


BMJ Open Randomised controlled trial comparing rituximab to mycophenolate mofetil in children and young adults with steroid-dependent idiopathic nephrotic syndrome: study protocol

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ABSTRACT

Introduction Glucocorticoids induce remission in 90% of children with idiopathic nephrotic syndrome (INS). Some become steroid-dependent (SD) and require the addition of steroid sparing drugs such as calcineurin-inhibitors (CNI) or cyclophosphamide, to maintain remission. Considering the toxicity of these drugs, alternative interventions are needed for long-term treatment. The anti-CD20 antibody rituximab has shown promising steroid-sparing properties, with conflicting results in complicated forms of SD-INS. Mycophenolate mofetil (MMF) resulted effective in maintaining free-steroid remission, however, studies are limited to few uncontrolled trials with reported different dose of MMF.

Methods and analysis This open-label, two-parallel-arm, superiority controlled randomised clinical trial will enrol children with SD-INS maintained in remission with oral glucocorticoids or CNI. Children and young adults will be randomised to either MMF (1.200 mg/m²) or rituximab (375 mg/m²) infusion. After enrolment, glucocorticoids will be tapered until complete withdrawal. We will enrol 160 children and young adults to detect as significant at the two-sided p value of 0.01 with a power >0.8 a reduction in the risk of 1-year relapse (primary end-point). As secondary endpoints, we will compare the amount of glucocorticoids required to maintain complete remission at 6 and 24 months.

Ethics and dissemination The trial was approved by the local ethics boards (Comitato Etico Regione Liguria CER Liguria <https://www.portalericerca-liguria.it/>). We will publish the study results at international scientific meetings.

Trial registration numbers NCT004585152.

INTRODUCTION

Idiopathic nephrotic syndrome (INS) is a podocyte renal disease characterised by loss of the impermeability functions versus circulating proteins causing severe proteinuria and hypoalbuminaemia with oedema. In Western countries, NS affects 2–2.7 new

Strengths and limitations of this study

- Strengths include objective and clinical outcomes, identification of a well defined population, methods to reduce bias and careful collection of safety data.
- The possible crossing over, from one drug to the other, offers to patients more chances of clinical success.
- Limitations are the non-blinded interventions due to the different types of drugs administration and the primary end-point that is an intermediate rather than a final outcome.

children per 100.000 children per year and has a prevalence of 16 cases per 100.000. Oral corticosteroids are the cornerstone of therapy, inducing remission of NS in ~90% of treated children.¹ However, up to 85% of cases relapse within 5 years and many will develop steroid dependence NS (SDNS).² According to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines³ administration of low-dose prednisone is suggested to maintain remission in SD-INS (evidence 2C-D), and mycophenolate mofetil (MMF) or calcineurin inhibitors (CNI) as corticosteroid-sparing agents for children who develop serious corticosteroid-related adverse effects (evidence 1B). The list of steroid-sparing agents has minimally evolved over years: in the original 2012 guideline a single 6-month course of cyclophosphamide or chlorambucil were the first choice; 1-year levamisole in milder case and CNI and MMF for at least 12 months were alternatives. Rituximab was suggested only in those children who relapsed in spite of former alternatives. In the recent update of KDIGO, the order of presentation of steroid sparing agents to

be used in SDNS is MMF, rituximab, cyclophosphamide and CNI that seems to have promoted rituximab as major option.⁴ Given the toxicity of the last two drugs there is a need to clarify which is, between MMF and rituximab, the most effective approach.

MMF inhibits purine synthesis in activated lymphocytes and reduces, in this way, the immune-response. A randomised controlled crossover trial involving 60 children with Frequently Relapsing-INS compared the efficacy of MMF (600 mg/m² two times a day) and cyclosporine directly. Relapses occurred in 36% of subjects during MMF therapy vs only 15% during cyclosporine (p=0.06). The time without relapse was significantly longer with cyclosporine than with MMF during the first year (p<0.05), but not during the second year (p=0.36). Notably, adverse events were similar between the treatment arms with the exception of a lower estimated glomerular filtration rate (eGFR) and lower haemoglobin values in the cyclosporine arm suggesting more nephrotoxicity.⁵ Other small randomised controlled trials (RCTs) reported that MMF is inferior to CNI in both SDNS⁶ and in SRNS.⁷ There are still doubts on the dose to be administered, that is, few studies used 1 g two times a day but lower amounts could be considered.⁸ Moreover, the need to test the effective moiety mycophenolic acid exposure to optimise MMF therapy is still debated.⁹

