneity across subgroups will be tested by adding an interaction term to the appropriate statistical model.

5.2 Secondary outcomes

Time to secondary outcome events will be analysed similarly to the primary outcome analysis.

5.2.1 Change in eGFR:
The rate of eGFR decline (ml/min/1.73m^2 per year) for each patient will be acquired 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 compared between the two treatment groups using a t-test. A sensitivity analysis will be performed using the same methodology, but excluding eGFR values at the time of high-dose treatment exposure (i.e. excluding values from month 1 and month 3, or visits 5 and 6 respectively).

The trajectory of eGFR over time will be presented by graphing the mean value of eGFR for the two randomized groups (instead of individual patients) at each time point (i.e. randomization, 3, 6, 12 and 24 months), and will be modelled using mixed models (with visual inspection to confirm an assumption of linearity) The difference of average eGFR over time will be shown in the graph using linear mixed model with assumption of exchangeable correlation among visits. Autoregressive structure will be used in the mixed model as sensitivity analysis.

The trajectory of eGFR over time will be visually presented by plotting the mean eGFR at each time point in the different treatment groups, and will be modelled using mixed models with time and treatment groups as fixed effects. Random effects will be assumed to be normally distributed and independent of each other. The model will assume a linear rate of

GFR decline within each patient, this will be confirmed using the visual plot and alternative modelling strategies accounting for non-linear functional forms will be adopted if needed.

5.2.2Time average proteinuria:

The distribution of proteinuria will be examined and whenever appropriate a log transformation may be applied. The mean time average proteinuria for each treatment group will be compared using a t-test.

5.3 Exploration secondary outcomes

1. The composite outcome comprising ESKD, persistent 25% reduction in eGFR and death from any cause.
2. Individual component of persistent 25% decreased in eGFR

1 & 2. Will be analyzed as described in 5.2.

3. Proportion of patients in complete proteinuria remission (definition as 3.6.3 #6) AND stable renal function (eGFR loss of < 5 ml/min/1.73m^2 from baseline eGFR) evaluated at the following time points: 6, 12 and 24 months, and at the end of follow-up

Due to differential follow-up times, the number of patients evaluated at each time point will be clearly indicated

4. Mean annual change of 1/creatinine concentration

   Defined by the mean slopes resulting from regression of time to the reciprocal of the serum creatinine concentration at baseline, 6, 12 and 24 months.

The relation between time and 1/Creatinine concentration will be individually described by a linear regression line using method described above for rate of eGFR decline. In case of more than two missing observations per individual a slope of 0 (e.g. no annual change) will be assumed.

5. Disappearance of microhaematuria

A logistic regression model will be fitted to the data of the rates involving treatment. In the case of a missing observation at the final study visit, this will be handled as a treatment failure.

6. The change in proteinuria

The 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. Cox proportional hazards models will be used to generate a HR to compare the two groups. When analysing time to proteinuria remission, the outcome will consider persistent proteinuria remission as defined in 3.6.3 #6.

The proportion of patients achieving CR, PR and TR at the following fixed time points will be evaluated and compared across the treatment groups: 6, 12, and 24 months, and at the end of follow-up. The number of patients evaluated at each time point will be clearly indicated. When analysing proteinuria remission (with definitions in 3.6.3 #6) at specific time points,

the outcome will consider the proteinuria remission status only at the appropriate time point

5.4 SAE outcomes

SAE event rates will be compared as 3.6.2 point #7. Summary of each safety endpoints will be provided. Continuous outcome will be summarised by their mean (SD) or median (IQR) as appropriate, while binary outcome will be summarised by n and percentages. In addition a listing of SAEs will be presented according to randomisation group, which will include the time from randomization, the current treatment dose, and cumulative dose of study drug at the time of the SAE.

Survival outcome will be summarised by proportion of events by group and their median times will be reported. The intervention effect on each SAE will be assessed in relation to the study drug based on cumulative dose and/or dose exposed at the time of SAE occurrence, and the time from randomization to the SAE occurrence.

Further analyses: Further analyses for the cohort phase of the study will be subject to a separate report when data are available.

Appendices

Appendix A. CKD-EPI formula

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

where:

S_{cr} is serum creatinine in mg/dL,

κ is 0.7 for females and 0.9 for males,

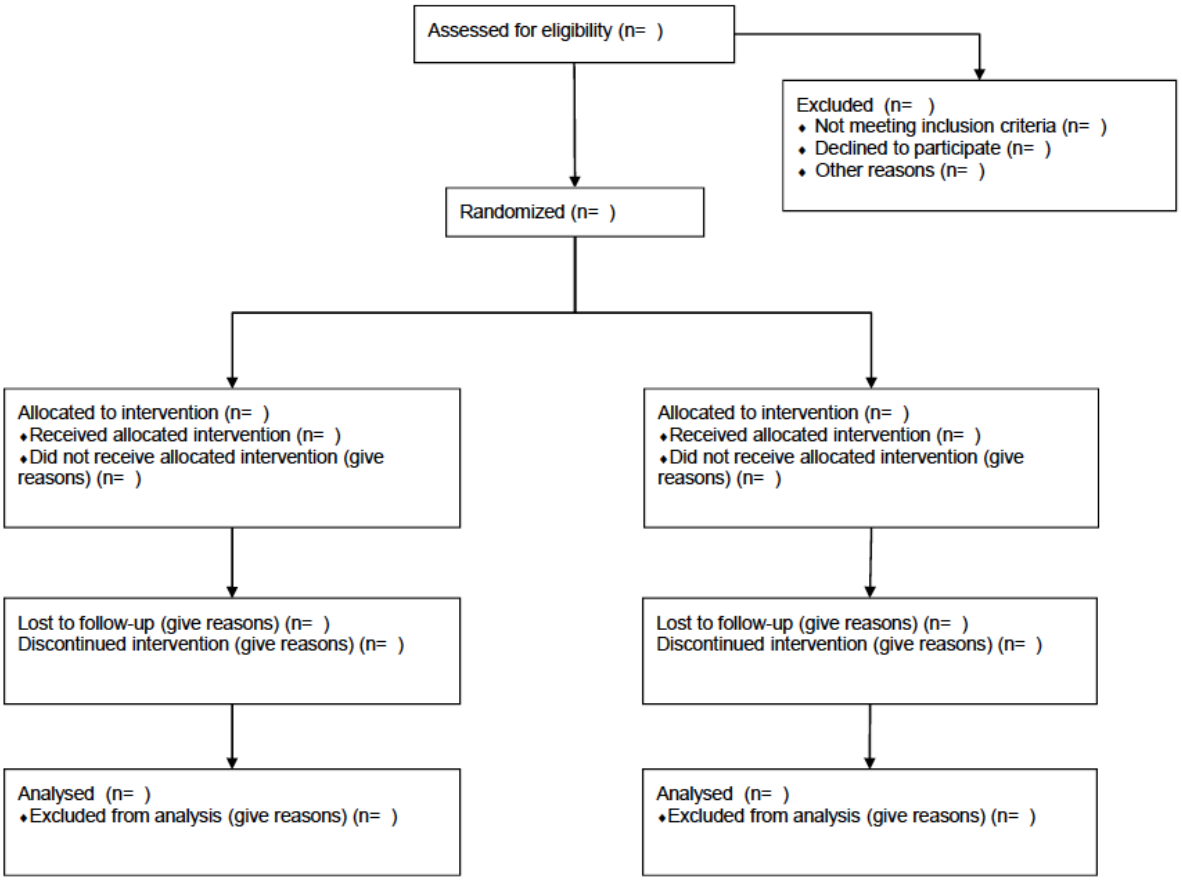
α is -0.329 for females and -0.411 for males,

min indicates the minimum of S_{cr}/κ or 1, and

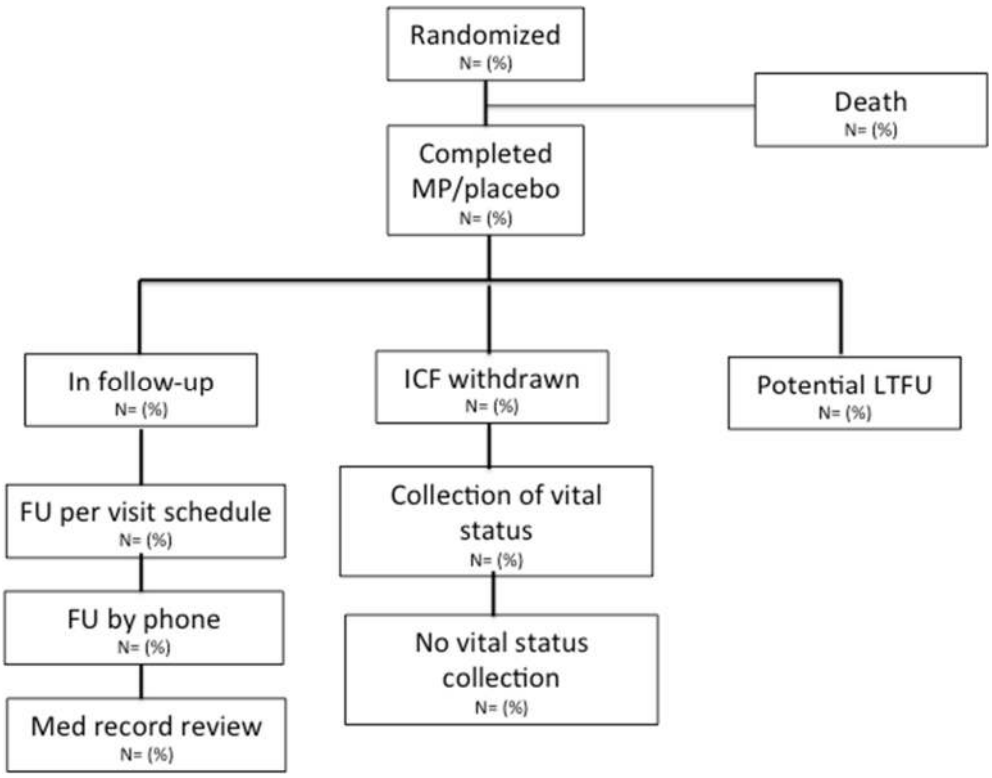
max indicates the maximum of S_{cr}/κ or 1.

