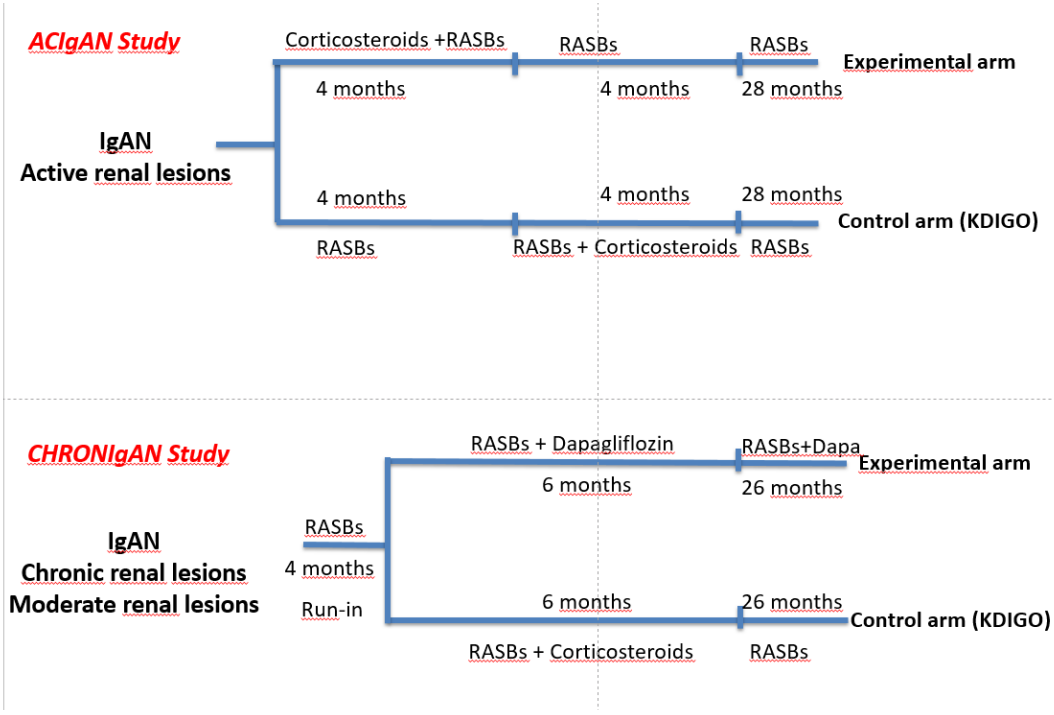
SYNOPSIS

Study Title	"Early start corticosteroids versus standard care (RASBs followed by corticosteroids) for proteinuria in Immunoglobulin A Nephropathy (IgAN) patients with active renal lesions identified by kidney biopsy and RASBs combined with corticosteroids versus sodium-glucose cotransporter2 inhibitor combined with RASBs for proteinuria and renal function in IgAN patients with chronic renal lesions identified by kidney biopsy. **A PROJECT FOR TWO MULTICENTRE, PROSPECTIVE OPEN LABEL RANDOMIZED CLINICAL STUDIES TO EVALUATE THE EFFECT OF TARGETED THERAPY BASED ON KIDNEY BIOPSY FINDINGS IN IgAN PATIENTS (CLIgAN)"**
Protocol Number	CLIgAN
Study Phase	III
Study Design:	The flow of this group of two prospective, multicentre, open-label randomized clinical trials on IgAN patients (CLIgAN) based on the kidney biopsy findings, is illustrated in the figure: 
Target Patients	Men and women aged 18 to 75 years with biopsy-proven IgAN will be enrolled in the CLIgAN project