Anti-CD20 chimeric and humanised antibodies induce apoptosis of B-cell and probably of other cells and also reduce the number of B memory cells that means the immunoglobulin secretory potential. Observational studies^{10 11} and two recent RCTs^{12 13} support the use of rituximab in subjects SDNS, achieving stable steroid withdrawal formore than 1 year with a single infusion of rituximab (375 mg/m²). Suboptimal benefits were also obtained in complicated forms of the disease requiring the use of CNI.^{14 15} A recent meta-analysis¹⁶ concluded that rituximab is a valuable agent in SDNS but also suggested further comparative studies to address comparison with other drugs.

The aim of this trial is to test whether rituximab is superior to MMF in maintaining complete disease remission in children and young adults with steroid and/or CNI-dependent NS and is a part of major study aimed to define the proper dose of MMF to be used in these cases. We initially planned to show superiority of rituximab (given in standard does of 375 mg/m²) compared with low dose MMF (350 mg/m² two times a day) (NCT04402580): the trial was closed for futility after 30 subjects were enrolled because the 90% of subjects of the MMF arm relapsed after a median of 4.5 months.¹⁷ In the second part, we are seeking to compare superiority of rituximab (same dose) with MMF given in standard dose of 600 mg/m² two times a day.

METHODS AND DESIGN

Most of the issues described below have been already presented in a companion paper describing another RCT

comparing the effects of rituximab with ofatumumab in the same disease.¹⁸

Rationale and justification of the active comparator

The use of steroid-sparing agents is an important unmet clinical goal in paediatric nephrology, especially for children with complicated forms of SDNS requiring both glucocorticoids and CNI and new drugs represent an attractive opportunity. Due to its fully and strong affinity for the CD20 antigen, rituximab can be administered in a single dose,^{13 19 20} much lower than previous reported multi-infusion protocols and with reduced risk of adverse events.²¹ Clinical trials in SDNS subjects have already demonstrated long-term effectiveness of single infusions, repeated over years if needing.^{12 13} MMF has been evaluated in previous studies⁵ and in small RCTs^{6 7} showing effectiveness in reducing recurrence of proteinuria, but a standard dose is not defined. Head-to-head comparison of these two agents is justified on the basis of available data and awaited by clinicians who need drugs with reduced side effects for treating SDNS.

Objectives

This trial will test whether rituximab is able to achieve and maintain drug-free disease remission in subjects with SD-INS at 12 months (primary objective) and reduce the risk of relapse in a longer follow-up of 24 months (secondary objective) in children and young adults with SD-INS. This outcome will be compared with MMF, a drug recommended by Clinical Practice Guidelines (KDIGO) as steroid-sparing agents in the treatment of INS. This study will also collect information on occurrence of side effects as assessed by Common Terminology Criteria for Adverse Events (CTCAE) V.5.0 (ie, acute and long-term drug-related adverse events) and need to restart the use of glucocorticoids following the infusion of the trial interventions.

Design

This is an open-label, two-parallel-arm, controlled, phase II randomised clinical trial testing the superiority of rituximab over MMF in maintaining steroid-free and CNI-free disease remission in children with SD-INS (figure 1). Eligible participants are children and young adults (age between 3 and 24 years) with NS who are dependent on prednisone 0.3–1 mg/kg/day and have received prednisone for at least 6 months before enrolment. Previous treatment with MMF and CNI will be allowed. All participants, after inclusion criteria evaluation, will be engaged and after collection of the informed consent or assent, they will be randomised and start treatment. Randomisation will be stratified by age (<vs ≥9 years) and centre. Each list will be generated using random numbers with blocks of variables size. Subjects randomised in the comparator arm will start, or continue, MMF 1200 mg/m² orally in two daily doses and will taper glucocorticoids after 15 days by 0.3 mg/kg per week until complete withdrawal. During the enrolment visit, instruction on