Appendix B. Patient deposition

(Sample to be redrawn: Patient deposition (Enrolment, randomization and follow up)



Appendix C. Method of follow-up for randomized patients



Appendix D. Sample figures and tables.

See separate attachment.

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.

TESTING
Therapeutic Evaluation of Steroids in IgA Nephropathy Global Study

Statistical Analysis Plan

Version: 1.0 (Final)
Date: 21 July 2021

Authors:

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Muh Geot Wong, The George Institute, UNSW Sydney

Vlado Perkovic, UNSW Sydney

On behalf of the TESTING steering committee

Study identifiers:
Protocol Number: GI-R-01-2011

The George Institute for Global Health Australia

Contents

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.

Laurent Billot

<signature> <date>

Helen Monaghan

<signature> <date>

Muh Geot Wong

<signature> <date>

Vlado Perkovic

<signature> <date>

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): ≥1.0g/day while receiving the maximum tolerated dose of RAS blockade
   - ≥1.0g/day on most recent available lab tests on Visit 1
   - ≥1.0g/day while receiving the maximum tolerated dose of RAS blockade on Visit 3
3) eGFR (on most recent test): 20 to 120mL/min per 1.73m^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 eGFR >120 mL/min per 1.73m^2 at screening stage, while reaching less than 120 mL/min per 1.73m^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 (α=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 CONSORT[1] (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" $\geqslant$ 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 m^2 on 2 blood tests at least 30 days apart and the presence of symptoms ascribed to uraemia
- eGFR <8 mL/min/1.73 m^2 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<15mL/min/1.73m^2 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<15mL/min/1.73m^2 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 ≥50mL/min per 1.73m^2),
4) Baseline histological lesion scoring (E1 vs E0)

5) Race (Chinese vs non-Chinese)
6) Age (<50 vs ≥50 years)
7) Time between biospsy 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/1.73m^2 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 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 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 < 5phf 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 <200mg/day.
   ii) *Partial proteinuria remission* (PR) is defined as proteinuria less than 50% of baseline by 24-hour urinary protein, AND <1gm/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 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
- Total white blood cell count
- Platelet count
- Lymphocytes
- Sodium
- Potassium

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

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

1. Lv J, Xu D, Perkovic V, et al; TESTING Study Group. Corticosteroid therapy in IgA nephropathy. J Am Soc Nephrol. 2012;23(6):1108-1116.

2. Lv J, Zhang H, Wong MG, et al. Effect of Oral Methylprednisolone on Clinical Outcomes in Patients With IgA Nephropathy: The TESTING Randomized Clinical Trial. JAMA. 2017;318(5):432–442. doi:10.1001/jama.2017.9362

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Appendix 1: Concurrent Medications Class and Subclass Categories

Class/ Subclass
Other Antihypertensive Agents *
Calcium channel blocker - dihydropyridine
Diuretic
Aldosterone antagonist
Calcium channel blocker - non-dihydropyridine
Beta blocker
Centrally acting
Beta and alpha blocker
Alpha blocker
Others
Lipid Lowering
Statins
Fibrates
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

Class/ Subclass
Inhaler steroid
Insulin
Pain killer
Anti-vertigo drug
Anticoagulant
Anticonvulsant
Antidepressant
Beta blocker
Immunosuppressant
Migraine drug
Prostacyclin analogue
Sleeping tablets
SGLT2 inhibitors
Others

