Supplementary Online Content 1


Study Protocol
CLINICAL TRIAL PROTOCOL

TESTING Study

Therapeutic Evaluation of STeroids in IgA Nephropathy Global study

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Version Number: 5.0

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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”

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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).

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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  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- Therapeutic Evaluation of STeroids in IgA Nephropathy Glocal 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 1.73m²(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 (nodos, 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 ($\alpha=0.05$) to detect a 30% risk reduction with methylprednisolone, after an expected average follow-up of 5.5 years.
### Inclusion criteria

- Biopsy proven IgA nephropathy
- Proteinuria: >=1.0g/day
- eGFR: 20 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 in a renal biopsy within the last 12 months.
- Contraindication to immunosuppressive therapy with corticosteroids, including 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).
- 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.
- Malignancy within the last 5 years, excluding non-melanoma skin cancers.
- Active infection, including HBV infection, clinical evidence of latent or active tuberculosis (including cavities or tuberculoma)
- Malignancy within the last 5 years, excluding non-melanoma skin cancers.
- Minimal change renal disease with IgA deposits.
- Malignant/uncontrolled hypertension (>160/110mmHg).
- Patients who are unlikely to comply with the study protocol in the view of the treating physician.

### Study population

#### Methylprednisolone 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.

All the patients will also receive optimal blood pressure control and full dose of ACE inhibitors or ARBs as recommended by guidelines throughout the trial.

#### Placebo Group

### Study duration

- **Enrolment:** More than two years
- **Follow-up:** 4 to 6 yrs (average 5.5 yrs)
- **Interim analysis:** One third and two thirds of endpoint events have occurred

### Endpoint

- **Primary endpoint:** Composite of eGFR reduction by 40% or ESKD or death due to kidney disease
- **Secondary endpoint:**
  - The composite of ESKD, eGFR reduction by 40% and all cause death
  - Composite of eGFR reduction by 50% or ESKD or death due to kidney disease
  - Each of ESKD and renal death

### Overview of study design

Note: SCr: serum creatinine; ESKD: end stage of kidney disease;
2. Background & Rationale

2.1 Epidemiology
Immunoglobulin a (IgA) nephropathy is an immune-complex mediated glomerulonephritis defined immuno-histologically 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

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

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<td>34.5</td>
<td></td>
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</tr>
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<td>Italy</td>
<td>Schena FP (1997)</td>
<td>National Registry of Renal Biopsies (13835)</td>
<td>36.9</td>
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<td></td>
<td>Stratta P 1996</td>
<td>Population based survey</td>
<td></td>
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<tr>
<td>Spain</td>
<td>Rivera F (2002)</td>
<td>National Registry of Renal Biopsies (7016)</td>
<td></td>
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<tr>
<td>UK</td>
<td>Hanko J (2009)</td>
<td>Regional biopsy registry (1844)</td>
<td></td>
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<td>Americas</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>USA</td>
<td>Nair R (2006)</td>
<td>Nephropathology Associates from 24 states (4504)</td>
<td></td>
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<td>22</td>
</tr>
<tr>
<td>Brazil</td>
<td>M. G. Polito (2010)</td>
<td>National biopsy data</td>
<td>20.1</td>
<td></td>
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</tr>
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</table>
### Table 2: Clinical and Histological Prognostic Factors in IgA Nephropathy

<table>
<thead>
<tr>
<th>Clinical§</th>
<th>Histological¶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Strong predictors</strong>*</td>
<td><strong>Mesangial hypercellularity</strong></td>
</tr>
<tr>
<td>Elevated serum creatinine or reduced eGFR level</td>
<td>Segmental</td>
</tr>
<tr>
<td>Severe proteinuria</td>
<td>Glomerulosclerosis</td>
</tr>
<tr>
<td>Higher BP levels</td>
<td>Endocapillary hypercellularity</td>
</tr>
<tr>
<td>Tubular atrophy/interstitial fibrosis</td>
<td></td>
</tr>
</tbody>
</table>

| **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 autoantigen/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 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 (Methylprednisolone1g × 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 and 1999, 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 subjects 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 (p=0.032, Figure 4).