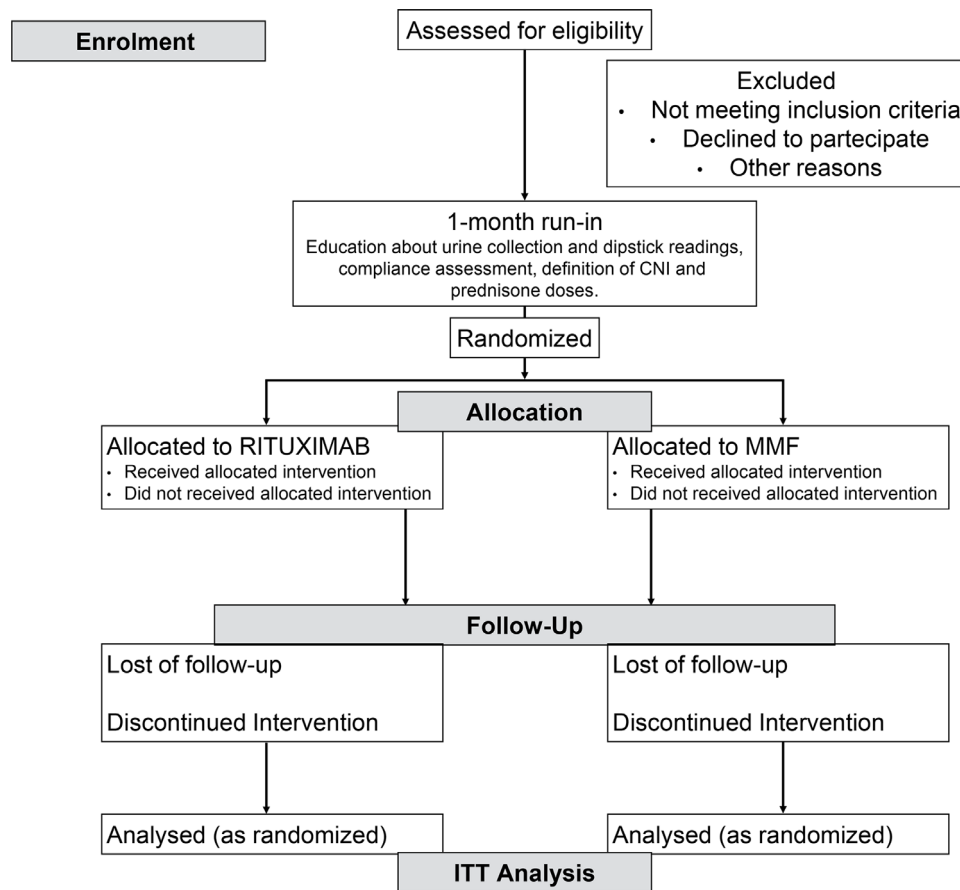


Figure 1 Schematic view of trial design. CNI, calcineurin inhibitors; ITT, intention to treat; MMF, mycophenolate mofetil.

urine collection and dipstick readings will be carefully reviewed and compliance assessed. Children or young adults randomised to the intervention arm will receive drug infusion (rituximab, 375 mg/m²). One month after infusion, other therapies already used before (as MMF or CNI) will be decreased by 50% and withdrawn within two additional weeks, similarly only MMF will be maintained in the comparator. All subjects will be followed for up to 24 months. In case of relapses during this period subjects will be treated with oral prednisone (60 mg/sqm day). Following remission, glucocorticoids will be maintained at the initial dose for 7 days and then tapered off by 0.3 mg/kg per week until complete withdrawal in subjects of the MMF arm. Subjects of the intervention arm will instead be treated with another infusion of rituximab (375 mg/m²) immediately following steroid-induced remission. The study allows drop-in from one arm to the other after two relapses (ie, investigators will be allowed to use rituximab in the comparator arm and vice versa MMF in intervention arm). Study enrolment started in October 2020 and is expected to be completed within 1 year.

Setting

The trial will be carried out at two paediatric nephrology departments in Italy: the Nephrology Unit of the Giannina Gaslini Children's Hospital, Genoa and at the Nephrology Unit of the Bambino Gesù Pediatric Hospital, Rome. Interventions will be administered during an in-patient

setting. Follow-up visits will be performed at the same institutions or by local nephrologist if travel to Genoa or Rome is not possible, in particular in case of a new COVID-19 pandemic waves.