Appendix 2: CKD-EPI formula

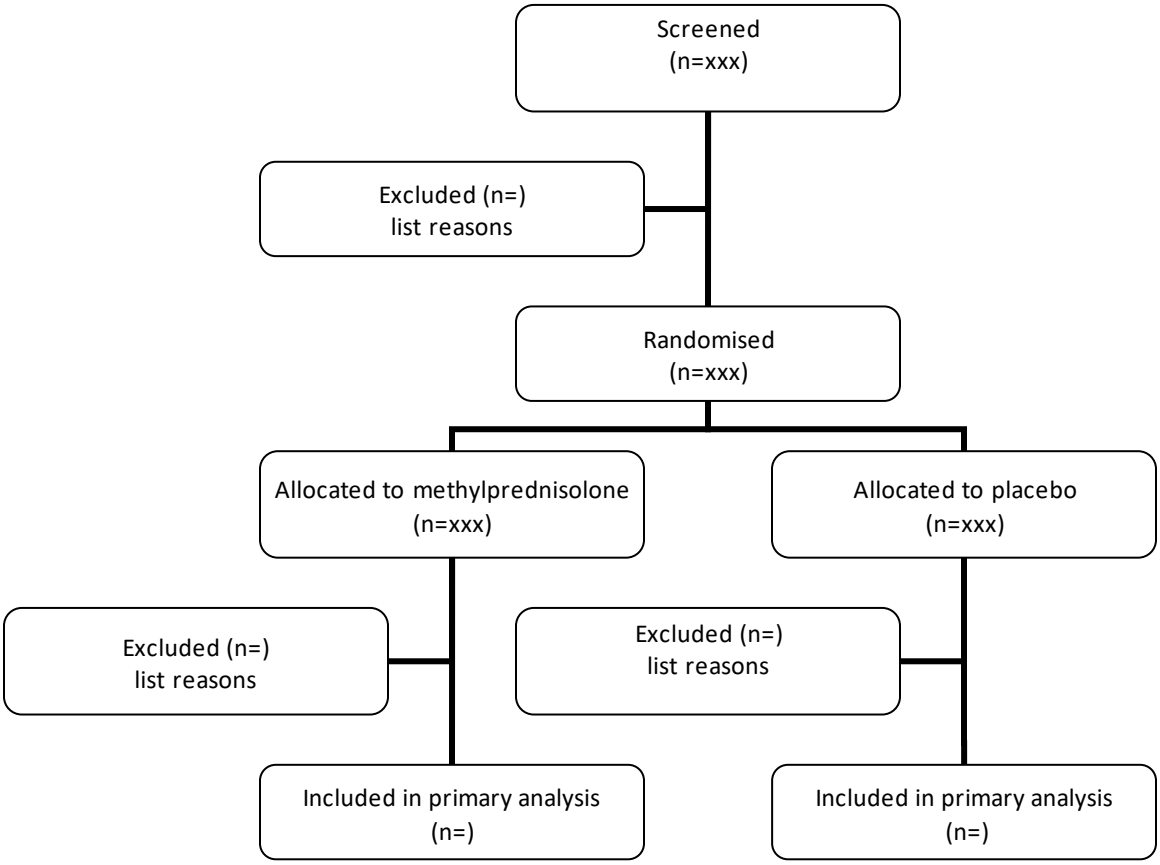
$GFR = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] × 1.159 [if black]

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



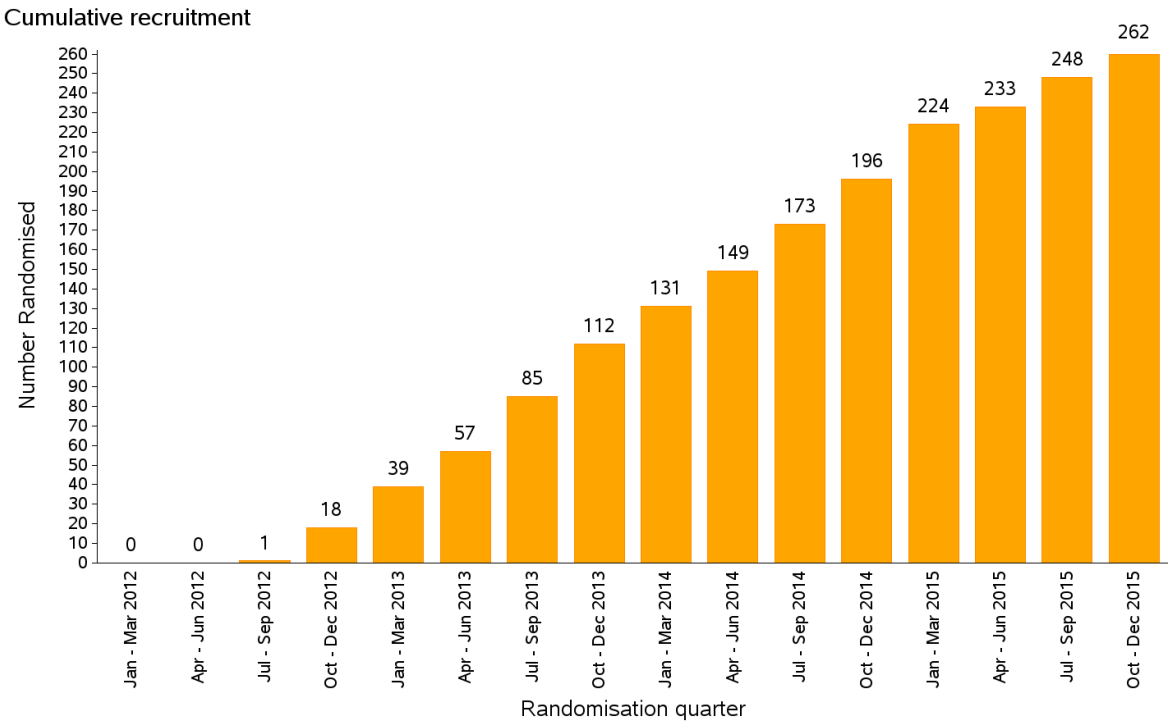
Programming note: do overall and by dose cohort