### Subgroup Analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Events/patients</th>
<th>Risk ratio (95% CI)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroids</td>
<td>control</td>
<td></td>
</tr>
<tr>
<td>Katafuchi 2003</td>
<td>3/33</td>
<td>1.09 (0.23, 5.13)</td>
<td></td>
</tr>
<tr>
<td>Julian 1993</td>
<td>1/18</td>
<td>0.31 (0.04, 2.74)</td>
<td></td>
</tr>
<tr>
<td>Pozzi 2004</td>
<td>1/33</td>
<td>0.08 (0.01, 0.56)</td>
<td></td>
</tr>
<tr>
<td>Lv 2009</td>
<td>0/33</td>
<td>0.18 (0.01, 0.65)</td>
<td></td>
</tr>
<tr>
<td>Manno 2009</td>
<td>2/38</td>
<td>0.15 (0.04, 0.65)</td>
<td></td>
</tr>
<tr>
<td>Lai 1986</td>
<td>0/10</td>
<td>(Excluded)</td>
<td></td>
</tr>
<tr>
<td>Shoji 2000</td>
<td>0/11</td>
<td>(Excluded)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall (95% CI)</strong></td>
<td><strong>7/213</strong></td>
<td><strong>0/11</strong></td>
<td><strong>0.26 (0.10, 0.70), p=0.008</strong></td>
</tr>
</tbody>
</table>

- **Doubling of serum creatinine or ESKD**
- **ESKD**

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 1.73m². 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>No. Patients</th>
<th>Steroids group</th>
<th>Control</th>
<th>Follow-up (Mon)</th>
<th>Event number (rate, per year)</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lai 1986</td>
<td>IgA nephropathy with nephrotic syndrome</td>
<td>34 (17/17)</td>
<td>Pred 40-60mg/d</td>
<td>No treatment</td>
<td>38</td>
<td>0(-) 0(-) 0(-) 0(-)</td>
<td>Reduced proteinuria; No effect on the GFR</td>
</tr>
<tr>
<td>Julian 1993</td>
<td>CCr &gt;25ml/min per 1.73m</td>
<td>31 (18/17)</td>
<td>Pred 60mg/qod</td>
<td>No treatment</td>
<td>6-24</td>
<td>1(-) 2(-) 1(-) 2(-)</td>
<td>No effect on change of Proteinuria; A trend to preserve renal function (defined by 1/Scr, p=0.06)</td>
</tr>
<tr>
<td>Shoji 2000</td>
<td>Proteinuria &lt;1.5g/d Scr&lt;1.5mg/dl</td>
<td>19 (11/8)</td>
<td>Pred 0.8mg/kg/d</td>
<td>Dipyridamole 300mg/d</td>
<td>12</td>
<td>0(-) 0(-) 0(-) 0(-)</td>
<td>Reduced Proteinuria; No effect on the GFR</td>
</tr>
<tr>
<td>Katafuchi 2003</td>
<td>Scr&lt;1.5mg/dl</td>
<td>90(43/47)</td>
<td>Pred 20mg/d</td>
<td>Dipyridamole 150-300mg/d</td>
<td>65</td>
<td>3 (1.3%) 3 (1.2%) 3 (1.3%) 3 (1.2%)</td>
<td>Reduced proteinuria; No effect on the renal survival (defined as ESKD)</td>
</tr>
<tr>
<td>Pozzi 2004</td>
<td>Proteinuria &lt;1.5g/d day</td>
<td>88 (43/43)</td>
<td>MP 1g = 3days; then 0.5mg/kg/day</td>
<td>Supportive</td>
<td>82</td>
<td>1 (0.3%) 13 (4.3%) 1 (0.3%) 5 (1.7%)</td>
<td>Reduced Proteinuria; Improve renal survival (defined as doubling of Scr)</td>
</tr>
<tr>
<td>Hogg* 2006</td>
<td>Proteinuria (UP/C) &gt;1.0 or &gt;0.5 with renal lesions at risk; GFR&gt;50</td>
<td>64 (33/31)</td>
<td>Pred 60mg qod</td>
<td>placebo</td>
<td>24</td>
<td>- - - -</td>
<td>No effect on the Proteinuria reduction or renal survival (defined as 60% decrease of GFR)</td>
</tr>
<tr>
<td>Lv JC 2009</td>
<td>Proteinuria 1.0-5g/day GFR&gt;30ml/min.1,73m²</td>
<td>63 (33/30)</td>
<td>Pred 0.8-1mg/kg/d</td>
<td>Cilazapril mean dosage 3.75mg/d</td>
<td>27.3</td>
<td>0 (-) 2 (3.0%) 0 (-) 2 (3.0%)</td>
<td>Reduced Proteinuria and improved renal survival (50% increase of Scr)</td>
</tr>
<tr>
<td>Manno 2009</td>
<td>Proteinuria&gt;1g/day GFR&gt;50ml/min.1,73m² Moderate renal lesions</td>
<td>97 (48/49)</td>
<td>Pred 1mg/kg/day</td>
<td>Ramipril mean dosage 7.5mg/d</td>
<td>60</td>
<td>2 (0.9%) 13 (5.7) 1 (0.4%) 7 (3.0%)</td>
<td>Reduced Proteinuria and improved renal survival (defined as doubling of Scr and or ESKD)</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Drug/Ingredient</th>
<th>Methylprednisolone/Medrol</th>
<th>Matching Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation</td>
<td>methylprednisolone/Medrol tablets 4mg/tablet</td>
<td>Tablets containing excipient, identical in appearance to methylprednisolone/Medrol but without the active ingredient</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Pfizer Pharmaceuticals</td>
<td>Pharmaceuticals</td>
</tr>
</tbody>
</table>