Background and study rationale	Idiopathic Immunoglobulin A nephropathy (IgAN) is the most common glomerulonephritis in the world. It is more prevalent in Asia than in Europe and the US. IgAN is estimated to affect more than 500.000 people in Europe and it is the leading nephritis in kidney-biopsied patients. Approximately 40% of IgAN patients reach end-stage kidney disease (ESKD) 20 years after their kidney biopsy. The high prevalence of ESKD shows that IgAN has a significant economic impact in the countries because renal replacement therapy is costly. Moreover, the disease's onset in the second and third decades of life represents a social challenge because patients are typically very active and highly productive in the workplace. This challenge is one more reason to move from a generalized therapy for all IgAN patients to personalized therapy. The first edition of the KDIGO guidelines, published in 2012 and based on existing evidence from randomized controlled trials, suggested different therapeutic approaches for IgAN patients based on the clinical setting. Three sets of patients were considered: i) *Patients with low risk* manifest minor urinary findings and proteinuria < 0.5 g/day, normal estimated glomerular filtration rate (eGFR) and normal blood pressure; they need only annual or biannual checks without therapy. They represent only 5-10% of the IgAN patient population. ii) *Patients with intermediate risk* have proteinuria >0.5 g/day with normal or reduced eGFR and normal or high blood pressure. They may benefit from continuous supportive therapy (renin-angiotensin system blockers; RASBs) when proteinuria lowers less than 1g/day, and eGFR remains stable. When proteinuria is > 1g/day and eGFR (normal at baseline) declines to >50 ml/min/ 1.73 m^2, after three months of continuous supportive therapy, patients may benefit from corticosteroids combined with supportive therapy for six months. When eGFR is less than 30 ml/min or between 30 and 50 ml/min/1.73 m^2, only supportive treatment is recommended with no immunosuppression, except for patients with rapidly progressive glomerulonephritis. iii) *Patients at high risk* for acute or rapid loss of eGFR caused by rapidly progressive glomerulonephritis or nephrotic syndrome may benefit from corticosteroids combined with immunosuppressive agents and supportive therapy. These patients represent 2-5% of the IgAN population. In the presence of acute kidney injury (AKI) caused by red blood cells stacked in the tubules during the macrohematuria episode, only supportive therapy is suggested. These indications have been confirmed in the recent edition of the KDIGO 2021 guidelines (5). Unfortunately, due to the lack of experimental evidence from randomized controlled trials in this setting, the KDIGO guidelines could not consider the presence of active and chronic renal lesions at the time of the kidney biopsy as a potential *effect modifier* that could drive treatment decisions; this knowledge, nonetheless, is well recognized in clinical practice where patients with chronic renal lesions do not seem to respond to immunosuppressive treatment as opposed to those with active renal lesions. Observational studies support these clinical findings and their number, consistency and effect sizes shown for interventions

	based on the findings of kidney biopsy provide equipoise for the design and conduct of randomized trials based on the specific hypothesis that response may be modified by the baseline kidney biopsy findings. Our clinical study in IgAN patients (CLIgAN) will consider, first, the type of renal lesions, and will enrol patients in the ACIgAN and CHRONIgAN study based on current recommended practice (RASB followed by steroids) versus a differential approach (early start steroids or SGLT2) based on the biopsy findings.
Study objectives	**Primary objectives:** • To evaluate the therapeutic effect on proteinuria with early corticosteroid therapy, administered after the kidney biopsy in IgAN patients with active renal lesions (ACIgAN) versus standard care of RASBs alone followed by corticosteroids combined with RASBs; • To evaluate the therapeutic effect of SGLT2i (Dapagliflozin) combined with RASBs versus corticosteroids combined with RASBs on proteinuria in patients with chronic or moderate renal lesions (CHRONIgAN); thus, to avoid the potential side effects of corticosteroid therapy. **Secondary objectives:** • To evaluate the effect of study treatments on the renal function and on the progression of the kidney damage in IgAN patients at 3 years • after the prediction of ESKD through our IgAN CDSS tool (DialCheck) at the time of the kidney biopsy, to determine whether this personalized approach to therapy delays the impairment of the renal function.
Endpoints	**Primary endpoint:** • Between-arms difference in proteinuria reduction within 4 months and in non-responders within 8 months in ACIgAN study. • Between-arms difference in proteinuria reduction within 10 months in CHRONIgAN study. **Secondary endpoints:** • eGFR slope calculated as mean of individual slope obtained from individual linear regression of eGFR overtime (3 years); • eGFR decline > 40 % from the baseline value; • composite end point: GFR decline > 40%, ESKD (defined as long-term GFR $\leq$ 15 ml/min/1.73m^2 for more than three months or need for maintenance dialysis or kidney transplantation) or death due to kidney disease; • absolute difference between last GFR value and baseline GFR; • stable renal function defined as a decline in GFR $\leq$ 5 ml/min/1.73m^2 at the end of three years follow- up; • mean annual change in the slope of the reciprocal of serum creatinine concentration;