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 JaÃ¡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



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 - <1/4th	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
C2 - >1/4th	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
	Methylpredni-solone (N = xxx)	Placebo (N = xxx)	Methylpredni-solone (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%)

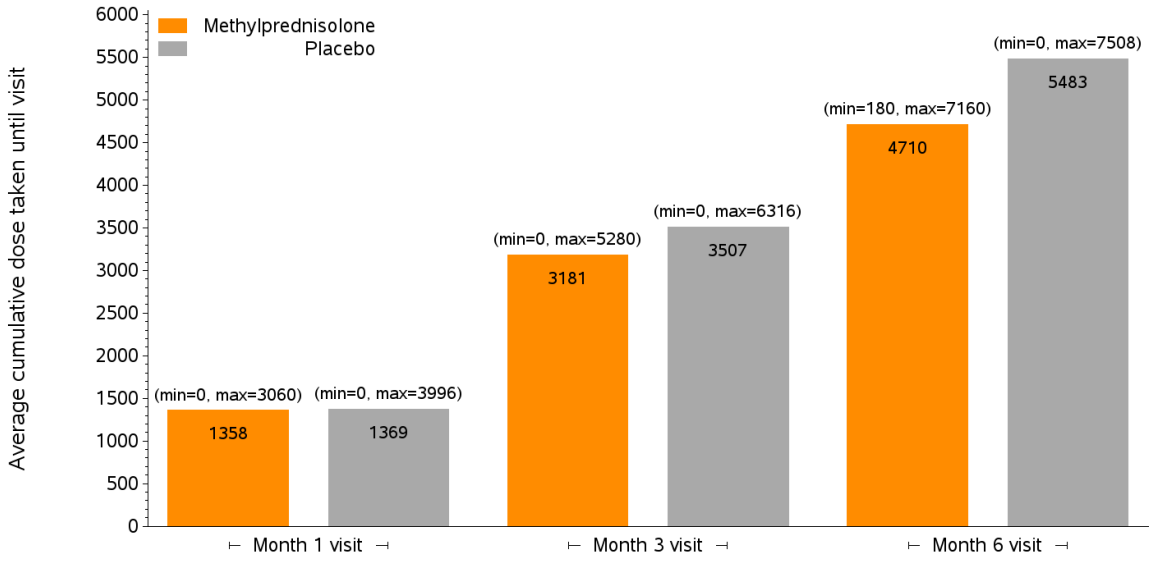
Note: the number of randomised patients is used to compute percentages.

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				
Average daily dose (mg)	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
Compliance (%)	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				
Average daily dose (mg)	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
Compliance (%)	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				
Average daily dose (mg)	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
Compliance (%)	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				
Average daily dose (mg)	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
Compliance (%)	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 ARB 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 occuring 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%)

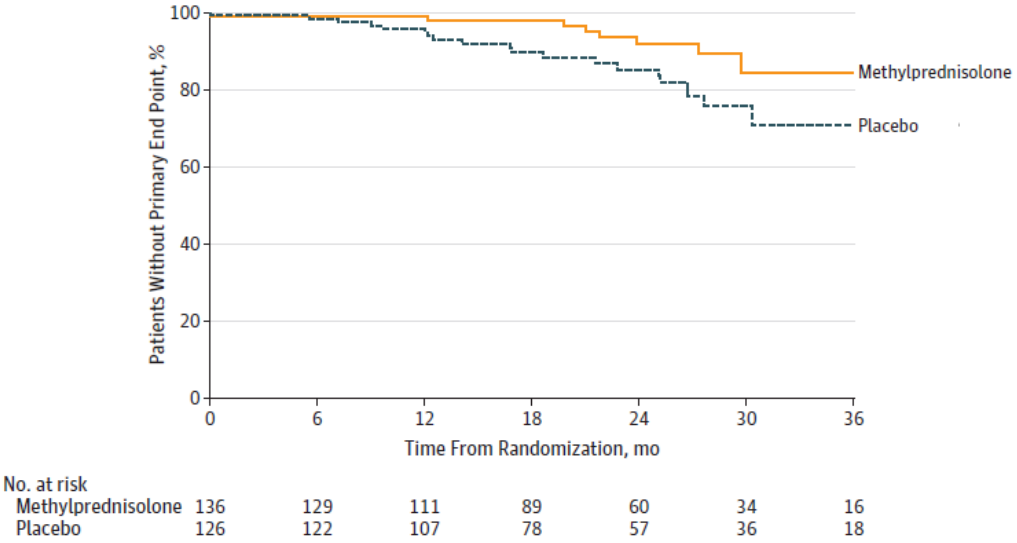
** Death due to kidney disease, kidney failure or eGFR reduction*
*** Death due to any cause, kidney failure or eGFR reduction*