Eligibility criteria

Inclusion criteria: Subjects aged 3–24 years, in complete disease remission and with a proven clinical history of SDNS are eligible for inclusion in the study. SDNS will be defined by two consecutive relapses during corticosteroid therapy tapering or within 14 days of steroid withdrawal. Subjects have been enrolled if they were receiving steroid alone or in association with MMF or CNI to maintain stable remission. **Exclusion criteria** were positivity to autoimmunity tests (antinuclear antibodies (ANA), antibodies anti-DNA (nDNA), anti-neutrophil cytoplasmic antibodies (ANCA)); reduction of C3 levels; eGFR <90/mL/min/1.73 m² evaluated according to revised Bedside Schwartz Formula for subjects between 2 and 17 years and with CKD-EPI Creatinine 2009 Equation for 18–24 years old subjects; pregnancy; neoplasm; previous or actual hepatitis B virus (HBV) (with hepatitis B surface antigen (HBeAb) and antibody to hepatitis B core antigen (anti-HBc) Abs positivity) or hepatitis C virus (HCV) infection; CD20 B lymphocytes count <2.5% and treatment with rituximab or cyclophosphamide in the last 6 months; previous reported severe adverse events (grade ≥3) to study agents.

Participant identification

Patients with SDNS afferring to the Nephrology units of Giannina Gaslini Children's Hospital, Genoa and of Bambino Gesù Pediatric Hospital, Rome will be interviewed to verify the existence of prerequisites for enrolment in the study. Information on treatments, randomisation procedure and follow-up steps will be given by specialised personnel of the medical staff; a sheet specifying the points above and the informed consent/assent format will be given to patients or their parents depending to ages (not to children under 4 years). Before randomisation the assent will be required to children <18 years and the formal consent to their parents; patients over 18 years will be required to sign the consent. At this step, every patients will be assigned an unique number and the request of randomisation will be sent to a distant site analyst who is encharged of all the statistic procedures.

Randomisation

Participants will be randomised 1:1 to the intervention or active comparator arm. A distant site with no clinical involvement in the trial will generate two randomisation lists (for age ≥ 9 years and <9 years) using permuted blocks of variable size. Stratification by age is motivated by the need to maximise the likelihood of balancing factors potentially affecting the effects of the intervention on outcomes, which are associated with age (disease duration, age at onset, relapse history and disease severity).¹⁴ A study investigator responsible for recruitment will obtain signed consent (and assent for participants capable of assenting), assign a unique participant study number and request randomisation. An analyst from a distant site not involved in patient care, where the randomisation lists have been generated and kept concealed from the clinical investigators, will communicate the allocation arm to the study coordinator (based on the participant study number).

Randomisation 1:1 to rituximab (intervention) or to MMF (active comparator) will be generated by permuted block at a distant site by an analyst who is responsible of the final analysis of data. Patients in both arms will be stratified by age (\geq or <9 years) to balance potential modifiers of the drug response such as disease duration, other treatments and others.¹⁴ The allocation arm will be communicated by the principal investigator (PI) of the study to participants and to their parents depending on age.

Treatment arms

Intervention

Patients in the intervention arm will be treated with rituximab 375 mg m² (Rixathon, Sandoz Schafteuau Biochemiestr. 10 6336 Langkampfen Austria) diluted in normal saline in accord to what already reported in this journal.¹⁸ Details on concentration of rituximab and speed of infusion have been already reported together

with the composition of the premedication scheme. All the procedures will be carried out by a registered nurse.

Active comparator

Patients assigned to the active comparator will be treated with MMF (Tillomed, Milano, I) 1.200 mg m² in two doses.

Relevant concomitant care and interventions that are permitted or prohibited during the trial.

With the exception of those drugs listed as criteria for exclusion, starting from the signature of the informed consent, any other medication could be given based on the investigator decision who will be encharged to register all drugs in the report form. ACE inhibitors/angiotensin II receptor blockers (ARBs) will be stopped and replaced in hypertensive patients with other medications: carvedilol 0.2–1 mg/kg per day will be the first line choice followed by amlodipine 0.06–0.3 mg/kg per day; in all cases it will be associated restriction in dietary sodium intake.

Outcomes

Relapse of proteinuria or start of prednisone in the first year from treatment will be the primary end-point. The urinary protein/creatinine ratio (uPCR >2.000 mg/g or >200 mg/mmol) is the basic criterium for defining relapse. Positive urine protein dipstick (>3+ for 3 consecutive days) while being indicative of relapse will be confirmed by the uPCR ratio. Values of uPCR under the 50% of the limits above defines the partial remission. Failure to obtain complete withdraw of prednisone and/or of MMF or CNI will indicate relapse.