	• time-averaged proteinuria (TA-P) calculated as the weighted mean of all post-randomisation measurement, with weights representing the time elapsed since the previous measurement; • proteinuria slope, calculated as a mean of individual slope, obtained from individual linear regression of daily proteinuria overtime (3 years); • complete remission of proteinuria defined as achievement of urinary protein level ≤ 0.2 g/day or a urinary protein-to-creatinine ratio ≤ 0.2 g/g; • partial remission of proteinuria defined as achievement of a urinary protein reduction ≥ 50% or greater compared with the baseline value.
Number of Sites	Over 30
Number of patients	432 patients: • 132 patients (66 patients per group, including a 10% dropout rate, in the **ACIgAN trial)** • 300 patients (150 patients per group, including a 10% dropout rate, in the **CHRONIgAN trial**)
Inclusion and exclusion criteria	**Inclusion Criteria:** **<u>ACIgAN study</u>** 1. Males and females aged 18 to 75 years 2. Written informed consent form. 3. Biopsy-proven idiopathic IgAN with active renal lesions (E1 and/or C1) within 2 weeks. 4. eGFR ≥ 30 ml/min/1.73 m^2. 5. 24 hour proteinuria ≥ 0.5 g. 6. Patients on treatment or candidate for the treatment with RASBs (either an ACEi or ARB), as per clinical practice, according to the current KDIGO guidelines. **<u>CHRONIgAN study</u>** 1. Males and females aged 18 to 75 years 2. Written informed consent form. 3. Biopsy-proven idiopathic IgAN with chronic (T1,2) or moderate (M0,1, S0,1, E0, T0, C0) renal lesions at high or very high CKD risk within 4 weeks. 4. eGFR ≥ 30 ml/min/1.73 m^2. 5. 24 hour proteinuria ≥ 0.5 g. 6. Patients on treatment or candidate for the treatment with RASBs (either an ACEi or ARB), as per clinical practice, according to the current KDIGO guidelines. **Exclusion Criteria**: 1. Non biopsy-proven IgAN

	2. IgAN patients with minimal change disease at kidney biopsy and nephrotic syndrome. 3. IgAN patients with macrohematuria and acute renal failure. 4. IgAN patients with rapidly progressive glomerulonephritis (extracapillary lesions in more than 25 % of glomeruli in the kidney biopsy). 5. Patients with secondary IgAN (lupus nephritis, Schoenlein-Henoch purpura, liver cirrhosis). 6. Patients with superimposed IgAN in a kidney transplant. 7. Patients with other types of glomerular diseases. 8. Patients with solitary kidney. 9. Patients with end-stage kidney disease. 10. Bleeding disorders not responsive to treatment. 11. Patients with myocardial infarction or cerebrovascular stroke in the previous six months. 12. Severe liver diseases, infections, malignancies. 13. Uncontrolled diabetes (glycemia > 200 mg/dL and HbA1c > 7.5%). 14. Aseptic necrosis of any bone. 15. Any prior immunosuppressive therapy. 16. Other morbidities that can be exacerbated by corticosteroids. 17. Previous adverse side effects and/or contraindications to RASBs and SGLT2is. 18. Pregnancy and breastfeeding. 19. If women of childbearing potential (WOCBP): patients not available to use highly effective contraceptive measures during the study treatment period and up to one month after the last dose of study drugs.
Study Products	Methylprednisolone succinate and prednisone (Corticosteroids, CS) Dapagliflozin (Sodium-glucose cotransporter 2 inhibitor, SGLT2i)