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

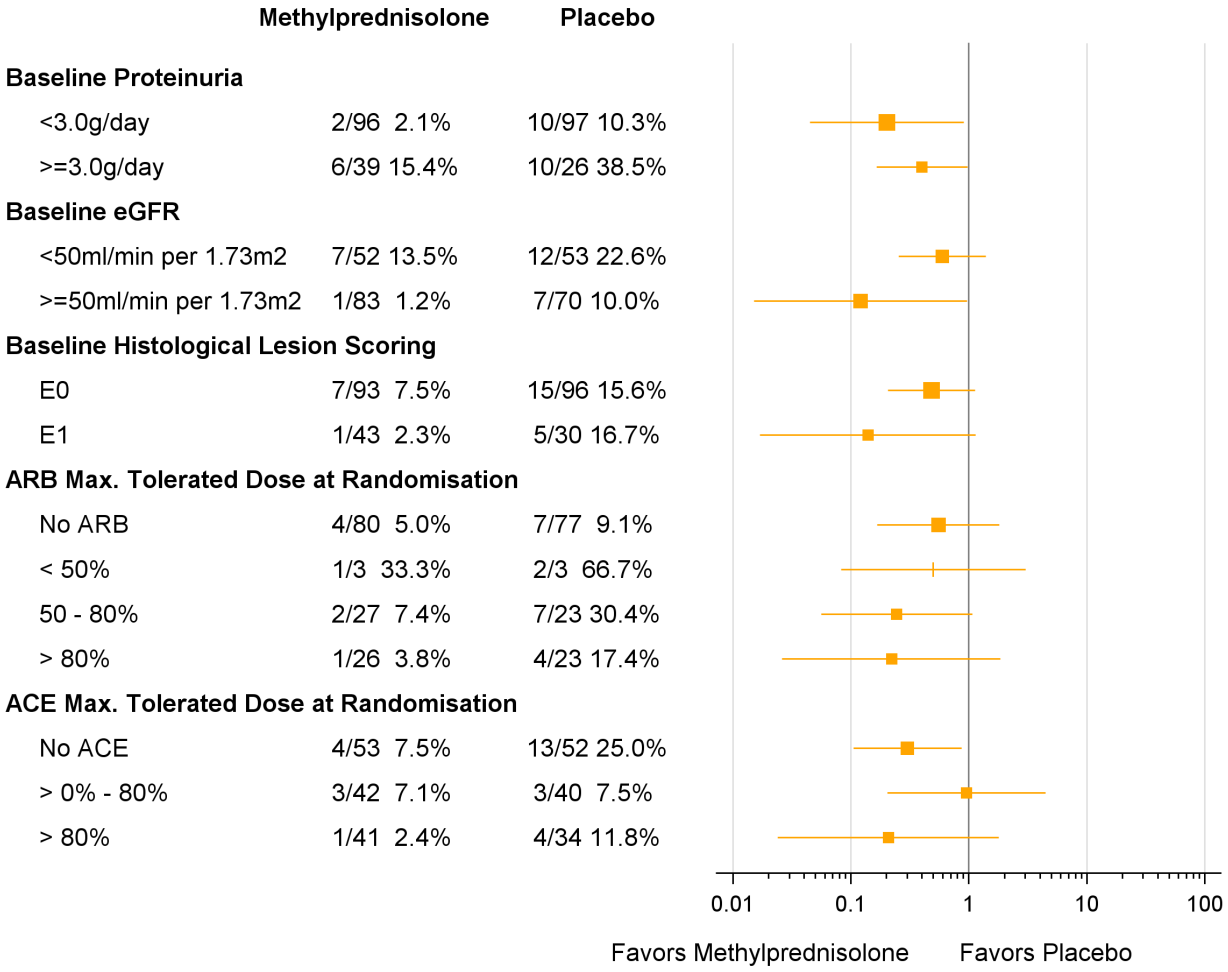
Figure 10: Kaplan Meier analysis of time to death due to any cause