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**

- **Register**
  - V1
  - V2
  - V3
  - V4 (0m)
  - V5 (1m)
  - V6 (3m)
  - V7 (6m)
  - V9 (12m)
  - V13 (24m)-final (every 12 month)

**Randomization**

- Methylprednisolone/matching placebo 0.6-0.8mg/kg/d (maximal 48mg/d) X2 mon
  - Tapered 8mg/day every mon
  - Stopped at 6-8mon

- ACE inhibitors or ARBs to full dose*
  - blood pressure control as guidelines

- Placebo

**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.

---

*ACE inhibitors or ARBs to full dose*
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)

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug (trade name)</th>
<th>Dose range (mg/day)</th>
<th>Usual daily frequency</th>
<th>Maximum doses used in major trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benazepril (Lotensin)</td>
<td>20-40</td>
<td>1</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Captopril (Capoten)</td>
<td>25-100</td>
<td>2</td>
<td>100-150</td>
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<td></td>
<td>Enalapril (Vasotec)</td>
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<td>20-40</td>
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<tr>
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<td>Fosinopril (Monopril)</td>
<td>10-40</td>
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<tr>
<td></td>
<td>Lisinopril (Prinivil, Zestril)</td>
<td>10-40</td>
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<tr>
<td></td>
<td>Moexipril (Univasc)</td>
<td>7.5-30</td>
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<td></td>
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<tr>
<td></td>
<td>Perindopril (Aceon, Servier)</td>
<td>4-8 or 5-10</td>
<td>1</td>
<td>4</td>
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<tr>
<td></td>
<td>Quinapril (Accupril)</td>
<td>10-80</td>
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<tr>
<td></td>
<td>Ramipril (Altace)</td>
<td>2.5-20</td>
<td>1</td>
<td>10</td>
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<tr>
<td></td>
<td>Trandolapril (Mavik)</td>
<td>1-4</td>
<td>1</td>
<td>3</td>
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<tr>
<td><strong>ARBs</strong></td>
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<td></td>
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<td></td>
<td>Candesartan (Atacand)</td>
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<td>16</td>
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<td>Eprosartan (Teveten)</td>
<td>400-800</td>
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<td>Irbesartan (Avapro)</td>
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<td>Losartan (Cozaar)</td>
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<td>Olmesartan (Benicar)</td>
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<td>Telmisartan (Micardis)</td>
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<td>80</td>
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<td></td>
<td>Valsartan (Diovan)</td>
<td>80-320</td>
<td>1-2</td>
<td>160</td>
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</table>
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 1.73m² 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 1.73m² (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 1.73m² at screening stage while reaching less than 120 ml/min per 1.73m² 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