Relapse of proteinuria after 24 months and number and severity of adverse events will be the secondary end-points. Clinical aspects in the form of signs and symptoms, together with abnormal biochemical and haematology findings will define safety. They will be approached according to criteria as outlined in online supplemental appendix. Immune competence will be characterised and described as an ancillary aspect.

The follow-up will be closed at the completion of the study procedures at 12 (primary outcome) and 24 months (secondary outcome).

Data collection, management, and analysis

Data collection methods and adherence during follow-up

Out of relapses or acute events, visits will be scheduled at 1 month and every 3 months after treatments up to 24 months. During these visits, plasma proteins, immunoglobulins, lipids status and lymphocyte subpopulation characteristics will be determined (table 1). A 24-hour urine collections for protein determination is requested at any visit. Daily dipstick will be registered in a diary form that will be sent every 1–2 months to the PI.

Data management

The PI will design a person deputed to record clinical and biochemical parameters in an electronic data sheet. The PI and the person encharged of the data storage at the Giannina Gaslini will be responsible for a correct data management.

Statistical methods

Patient characteristics in the two arms of the study will be summarised by common quantitative and qualitative methods. Logistic regression will be utilised for the analysis of the primary outcome and specifically for the calculation of the cumulative risk of relapse at 6 and 12 months considering a two-sided $p < 0.05$ as indicative of statistical significance. Survival methods will address the risk and the average time of relapse by treatment groups.²² An intention-to-treat approach will be used in all cases considering patients randomly adherent to the protocol. Replacement of missing data will reflect the worse case scenario that is success in the active comparator arm and failure in the intervention group.

Sample size

We will enrol 160 children and young adults in this study, and follow them for 2 years. Assuming a baseline risk of relapse at 1 year of 0.65 among children assigned to rituximab, this sample size will allow to detect as significant at the two-sided p value of 0.01 with a power > 0.8 a reduction in the risk of 1-year relapse of at least 0.3 (ie, from 0.65 to 0.35; risk reduction by 0.46). This sample size accounts for a total proportion of drop-out and drop-in $< 10\%$.

Patient and public involvement

No patients were involved in the study's design.

Study withdrawal

Participants will be informed of the right of withdrawing at any time from the study without furnishing any reason and people of the medical staff give from now their personal assurance that this will not modify their conduct. On the other end, the PI has the possibility to withdraw a patient in case new health occurrences advise against participation to the study. Among any other, development of glucocorticoid resistance, worsening of renal function by 5% GFR every 6 months, malignancy, pregnancy, severe hypertension, proven hypersensitivity or allergy to drugs represent potential valid conditions necessitating withdrawal. Legal and administrative reasons may also suggest withdrawal. Both medical and non medical causes will be reported in the register.

The sponsor itself may stop temporarily or permanently the study based on safety, ethical or other reasons. In this case, the PI and the sponsor will rapidly inform the independent ethics committee.

Data safety and monitoring board, study monitoring and end-point adjudication committee

Interim analyses or prespecified stopping rules are not planned. The data safety and monitoring board (DSMB) is scheduled when 50% of patients will be enrolled to decide about safety. DSMB is composed of experts in methodology and clinical nephrology and is under the responsibility of the sponsor. Monitoring of the study procedures (case report forms compilation, periodical visits, laboratory data) will be

Table 1 Participants timeline

	Enrolment	Allocation and treatment	Study period							
			Follow-up							Close-out
Time point	-1	0	t ₁	t ₃	t ₆	t ₉	t ₁₂	t ₁₅	t ₁₈	t ₂₄
Enrolment										
Relevant medical history	X									
Eligibility screen	X									
Project illustration	X									
Informed consent/assent	X									
Instruction about immunosuppressive drugs tapering	X	X								
Allocation		X								
Interventions										
Rituximab administration/starting MMF		X								
Assessments										
Dosage on 24-hour urine collection	X	X	X	X	X	X	X	X	X	X
Physical examination and vital signs	X	X	X	X	X	X	X	X	X	X
Haematology and biochemistry*	X	X	X	X	X	X	X	X	X	X
Adverse events data records		X	X	X	X	X	X	X	X	X

*Haematology and biochemistry includes: complete blood count, kidney function, plasma proteins immunoglobulins, lipid status—cholesterol and triglycerides—albumin, lymphocyte subpopulations—for CD 20 lymphocytes B count. MMF, mycophenolate mofetil.



done periodically by the PI or by a delegate who will have access to the study material. Number and frequency of visits will be determined by the number of patients enrolled (1 visit every 40 patients). At the end, a final visit will control the whole collection of documents and data reports. Detailed analysis of each subject document will be done in a blind manner by a special committee that will be established at the end of the study.