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

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

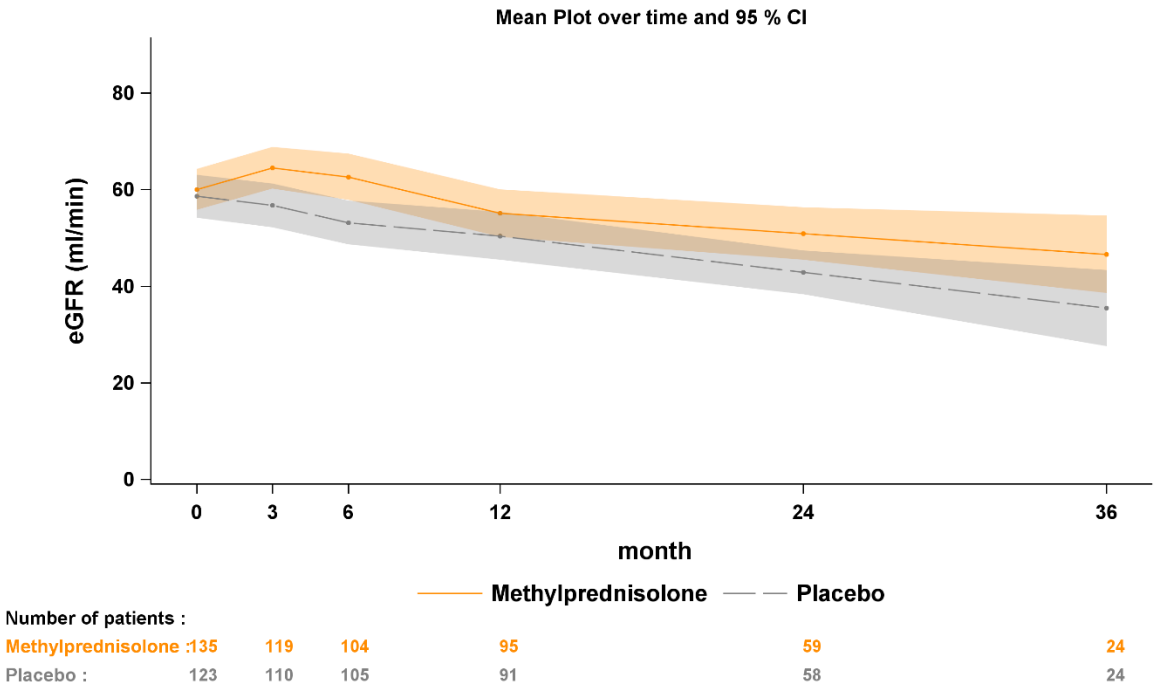
Figure 13: Kaplan Meier analysis of time to 50% eGFR reduction

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



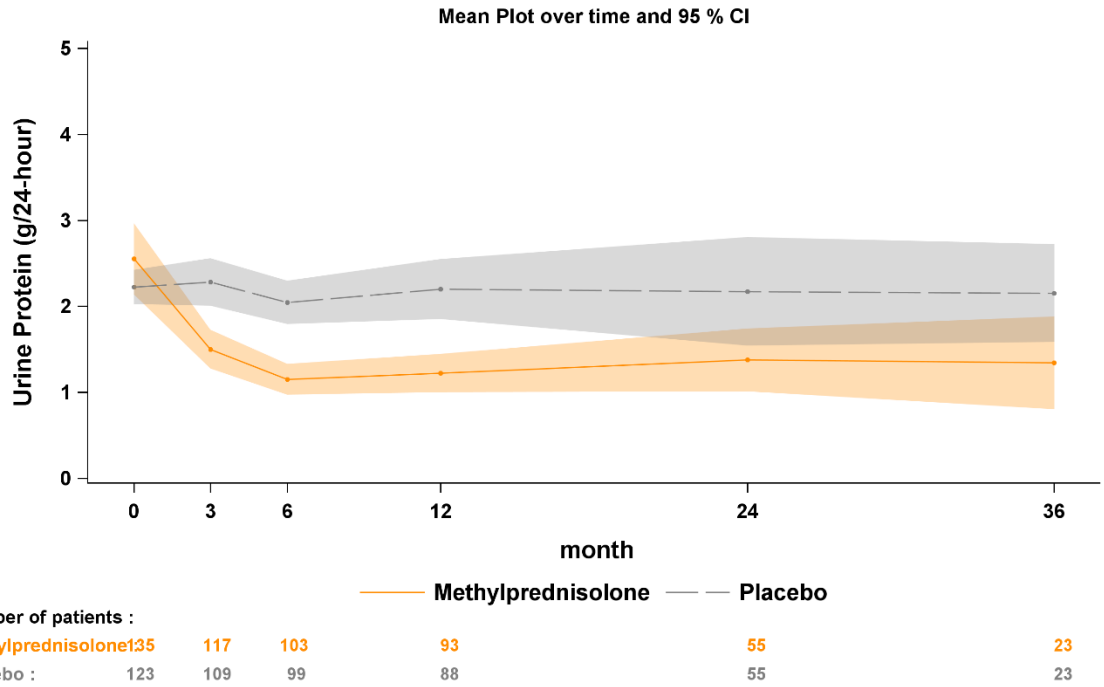
	Methylprednisolone					Placebo				
Month	N	Mean	SD	95% CI		N	Mean	SD	95% CI	
0	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
3	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
6	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx	xx.xx
12	xxx	xx.xx	xx.xx	xx.xx	xx.xx	xxx	xx.xx	xx.xx	xx.xx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



	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 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 < 5mL/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 < 5phf for those participants with micro or macrohaematuria at randomisation visit.
Macrohaematuria has been defined as urine analysis of RBC >= 5phf.
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.