<table>
<thead>
<tr>
<th>Race/Sex</th>
<th>Serum creatinine (mg/dl)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Black (CKD-EPI formula)</strong></td>
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</tr>
<tr>
<td>Female ≤0.7</td>
<td>GFR=166× (Scr/0.7)^0.329×(0.993)^Age</td>
<td></td>
</tr>
<tr>
<td>Female &gt;0.7</td>
<td>GFR=166× (Scr/0.7)^-1.209×(0.993)^Age</td>
<td></td>
</tr>
<tr>
<td>Male ≤0.9</td>
<td>GFR=163× (Scr/0.9)^0.411×(0.993)^Age</td>
<td></td>
</tr>
<tr>
<td>Male &gt;0.9</td>
<td>GFR=163× (Scr/0.9)^-1.209×(0.993)^Age</td>
<td></td>
</tr>
<tr>
<td><strong>White or others CKD-EPI formula</strong></td>
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<td></td>
</tr>
<tr>
<td>Female ≤0.7</td>
<td>GFR=144× (Scr/0.7)^0.329×(0.993)^Age</td>
<td></td>
</tr>
<tr>
<td>Female &gt;0.7</td>
<td>GFR=144× (Scr/0.7)^-1.209×(0.993)^Age</td>
<td></td>
</tr>
<tr>
<td>Male ≤0.9</td>
<td>GFR=141× (Scr/0.9)^0.411×(0.993)^Age</td>
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</tr>
<tr>
<td>Male &gt;0.9</td>
<td>GFR=141× (Scr/0.9)^-1.209×(0.993)^Age</td>
<td></td>
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</tbody>
</table>

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.per1.73m² or ≥50ml/min. 1.73m²) 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>
<thead>
<tr>
<th>Time</th>
<th>Visit</th>
<th>Informed consent form</th>
<th>In/exclusion criteria</th>
<th>Med History/ Demography</th>
<th>Height (H)</th>
<th>Weight (W)</th>
<th>Vital signs</th>
<th>Physical Exam</th>
<th>Short physical exam</th>
<th>Screening log</th>
<th>Randomisation</th>
<th>Chest X-ray (CXR)</th>
<th>Urinary analysis</th>
<th>24-hour urine protein</th>
<th>24-hour urine sodium</th>
<th>HBV screening</th>
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Table 7. Schedule of Study Tests, Procedures and Clinic Visits
### Table 7. Schedule of Study Tests, Procedures and Clinic Visits

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#### Background therapy (ACE inhibitors or ARBs)

- **Phase 1**: Screening and run-in
  - Week 1: 12
  - Week 2: 21
  - Week 3: 24
  - Week 4: 27
  - Week 5: 30
  - Week 6: 33
  - Week 7: 36
  - Week 8: 39
  - Week 9: 42
  - Week 10: 45
  - Week 11: 48
  - Week 12: 51
  - Week 13: 54
  - Week 14: 57
  - Week 15: 60
  - Week 16: 63
  - Week 17: 66
  - Week 18: 69
  - Week 19: 72

- **Phase 2**: Study Drug Treatment

- **Phase 3**: Follow-up

#### Time

- **Visit 1**: 1
- **Visit 2**: 2
- **Visit 3**: 3
- **Visit 4**: 4
- **Visit 5**: 5
- **Visit 6**: 6
- **Visit 7**: 7
- **Visit 8**: 8
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- **Visit 21**: 21
- **Visit 22**: 22
- **Visit 23**: 23
- **Visit 24**: 24
- **Visit 25**: 25
- **Visit 26**: 26
- **Visit 27**: 27
- **Visit 28**: 28
- **Visit 29**: 29
- **EOTh**: 30

#### Tests and Procedures

- **Blood chemistry panel-2**: Hemoglobin, WBC, platelet count
- **HbA1C (if diabetic)**
- **Lipid profile**
- **Pathology scoring**
- **Study drug dispensation**
- **Study drug accountability**
- **Co-Med**
- **Adverse events**
- **Endpoints**
- **EQ-5D**
- **No food or drink** (except water for 8 hours)