ETHICS APPROVAL, TRIAL STATUS AND DISSEMINATION

Before initiation of the study, we obtained written approval of the protocol, Informed Consent/assent Form and any information presented to potential subjects from the local Independent Ethics Committee (Comitato Etico Regione Liguria). We also obtained approval from the Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA). The trial is currently recruiting; study enrolment started on 15 October 2020.

The completed randomised clinical trial study will be summarised in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study and interpretation of findings. The authors of this study protocol will inform the contributing investigators (primary healthcare providers of study participants) in advance about any plans to publish or present data from this RCT. Any publications and presentations of the results (abstract in journals or newspapers, oral presentations, etc), either in whole or in part, by investigators or their representatives will require presubmission review by the authors of this study protocol and all coauthors.

DISCUSSION

According to 2012 KDIGO Recommendations,³ CNI and cyclophosphamide represent the treatment of choice in case of SDNS, causing a high risk of systemic toxicity due to the long term administration with both glucocorticoid-sparing and/or standard steroid-sparing agents.

Cyclophosphamide, popular in early 1980s, presents serious limitations mostly because readministration over time is avoided for neoplastic complications, therefore, current management is limited. CNI result effective in SDNS, but the consequent direct and specific renal injury over years limits a prolonged use.²³ Alternative treatments such as rituximab and MMF are considered as effective options in the 2019 updated revision of KDIGO.⁴

Recent RCTs^{12,13} support the use of rituximab as an effective steroid-sparing agent in SDNS, mainly in subgroup of children presenting with moderate glucocorticoid-dependence, resulting really sensitive to the drug.¹³ On the other hand, effectiveness of rituximab may be suboptimal in SDNS subjects who remain dependent to glucocorticoids after the start of CNI, representing a category of subjects for whom more evidence relative to the efficacy of rituximab are needed.^{14,24}

MMF has been tested in retrospective studies and in small RCTs, showing a satisfactory efficacy in treatment of SDNS, also if with inferior power than CNI.⁶

A recent meta-analysis¹⁶ confirmed effectiveness of rituximab still recommending further studies comparing rituximab with drugs, such as MMF, causing limited side effects.

This is the first RCT comparing the risk of relapse in patients with SDNS treated by one of the two drugs. There are several strengths in the study that are mainly based on the choice of a well-defined category of patients with glucocorticoid dependent NS and on the definition of clear outcomes. Blinding, allocation system and definition of follow-up steps and evaluation of safety together with the expertise in research and clinical nephrology reinforce the quality of the study. Finally, the possible crossing over from one drug to the other offers to patients more chances of clinical success.

The design of this trial has also limitations. First, interventions are not blinded because rituximab and MMF require different types of administration. Second, the primary end-point is an intermediate rather than a final outcome. However, the lab-based measures adopted to define disease relapse are objective and more distant outcomes, including cardiovascular or infectious complications of NS, or progression of kidney disease to kidney failure, are rarely observed during childhood. A very large multinational trial would be necessary to study these hard end-points. On the other hand, relapse of NS is an important outcome for children and their families, often requiring travel to the nephrology centre in order to access urgent care. Third, this trial will compare the risk of relapse at 1 year based on the first event that occurs. Finally, according to the study model, participants are maintained in the assigned arm for follow-up studies up to presentation of two relapses, after then relapsing subjects are crossed over to the comparator (see above). In this way, comparison of the effect of each treatment on the risk of repeated relapses is not included in the present trial.

In summary, this study addresses an intervention question that is relevant to children and young adults with SDNS and their families. Results from this study may impact the management of SDNS in young children, providing efficacy and safety of these therapies justifying a widespread in specific renal clinical setting.

Improvement in quality of life, reduction in hospitalisation rates and use of healthcare resources are other important expected benefits.

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Contributors PR, MV, FE and GMG were involved in conception and trial design and in drafting of the article. FL, AA, MC, GC and EV reviewed/edited the manuscript.

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Disclaimer The study sponsor had no role in the study design and protocol development of this study. The sponsor will not have any role in the collection, analysis or interpretation of the data, or in the writing of report for publication. The researchers have complete independence from the sources of funding in all aspects of this study.

Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

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