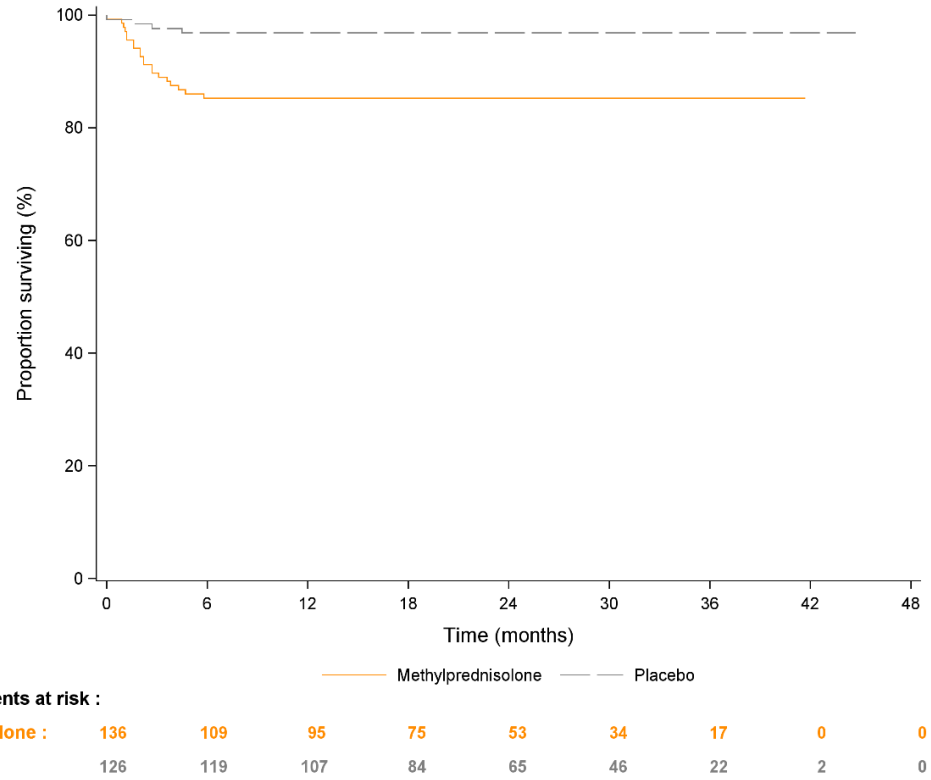
Table 20: Adverse Events during Treatment Period

	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

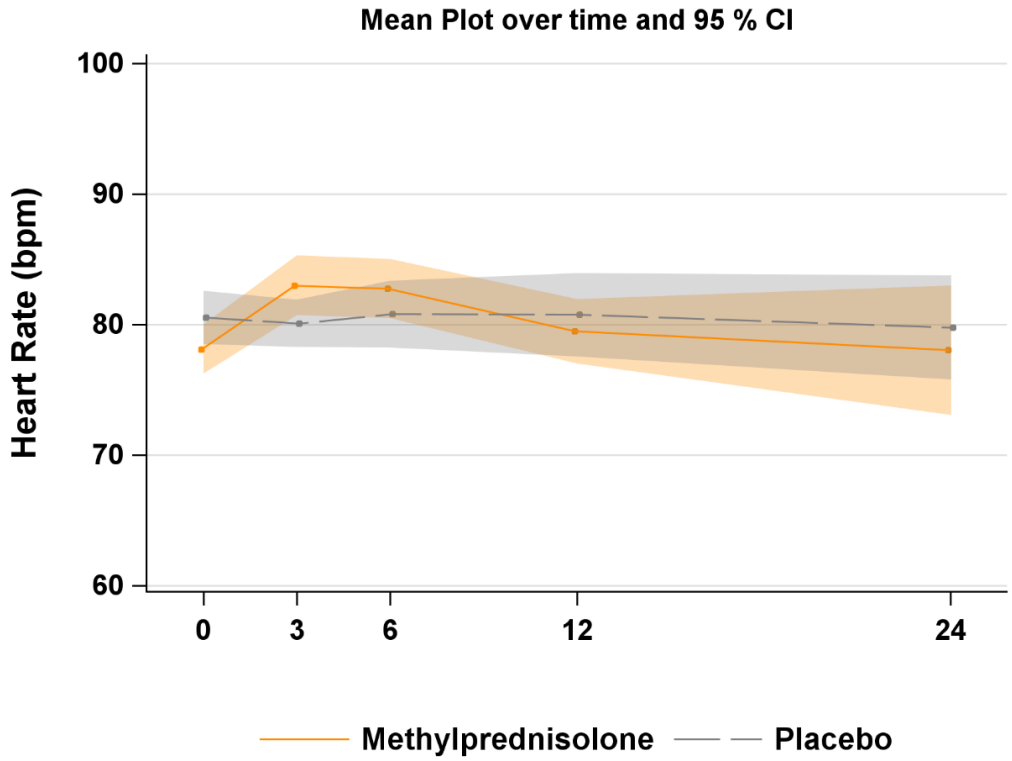
Figure 17: Kaplan-Meier plot of time to first SAE



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)			
Screening			
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
Baseline			
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
Month 3			
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
Month 6			
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
Month 12			
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
Month 24			
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