#### Notes

- **a)** Urinary analysis: qualitative microscopic determination
- **b)** Hematological: hemoglobin, WBC, lymphocyte, platelet count
- **c)** Blood chemistry panel 1: Blood urea, creatinine, total bilirubin, SGPT, alkaline phosphatase, sodium, potassium, calcium, phosphorus, total protein, albumin, glucose and uric acid, total cholesterol
- **d)** Blood chemistry panel 2: Blood urea, creatinine, total bilirubin, SGPT, alkaline phosphatase, sodium, potassium, calcium, phosphorus, total protein, albumin, glucose and 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 to 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

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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 ±2 weeks; for V5-V8 ±2 weeks for annual on-site visits, ±2 months for phone visits.

l) Reduction of eGFR by 50% from the baseline value (pre-randomisation) if 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.

<table>
<thead>
<tr>
<th>Mild</th>
<th>discomfort noticed but no disruption of normal daily activity.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate</td>
<td>discomfort sufficient to reduce or affect daily activity.</td>
</tr>
<tr>
<td>Severe</td>
<td>inability to work or perform normal daily activity</td>
</tr>
</tbody>
</table>

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

10.1 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 (<3.0g/day, ≥3.0g/day), renal function (eGFR<50 versus ≥50ml/min per 1.73m²), histological lesion scoring (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 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.1.73m². 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 eGFR20-120ml/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: 20-120ml/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 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

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

*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

<table>
<thead>
<tr>
<th>Race/Sex</th>
<th>Serum creatinine (mg/dl)</th>
<th>Equation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Black (CKD-EPI formula)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female ≤0.7</td>
<td></td>
<td>( \text{GFR} = 166 \times (\text{Scr}/0.7)^{0.329 \times (0.993)^{\text{Age}}} )</td>
</tr>
<tr>
<td>Male ≤0.9</td>
<td></td>
<td>( \text{GFR} = 163 \times (\text{Scr}/0.9)^{0.411 \times (0.993)^{\text{Age}}} )</td>
</tr>
<tr>
<td>Female &gt;0.7</td>
<td></td>
<td>( \text{GFR} = 166 \times (\text{Scr}/0.7)^{1.209 \times (0.993)^{\text{Age}}} )</td>
</tr>
<tr>
<td>Male &gt;0.9</td>
<td></td>
<td>( \text{GFR} = 163 \times (\text{Scr}/0.9)^{1.209 \times (0.993)^{\text{Age}}} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>White or Others (CKD-EPI formula)</strong></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Female ≤0.7</td>
<td></td>
<td>( \text{GFR} = 144 \times (\text{Scr}/0.7)^{0.329 \times (0.993)^{\text{Age}}} )</td>
</tr>
<tr>
<td>Male ≤0.9</td>
<td></td>
<td>( \text{GFR} = 141 \times (\text{Scr}/0.9)^{0.411 \times (0.993)^{\text{Age}}} )</td>
</tr>
<tr>
<td>Female &gt;0.7</td>
<td></td>
<td>( \text{GFR} = 144 \times (\text{Scr}/0.7)^{1.209 \times (0.993)^{\text{Age}}} )</td>
</tr>
<tr>
<td>Male &gt;0.9</td>
<td></td>
<td>( \text{GFR} = 141 \times (\text{Scr}/0.9)^{1.209 \times (0.993)^{\text{Age}}} )</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.50</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50-24.99</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥25.00</td>
</tr>
<tr>
<td>Preobese</td>
<td>25.00-29.99</td>
</tr>
<tr>
<td>Obese class I</td>
<td>30.00-34.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>35.00-39.99</td>
</tr>
<tr>
<td>Obese class III</td>
<td>≥40</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt; 18.50</td>
</tr>
<tr>
<td>Normal range</td>
<td>18.50-22.99</td>
</tr>
<tr>
<td>Overweight</td>
<td>≥23.00</td>
</tr>
<tr>
<td>Preobese</td>
<td>23.00-24.99</td>
</tr>
<tr>
<td>Obese class I</td>
<td>25.00-29.99</td>
</tr>
<tr>
<td>Obese class II</td>
<td>≥30</td>
</tr>
</tbody>
</table>
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

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

![Structural formula of Methylprednisolone](image)

**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 L 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 the 10mL 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”
References


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